

Module 201

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Hello, my name is Terry Fisher. This is the first in a series of five lectures discussing the global health crisis and how legal reforms could help alleviate it.

Let's start with some terminology. The original meaning of the word "crisis" was a point of uncertainty or inflection in the progress of an illness – in other words, the point at which a sick person starts either to recover or to worsen irrevocably. Over time, the meaning of the word expanded to refer to any highly unstable, difficult, or dangerous situation – such as the Cuban missile crisis of 1962 or the global financial crisis of 2008-2009.

By describing our current situation as a global health crisis, I mean to invoke both the original definition and the more modern, general definition.

The crisis has two dimensions.

- (1) The threats to human health posed by many diseases are currently increasing, alarmingly.
- (2) The disease burdens borne by low and-middle income countries radically exceed the burdens borne by upper-income countries – and the threats on the horizon may increase that disparity.

In short, the first aspect involves growing threats to the health of all people in the world. The second involves inequality of access to the means of preserving health.

As will soon become apparent, these two dimensions are intertwined, but the moral questions they raise – and some of the ways in which they might be addressed – are different. Thus it's important to differentiate them.

In the first part of this lecture, I'll provide an overview of principal manifestations of these two dimensions. In the second and longer part, I'll explore the potential roles of drugs as part of a composite effort to control the crisis.

To describe and measure the crisis, we'll need some metrics. Some of these will likely be familiar to you, but not all.

Life expectancy at birth is an estimate of how long a person born at a particular moment in time would live if the conditions affecting health did not change during that person's lifetime.

A more complex metric is known as Healthy Life Expectancy. It adjusts simple Life Expectancy downward to take into account periods of time in which people spend in ill health. Ill health, in turn, is conventionally measured using yet another metric, known as a

Disability Adjusted Life Year, commonly abbreviated a DALY. A DALY is best understood as one lost year of healthy life.

The way the DALY metric works is perhaps best seen through example. If you lose a finger and then live that way for a year, that's treated as a loss of 3 one hundredths of a DALY, reflecting a modest diminution in the quality of your life. By contrast, a year of blindness is treated as a loss of approximately 2 tenths of a DALY, and a year suffering from an advanced form of Alzheimer's is treated as a loss of two thirds of a DALY.

The methodology that has been used to identify these fractions is controversial, but it's the best we have – and will suffice for comparative purposes.

Deaths should be obvious: the number of people who died from a specific cause, usually measured with reference to a specific year.

Mortality rate measures the percentage of the relevant population who died from a specific cause. It's usually expressed as a number per year, per 100,000 people in the relevant country or group.

Incidence refers to the occurrence of new cases of disease in a population over a specified period of time, typically a year.

Prevalence is the percentage of persons in a population who have a particular disease at a specified moment or over a specified period.

Age standardization refers to a method of adjusting a metric, such as mortality or prevalence, to control for the facts that (a) the age distribution in two jurisdictions (or in the same jurisdiction at 2 points in time) are likely to be different and (b) that the incidence of many diseases (such as cancer) varies by age. There are two main ways of making such adjustments. Either one population is mathematically adjusted to have the same age structure as the other; or both populations are mathematically adjusted to have the same age structure as a standard population.

Age standardization facilitates comparisons – enabling us to say, for example, that a disease is worse in country A than in country B or that the situation in a given country is getting worse or better.

OK, let's put these tools to work.

Starting in the 19th century, humans made tremendous progress in controlling diseases. The clearest indicator of that progress was the increase in average global life expectancy. Estimates vary somewhat, but as James Riley has shown, the overall picture is pretty clear.

For millennia, average life expectancy was between 20 and 30 years. After 1800, it began to creep upward. After 1900, the rise accelerated. In the 1980s it slowed, but the march upward seemed inexorable. By 2000, it had reached 66 years. By 2020, over 72. But in the past two years, it has begun to decline.

The principal cause of the reversal is not a mystery. Starting in late 2019, the COVID-19 pandemic swept over the world. At its peak, it killed 100,000 people a week. As of January 2023, it has killed well over 6 million people. And it's far from over.

COVID is surely the most visible and most serious of the outbreaks of contagious diseases in recent years. But it is not the only one. Ebola simmered in West Africa for decades, then suddenly surged. For the time being, it has once again been contained, but it has not disappeared. Marburg, an equally deadly virus, is also simmering in central Africa.

