AT THE EREZ CHECKPOINT

Dear Palestinian colleague

We are both doctors. We have both trained long and hard, perhaps even in the same institutions at some point in our careers. Both of us have longed to practice our art and work daily to perfect it. Because we are both doctors, we want people to stay well, and, if they sicken or are injured, to recover quickly and fully. We both want medicine to advance on both sides of our fraught border and maybe even one day to work together on a research project. As a geriatrician I can imagine frail older people on both sides of the border, scurrying for shelter and some not making it.

We are both doctors. Although we will each have our own political opinions and interpretations of our shared history, these are ours alone and have nothing to do with our profession. I know that on our side, when called upon, we look after Palestinian patients from Gaza in peace and even now in war. I know you would do the same, were an Israeli to need your help.

We are both doctors working in southern Israel and Gaza; and both of our peoples are hurting badly. I can imagine what you are seeing and trying to cope with. The fact that I hold the Hamas government responsible for this conflict does not mean I blame you or wish you any harm. For my part I am trying to look after our frail elderly charges, who are under constant threat in buildings largely unprotected from rocket fire. I know your hospitals have taken hits. So far, the armed militias on your side have tried hard to attack our hospital. So far, we have been remarkably lucky, thanks both to chance and our antimissile technology.

I thank God that our government invested in a response to the nightmare scenario of attacks on civilians, at least from the air. In my view, and I am sorry to have to say this to you, it is tragic that your government spent so much of its scarce resources on preparing these weapons, both above and below the ground. Where has this got the people of Gaza? Neither you nor I can take credit or blame for this situation. We are both doctors.

My younger son, our "baby," serves in our armed forces just a few tens of kilometres away from where my wife and I work. I know that he is fighting not only for the country but also to protect his dad. He is doing so for me personally and so that I can look after my patients, both Arab and Jew. Last week five of his mates were buried after being attacked on our side of the border from a tunnel dug solely for the purposes of murder and kidnapping civilians. His older brother is in the reserves and has his kit ready in case he is needed and must go too.

My sons serve with nary a sliver of hatred against the people of Gaza. I know this not only from how we brought them up but from what they say and, above all, from how they act. Almost all their friends hold similar views, although I do recognise a spreading stain of racism among a small but vocal minority in the country. You too must have to cope with a similar reality but I am certain that you too teach your children to live and let live, hoping for better days.

We are both doctors and fathers, and I hope that neither you or your partner are in the terrible situation of worrying about your children's fate as soldiers. I would not wish it on my worst enemy and you are surely not that.

Some may say that a medical journal is not the place to debate politics but dialogue can only be a good thing. And my guess is that you and I would probably, to put it mildly, not see eye to eye on how we got to where we are today. But I do hope your response would not be more eye for an eye. Please prove me wrong.

After this round of fighting is over we will need to find a political solution

I believe with all of my heart that if most people of Gaza want to live with us in a good neighbourly way, most people of Israel will not begrudge them a secure future for their children. If not, we are all in trouble. Unfortunately, I think I know what the Hamas government that rules you and your family over the border wants for me, and it is not pretty. I am sure you have read their charter and I cannot and will not believe that you accept most of what appears in this pernicious document. I absolutely refuse to believe that all the Gazan people, including you, my friend, want the same thing.

After this round of fighting is over we will need to find a political solution. We must make peace. I will talk to my people. Please: I implore you to talk to yours. Our patients need us to do so. Let us never forget that we are both doctors.

With warm wishes and hope for better days

Your colleague

Mark

PS: As I am going over the proofs to this manuscript, a 72 hour ceasefire has just gone into effect. May it last 172 years.

PA

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Israeli doctor **A Mark Clarfield** reflects on life in a war zone and shares his thoughts with an imagined Palestinian colleague in Gaza. *The BMJ* asked the Palestinian doctor **Izzeldin Abuelaish** to respond

Dear Israeli colleague

We are both doctors. As a father, I understand how much you must love your sons and fear for them. My late wife and I had eight children. Five live with me in Toronto. They study and dream of a future denied to my other three daughters, who lie in a stone grave in Gaza, killed as teenagers by shellfire in the Israeli incursion of early 2009.

I was the first Palestinian doctor to be hired at Soroka University Medical Center in Israel. I helped couples experience the joy of parenthood. There is no happier moment than hearing a baby's first cry: it is a cry of hope, irrespective of the child's nationality or creed.