Actual or potential Pandemics of these sorts merit the attention they are now getting. But we also face serious threats from other quarters.

Tuberculosis, an ancient disease, still kills about 1.5 million people a year. For more than 30 years, that number had been slowly diminishing. No longer. In the last two years, the total number of TB deaths has gone up. Even more alarmingly, the mortality rate – the number of deaths per 100,000 people – has also risen.

Much of that rise is a secondary effect of the COVID pandemic – but not all. For reasons I'll address in a minute, we should not assume that curbing COVID will enable us to resume the gradual suppression of TB.

Much the same is true of malaria. Globally, over 200 million people are infected with malaria every year, and over half a million die, most of them children. Those numbers had been declining slowly until 2018, but are now rising.

The third member of the so-called "Big 3" infectious diseases is HIV/AIDS. Here the news is more encouraging. Global deaths from AIDS continue to fall – primarily because of the increasingly widespread distribution of antiretroviral drugs. The extraordinary impact of the drugs is readily apparent from this diagram.

However the number of deaths is still high. And, although the drugs usually control the disease, they do not cure it. Nor have we halted new cases of HIV.

When we turn from infectious diseases to noncommunicable diseases, we find other threats.

Until recently, we were winning the longstanding war against cancers. Although both the total number of cancer deaths globally and the crude global mortality rate continued to rise, the age-standardized death rate fell steadily. But very recently, progress seems to have slowed, even stopped.

To be sure, many forms of cancer are now increasingly curable. But global deaths from some others remain stubbornly high.

Even more worrisome is the rising prevalence of disorders of the central nervous system.

The disease that is growing most rapidly is Parkinson's. In 1990, 2.5 million people had the disease. By 2016, the number had grown to 6.1 million – a 21% increase in the age-standardized prevalence rate.

Annual deaths drew at the same alarming pace, reaching 211,000 globally.

And the total number of disability adjusted life years lost per year Parkinson's exceeded 3 million. Since then, the numbers have continued to rise.

The prevalence of depression also appears to be increasing – both in crude numbers and, more alarmingly, in terms of the age-standardized rate. It's difficult to measure, in part because of variations in how depression is defined, and in part because of the absence of a comprehensive reporting system. But all of the relevant studies indicate that prevalence is growing. One, for example, estimated that, in the decade ending in 2020, the prevalence of elevated depressive symptoms among adolescents globally was 14% higher than in the decade ending in 2010. Stress, anxiety, and depression then increased sharply during the pandemic.

In contrast to Parkinson's disease and depression, the age-standardized prevalence of Alzheimer's disease and other forms of dementia does not seem to be increasing significantly – but nor is it decreasing. In other words, this war is at a stalemate. Stalemate, however, has a major cost. Because the global population has been both growing and aging, the total number of deaths from dementia has increased sharply

And the number of people who will suffer from this cluster of diseases is forecast to keep rising. That's enough, for the time being on neurological disorders.

Diabetes, another major noncommunicable disease, is also becoming more common. In 2021, as you can see, over 500 million people had diabetes – a prevalence rate of around 10%. By 2045, the prevalence rate is forecast to be higher – and the total number of affected persons will approach 800 million. The annual costs to treating diabetes, already close to a trillion dollars a year, globally, will likely keep rising.

I don't want to leave this impression that the global health situation is all doom and gloom. We are making great progress in some sectors. Perhaps the most important is cardiovascular disease, which has long been the single largest cause of deaths worldwide. Although the total number of deaths continues to rise, the mortality rate has been marching steadily downward.

Even more dramatic have been the gains in the past 30 years with respect to lower respiratory infections – the most common of which is pneumonia. Here the total number of deaths has dropped sharply, primarily because of success in combatting pneumonia in young children, and the age-standardized mortality rate has plummeted.

Breakthroughs in the prevention and treatment of many other diseases continue to occur. The age-standardized rates for several cancers, for example, are going down.

The most dramatic of the recent successes was the extraordinarily rapid development of vaccines capable of preventing or at least reducing the severity of – COVID infections. One study recently published in the Lancet estimated that, between December 8, 2020 (when vaccines first became available) and the same date a year later, those vaccines prevented at least 14.4 million deaths – despite the limitations on the distribution of vaccines in low and middle-income countries, a topic to which we will return shortly.

But the visibility of such advances and breakthroughs should not blind us to the many sectors where we are not advancing – or indeed are in danger of losing wars.

So, to summarize, to the extent we are concerning with aggregate global health, we should be especially worried about the states of affairs with respect to:

- COVID-19 – and future pandemics of infectious diseases;
- TB;
- Malaria;
- HIV;
- Some cancers;
- Parkinson’s disease;
- Alzheimer’s and other forms of dementia;
- Depression;
- And diabetes

This list does not exhaust the set of threats, but it should suffice for now.

So far, we’ve covered only the first of the two dimensions of the global health crisis. We turn now to the second: the disparity in the burdens of disease borne by different countries.

Let’s start with overall life expectancy. At the outset of this lecture, I pointed to the dramatic rise in global life expectancy since the early 19th century. Unfortunately, the pace of improvement has varied considerably by country and region. Here are the numbers from 2019, the last time the WHO provided comprehensive comparisons.

In these countries, life expectancy was over 80. Japan had the highest number, but Canada, Australia, and most of the countries in western Europe were not far behind. Note that Chile is in this group, but the US is not. In these countries, life expectancy was in the high 70s. In these the low 70s. Now things get grimmer. These countries had numbers in the high 60s. These in the low 60s. And these in the 50s. More fine grained comparisons can be made by using this key.

So far, we’ve been comparing countries solely on the basis of when people typically die. If we supplement those data with information about morbidity, the numbers shift downward, but the differences persist.

Here are the 2019 numbers for Healthy Life Expectancy. You will recall, I hope, that Healthy Life Expectancy is the metric that adjusts life expectancy downward to account for periods of time in which people spend disabled or in poor health. Whereas the range for simple life expectancy was from 50 to 84, the range for HALE was from 44 to 74. Here are the numbers for a few representative countries to facilitate your use of the key.

Notice that the US, Brazil, and Russia have similar numbers – around 65. All three countries are below China, at 68, and way below Japan, Canada, and the countries of western Europe, which are all in the low 70s. But the numbers that really stand out are those of India, Mongolia, and most of subSahran Africa, where Healthy Life Expectancy is 60 or below.

A rough sense of the causes of this inequality can be obtained by dividing the countries of the world into 4 groups, using the categories developed by the World Bank: high-income countries, upper-middle-income countries, lower-middle-income countries, and low-income countries. This map shows the category into which each country currently falls. The lines between the categories, measured by gross national income per capita in US dollars, are 1,046, 4,095, and 12,695.

You will not be surprised to see that the United States, Canada, much of Western Europe, Australia, and Japan are all in the high-income zone. China, Russia, and the bulk of Latin America are in the upper-middle zone. India, Mongolia, substantial portions of Sub-Saharan Africa are in the lower-middle-income zone, and the remaining portions of Sub-Saharan Africa along with Afghanistan are in the low-income category.

We're now going to use these categories to examine the causes of mortality and morbidity throughout the world. Here are the four sets of countries. Here are the populations of the four groups. As you can see, most people in the world live in the two middle categories.

On the left-hand side of the page is a list of all of the things that people suffer from and die from in the world today.

Each of the cells in the chart I'm about to show you will contain three numbers, all of which were derived from the World Health Organization's most recent study of mortality and morbidity. The first figure in each box is going to be the number, in thousands, of disability-adjusted life years lost each year in the region in question, as a result of the cause in question. The second line of each cell will indicate the regional share of the global disease burden associated with the set of ailments in question. Finally, the third line in each cell will indicate the number of DALYs lost each year in each of these groups of countries per 100,000 people. Here, finally, are the numbers. I'm now going to pull out of this mass of data the comparisons that are most germane to our project.

At the grossest level, the number of DALYs lost per capita each year in low-income and lower-middle income countries is much higher than the numbers lost per capita in upper-middle and upper-income countries.

Some of the sources of that disparity are unsurprising. Infant mortality, as you might expect, is concentrated in poor countries. So is starvation. So are injuries – although the inequality here is not quite so severe. Each of these sectors is deeply troubling. But the largest single source of the disparity is up here: DALYs lost because of infectious and parasitic diseases. As you can see, these are extremely common and burdensome in poor countries. By contrast, except during pandemics (a topic to which we will return), they are uncommon in rich countries.

Lower respiratory infections, just mentioned, are also distributed highly unequally.