How many children must die or be maimed before a resolution can be found? While Israel continues to occupy Palestinian territory, depriving 1.8 million people the right to water, travel, education, jobs, and the most fundamental human need—freedom—then the violence will continue. We must find a way to stop the bloodshed, and as doctors we have a voice: we can treat these two patients and make them better.

I abhor any kind of violence in Palestine or Israel. It is a disease. The security of Israel and that of the nation of Palestine are interdependent. But to move forward there must be an end to the blockades and the occupation.

Hatred is a disease that results from exposure to harm, especially dehumanisation; it is contagious and therefore a public health problem. Let us come together as doctors to tackle the root causes of the current hatred and violence.

It is true that Palestinians are treated in Israel, but this is paid for by the Palestinian Authority, and patients are sent back to an uninhabitable ghetto. What is the value of treating patients and sending them back to the same miserable life? To use a medical analogy, the sickness on both sides of the Erez checkpoint is unequal. One side has a common cold; the other is trying to cope with cancer. Young children in Gaza and Palestine are so traumatised. They have seen so many family members killed. They will develop a sense of hatred and become radicalised. They live in an open prison with little chance to fulfil their dreams.

Hatred is a disease that results from exposure to harm, especially dehumanisation

In the past weeks there have been 7200 airstrikes by the Israeli armed forces, and most of the nearly 2000 people killed have been civilian, many of them women and children. Now the negotiations begin again, this time in Egypt, but the ultimate goal cannot be yet more negotiations but an independent Palestinian state.

Conflict turns casualties into faceless statistics. My daughters were regarded as collateral damage. I asked the Israeli government for an apology. But I'm still waiting and have to prove my daughters were victims.

PA

It is important for Palestinians and those living in Gaza not to become faceless. In the same way that the murder of three young Israeli hitchhikers will always be remembered, let's add the names of Ismail Bakr, aged 9, and his three cousins, Ahmed, 10, Zakariya, 10, and Mohammad, 11, cut down as they ran in terror across a Gaza beach. Hundreds of other children, who enjoyed playing on swings, kicking a football, and feeding pigeons with their grandfathers, have now been buried by their distraught parents. I know well the panic and chaos of Gaza's hospitals, with insufficient equipment and power, with patients on makeshift stretchers and exhausted doctors unable to cope.

We are both doctors. We do not blame patients for their sickness; we look for symptoms to treat the disease. Both patient and doctor need to take responsibility, in hospital but also outside. Doctors can be a great force for peace as communicators and messengers of humanity.

Recurring violence will never solve what is occurring between the Palestinians and the Israelis. The violence is a result of a violation of human dignity. Palestinians need to be allowed freedom and independence. The chronic disease here is the occupation.

Gaza is burying its dead but there are nearly 10000 people who are severely wounded. More than 10000 houses, schools, and hospitals have been destroyed. As fathers and doctors we need to teach our children to value human life.

We are both doctors, bound by the Hippocratic oath to preserve life, whether we are Muslims or Jews or Christians. Did you tell your sons that? I need you to tell your sons not to harm others, not to kill people. Your sons are fighting for a country that is occupying another nation. Did you tell them this? I ask you to tell your sons to lay down their guns and to speak up against these atrocities.

Your Palestinian neighbour

Izzeldin

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Izzeldin Abuelaish is author of the book *I Shall Not Hate: A Gaza Doctor's Journey*, published by Random House, 2010.

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WHY ARE POPULATION PROJECTIONS OFTEN WRONG?

Predicting the size of future populations is important for healthcare. Too bad our best guesses are so often wrong, finds **John Appleby**