The only sector in which the disparity in terms of DALYs per capita tilts in the opposite direction is the largest sector of all: noncommunicable diseases. Within this category, as we've seen, are cardiovascular disease, cancer, neurological disorders, diabetes and so forth. As you can see, these ailments together constitute the biggest source of mortality and morbidity in the world. And when measured by DALYs per capita, the burdens they

impost of high-income countries are the highest and the burdens they impose on low-income countries are the lowest.

We're now going to shift to a more fine-grained analysis. I'm going to break down the major categories of diseases into more specific sub-categories. And I'm going to break down the four World Bank groups into individual countries.

As you will see, this fine-grained approach will make it harder to keep track of general forces and trends, but its specificity will expose some variables that we'll need to consider when designing solutions to the crisis.

Let's begin with infectious diseases, which, as we saw, were the biggest source of inequality across the four major groups. Here's how the countries of the world compare in terms of DALY burdens. And here are the age-standardized mortality numbers. The range of the mortality data here is astonishing. I'll insert a few of the numbers for illustrative purposes.

As you can see, age-standardized mortality from infectious diseases was 5 per 100,000 people in Japan and Australia, 6 in China and France, 12 in the US, 26 in Brazil, 51 in the Philippines, 115 in India, 302 in Nigeria, and 582 in the Central African Republic.

OK, now let's take this category apart. The so-called big three infectious diseases, as we saw, are TB, malaria, and AIDS. Much less well known – but equally deadly, especially to kids, are diarrhoeal diseases. Here's how the DALYs that these four diseases cause are distributed by country – and the corresponding age-standardized mortality numbers.

First TB – in terms of DALYs, then mortality. Then Malaria. Then AIDS. And finally diarrhea. Now let's compare.

As you can see, their footprints are a little different. All four of the major infectious diseases bear most heavily on subSaharan African countries. But whereas AIDS is worst in the southernmost countries, malaria and diarrhoeal diseases are worst in west central Africa, while TB, the biggest killer, is somewhat more equally distributed in the continent.

Another major difference is that, whereas few countries outside of Africa now bear substantial burdens from malaria, several south Asian and southeast Asian countries suffer heavily from TB and diarrhea, and some Latin American and eastern European countries suffer heavily from AIDS. These comparisons hold true, when we turn DALYs per capita to mortality.

But we should not limit our attention to the big 4 killers. Here's a more complete list of the major infectious diseases. Except for meningitis, most of the remaining infectious disease cause only moderate numbers of deaths, but several cause enormous amounts of misery.

What about COVID-19? Comparing its impact in different countries is difficult, in part because of inconsistencies in data gathering and reporting systems, and in part because of deliberate concealment of information. But this map, which shows cumulative numbers of deaths per million people, from the beginning of the pandemic until today (February 28, 2023) is probably roughly accurate.

As you can see, some of the highest numbers have occurred in developing countries: Peru, for example, has the highest death toll per capita in the world. But, overall, developed countries have thus far suffered more heavily. We'll return to potential explanations for this pattern in due course.

As I noted previously, DALYs per capita from lower respiratory infections (of which the principal example is pneumonia) also disfavor the category of low-income countries. Here's a more precise breakdown.

Again, we see heavy burdens in Africa, but, at least with respect to mortality, several countries in Latin America (most notably, Argentina and Bolivia) and in south and southeast Asia are also suffering. Indeed, the age-standardized rate in the Philippines exceeds that of most African countries.

We come finally to the NCDs. As I've mentioned, the DALYs they cause are unequally distributed across the four World Bank categories – but in the opposite direction from all of the other categories. Here are the country-by-country breakdowns.

This map is eye-opening. The pattern here is completely different from the pattern of all of the previous maps. But we should not linger on it too long, because, when we change the metric to age-standardized mortality, the picture changes radically.

Now let's compare. The explanation for the sharp difference is that many NCDs affect older people more than younger people – and the populations of most high-income countries are older than that of most low-income countries. Age standardization controls for that effect – and reveals that, once again, Africa and most parts of Asia fare worse than North America, western Europe, Australia, and most parts of Latin America.

But in this respect, the category of NCDs is heterogeneous. Some of the diseases in this general category have been thus far concentrated in developed countries, while others have been concentrated in low and middle income countries. Here are the geographic footprints of the ones I've already mentioned.

Cardiovascular diseases disproportionately burden Asia and Africa. Heart disease, the most deadly of the cardiovascular diseases, is even more geographically concentrated – specifically, in North Africa and Northern Asia.

The footprint of cancer is hard to describe, primarily because the footprints of the various types of cancer are very different. Here are the six most common, in approximate order: Lung; Colon; Stomach; Breast; Pancreatic; Prostate.

Now let's juxtapose them. As you can see, they diverge radically in the weights they impose in different parts of the world. The ones that currently bear more heavily on low and middle income countries are breast cancer and prostate cancer.

What about the disorders of the central nervous system? The pattern associated with Parkinson's disease is eccentric. With the exception of Bolivia, Latin America seems largely to have dodged Parkinson's, as has Eastern Europe and the Philippines. But it's spread reasonably evenly elsewhere.

Alzheimer's and other forms of dementia currently most affect North America and northern Europe.

By contrast, the age-standardized mortality rate for diabetes is highest in tropical countries. As yet, morbidity (meaning pain and suffering) from diabetes remains lower in those countries because fewer people have the chronic disease – but that pattern will soon change. As you can see, the trends for low and lower-middle income countries are worse than the trends for richer countries .

OK. Let's not lose track of the overall picture. This is the aggregate situation with which we are concerned: Several serious threats to world health in general. And persistent inequality in the disease burdens borne by rich and poor countries.

As I indicated a few minutes ago, the most serious of the threats to overall global health are COVID and future pandemics; Tuberculosis; Malaria; Parkinson's Disease; Dementia; Depression; and Diabetes.

The material we've just reviewed shows that the greatest sources (actual and potential) of the disparity between rich and poor regions of the world are: COVID and future pandemics; Tuberculosis; Malaria; "Neglected diseases"; HIV/AIDS; Diarrhoeal Diseases; Pneumonia; Breast Cancer; Prostate Cancer; and Diabetes.

As you can see, there is partial overlap of these two lists – which suggests, at a minimum, that we should be especially concerned with the diseases circled in red. But the fact that the two lists are not identical poses complex questions about priorities. For the time being, I'm going to put aside the question of how we should allocate our scarce financial and human resources across these two dimensions when they don't overlap, but that fundamental question will resurface periodically in the coming weeks.

So those are the contours of the current global health crisis. In the second half of this lecture, I'll begin to explore how adjustments in the ways we develop and distribute drugs might help alleviate both aspects of the crisis.

Part B: The Potential Roles of Drugs

Hello. I'm Terry Fisher. This is the second half of the recorded lecture on the Global Health Crisis.

In the previous portion of the lecture, I described two dimensions of the crisis: the threats posed by several diseases to the health of all humans, and the disparity between the disease burdens borne by rich and poor countries.

In this portion, I'll discuss how drugs – meaning vaccines and medicines – have been used in the past to curb these two threats and the impediments that are preventing us from using drugs more effectively to address the crisis.

Here's an important disclaimer: As is surely apparent to all of you, suppressing diseases and reducing health disparities requires much more than developing and distributing vaccines and medicines. I surely don't meet to deflect attention from all of the other strategies that

could be – and, to some extent, already are – being pursued to address the crisis. I'll be focusing on the pharmaceutical sector, not because it could solve our problems, but because it could help substantially.

Let's start with the infectious diseases. How might we reduce both the aggregate impact of these diseases – and the disparity of that impact?

Considerable guidance in answering that question can be gleaned from the modern history of infectious diseases in the United States, where, as we have seen, the burden is currently quite low.

In 1900, the US had an infectious-disease mortality rate roughly the same as the rate in Zimbabwe today.

Between 1900 and 1980, the US managed to suppress, more or less, infectious diseases. The red line in this graph traces the decline.

The trend line contains one apparent anomaly – the large blip in 1918-1919. The explanation for that jump is the so-called Spanish flu pandemic, which killed, throughout the world, roughly 50 million people. We will undoubtedly see another blip (although I hope a smaller one) in 2020-21, from the Covid pandemic.

But more important for our purposes than these occasional jumps is the overall dramatic decline during the 20th century in the Crude Mortality Rate from infectious diseases.

What caused that dramatic decline? Three initiatives, overlapping in time, seem to have been the principal sources of the improvement. The first consists of public-health initiatives in the conventional sense. Between 1900 and the middle of the century, there were dramatic improvements, many of them engineered or forced by governments, in purging the food supply of contaminants, ensuring that most people had access to clean water, improving sanitation systems, and (through education) improving personal hygiene.

The second initiative was the deployment of vaccines. The world at large, and the United States in particular, were remarkably successful during the middle of the 20th century in developing and then broadly distributing vaccines that addressed the infectious diseases that were then common in the United States. The principal members of the first wave of vaccines are listed in the second column on the screen. In the aggregate, they did a remarkably good job in curbing transmissions of the diseases in the first column.

The third phase was the development and deployment of medicines – in particular, antibiotics – that could cure the diseases that people did acquire. The main inventions are shown at the bottom of the screen.

I pause to note that, recently, the efficacy of these drugs has begun to corrode because of the emergence of resistant strains. That's now becoming an increasingly serious problem – to which we will return in due course. But in the 20th century, the overwhelmingly majority of patients responded to at least one of these antibiotics.

Those, then, are the three initiatives that, in combination, radically reduced the burden of infectious diseases in the United States. Of the three, vaccines seem to have driven an especially rapid decline, but in truth the three initiatives worked in combination.

The implication seems clear: to suppress infectious diseases in developing countries, we might use the same three strategies.

Considerable progress has already been made on the first front. Many governments and financial institutions are funding public-health initiatives in developing countries. Those projects have already accomplished a great deal. As you can see from the figures on the screen, African countries are a little behind the curve, but a lot of money is being invested there, so conditions will continue to improve.

Unfortunately, these traditional public-health initiatives are turning out to be less efficacious in suppressing disease in the developing world than they were in the United States -- in part because fewer of the relevant infectious diseases in tropical countries are transmitted through water than was true of the US. More of them are transmitted through the air or through insects or other vectors, which are less susceptible of control through improvements in sanitation, the supply of drinking water, and so forth. So the impact of strategy #1 may be less impressive than it was in the global north, but it has been – and will continue to be large.

Considerable progress has also been made in distributing in developing countries the existing vaccines. As you can see, coverage is not yet universal, but it's still impressive.

The limiting factor with respect to this strategy is that, as I indicated a minute ago, the vaccines shown on the screen – and their successors -- were developed to fight the infectious diseases common in the global north. Many of those diseases are also common in the global south, but, in addition, there are many diseases in the south that have had little or no impact in the north – and thus, for which vaccines were never developed. Specifically, of the diseases we reviewed a minute ago, for only three are there vaccines, and even those are, for various reasons, highly imperfect.

In short, we just don't have the vaccines that we would need to implement the second strategy effectively. Why? Here are some rough numbers that suggest the answer.

As of 2002, 95% of the revenue of US pharmaceutical companies came from these countries, and 5% of the revenue came from these countries. Only 20% of the world's population lives in the countries that provided 95% of the revenue, and 80% of the population lives in countries that provide 5%.

As we have seen, most infectious diseases are now heavily concentrated in the light green zone. As you can imagine, the natural effect of this alignment is to provide an incentive for the pharmaceutical firms to focus on the diseases common in the dark green zone and to neglect the diseases common in the light green zone.

To be sure, these are outdated numbers, but the picture has not changed materially in the past 20 years.

In sum, the financial incentives of pharmaceutical firms disincline them to develop vaccines that address infectious diseases that are concentrated in developing countries.

To some extent, pursuit of the third strategy is hampered by the same problem: suppressing the infectious diseases rampant in developing countries through administration of drugs that cure those diseases is often infeasible because no such drugs exist – and why? Because there have not been adequate incentives to develop them.

But even when that's not true, we frequently encounter a different problem: The drugs that exist are often priced at levels that place them out of the reach of individual patients in poor countries – or the governments of those countries.

Tuberculosis provides a good example of the problem. To see its scale requires a bit of background.

Today, the main treatment for active TB is a course of antibiotics. The drugs most commonly used are rifampicin and isoniazid. They are now often combined with two more: ethambutol and pyrazinamide. Unfortunately, TB bacteria are unusually hardy. As a result, an effective cure typically requires a sustained course of drugs – at least 6 months. Partly because of the duration of treatment and partly because the drugs have unpleasant side effects, some patients fail to complete the course conscientiously. Their lapses accelerate the development of drug-resistant strains of the bacteria in their bodies, which not only reduces their own responsiveness to antibiotics, but heightens the hazard that they pose to others. The “Directly Observed Therapy Short-course” (DOTS) (developed by the WHO), in which a health-care worker monitors each patient's consumption of the antibiotics, is intended (among other things) to minimize such lapses, but its effectiveness in this particular respect is doubtful.

Several varieties of drug-resistant resistant strains have now been identified. “Rifampicin-resistant TB” (RR-TB), as its name suggests, is unaffected by one of the two most common first-line antibiotics. In 78% of the cases involving RR-TB, the strain is also resistant to isoniazid – and is thus classified as “Multiple-drug-resistant TB” (MDR-TB). Infections caused by these two strains are usually curable – but only with a painful two-year regimen of toxic drugs that can have severe side effects. “Extensively-drug-resistant TB” (XDR-TB) is worse still; it is unaffected by a majority of the second-line drugs. Last but not least, “totally-drug-resistant TB” (TDR-TB) is unaffected by all known antibiotics. Roughly 3.5% of all new cases of active TB now take one of these drug-resistant forms, and a much higher percentage of the cases in which the patient has been infected before. Those percentages are declining, but very slowly.

As you might expect, resistant forms of TB are especially common in poor countries. Here's the geographic pattern of the incidence of TB in general. Here's where the incidence of drug-resistant forms are highest.

With this as background, let's return to the problem of affordability. Whereas the average cost per patient of treating ordinary TB is currently between US\$200 and US\$1000 in most countries, the median cost per patient of treating MDR-TB is US\$5659. Here's a chart that combines information concerning the number of MDR-TB cases treated in each of the high-burden countries with the average costs of treatment in each country.

Distressingly similar stories could be told of the cost of So-called third-tier drugs for AIDS.

Even common antibiotics are often prohibitively costly in many poor countries. A simple course of antibiotics can cost in developing country more than the average resident earns in a month.

To summarize, in our ongoing fight against infectious diseases we are hobbled both by an incentive problem – the lack of adequate stimuli to induce the creation of the vaccines and medicines we need – and by an access problem – the prices of the drugs that do exist are too high for widespread deployment in developing countries.

These two problems are devilishly difficult to solve simultaneously, because efforts to reduce the prices of extant drugs may reduce the revenues of the pharmaceutical firms and thus corrode even further the incentives to invent and test new drugs aimed at the diseases in the global south.

As if that weren't enough, we are also plagued by what can be called a quality problem. All too often, the available stocks of the drugs aimed at infectious diseases are contaminated by falsified or substandard products.

The term, "Substandard," typically means that they contain too little of the active ingredient. As a result, they are not as effective in addressing of the disease in question as they should be.

"Falsified" means that they don't have any of the active ingredient. Such drugs are sometimes described as "counterfeit," but that's an ambiguous term. Counterfeit can mean that they're manufactured without the permission of patentees. Alternatively, it can mean that they do not contain the chemicals they purport to contain. For present purposes, we're primarily concerned with the second meaning – which is more clearly denoted by the term, "falsified."

Several studies – including a recent comprehensive one by the WHO – have found that over 10% of the pharmaceutical products in developing countries are bad in one or the other of these senses. Especially likely to be substandard are antimalarial drugs and antibiotics.

Almost all countries suffer from this problem to some extent, but it is worse in poor countries and worst of all in Africa.

Here, for example, is a summary of a survey of studies of the quality of antimalarial drugs. As you can see, the percentages of samples that failed quality tests varied widely, but none was lower than 5%, and in several studies, the percentage was over 50%. In a recent study of anti-malarials distributed in Malawi, the percentage of substandard was 88%.

This is especially problematic with respect to malaria, because the disease moves so fast, especially in young children. By the time it becomes apparent that the drugs given to a child are not working, it's often too late to find a replacement. The net result: roughly 122,000 children under the age of 5 die each year, solely because they consume substandard drugs.

The WHO estimates that a similar problem with respect to substandard antibiotics results in roughly 100,000 deaths per year from pneumonia.

So, to summarize, three problems impede our ability to use vaccines and medicines to fight infectious diseases in developing countries:

- 1) The existing Incentives to develop appropriate drugs are inadequate
- 2) Too often, the drugs that we do have are priced out of the reach of the affected patients – or the countries that wish to buy the drugs on the patients' behalf
- 3) Many of the drugs currently distributed in developing countries are substandard or falsified.