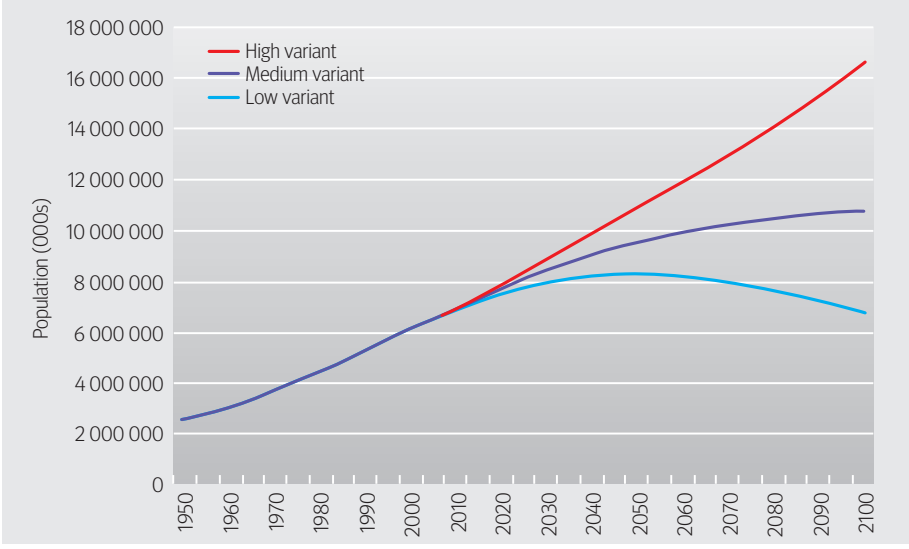

Fig 1 | World population projections to 2100[1]

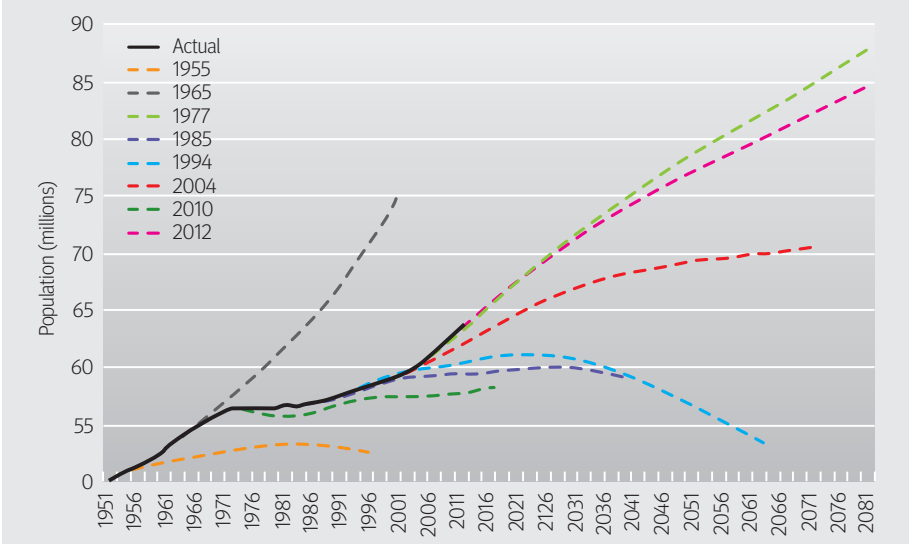

Fig 2 | Actual and projected total UK population[2]

As an economist it is always nice to come across another profession that, for many good and legitimate reasons, struggles to always make accurate predictions of the future; hello demographers. Predicting the size and composition of future populations is a fundamentally important thing to do. Population projections underpin our estimates of future healthcare needs, government spending and tax revenues (and possible debt and deficits), housing demand, and road, rail, and air transport needs. The list isn't endless, but it's certainly long. It's perhaps unfortunate then that it turns out that population projection is quite a difficult thing to do and one which we repeatedly get wrong.

Demographers who construct population projections know how difficult it is to get these right. The United Nations makes population projections for the world and its countries up to 2100 based primarily on assumptions about future mortality, fertility, and international migration rates.[1] These suggest that, for example, the populations of the more developed countries will shrink as a proportion of the world's population from around a third to just over a tenth by 2100. But, as fig 1 shows, they also show the enormous range of the overall projections depending on assumptions made about the future. The world's population could increase by 125% over the next 75 years, or perhaps peak at around 2050 and then shrink by 7% or so over the next half century, or maybe not.

For the UK, the Office for Budget Responsibility (OBR) has usefully pointed out just how wrong population projections can be.[2] Revisiting projections made from the mid-1950s through to the latest in 2012, the OBR shows that, in general, compared with actual counts of the population (and estimates based on censuses), past projections tend to have underestimated total population numbers and (as might be expected) to get them more wrong the further forward the projections go (figs 2 and 3). The 1965 based projections were an aberration and the most wrong of all the projections so far—assuming that the high birth rates of

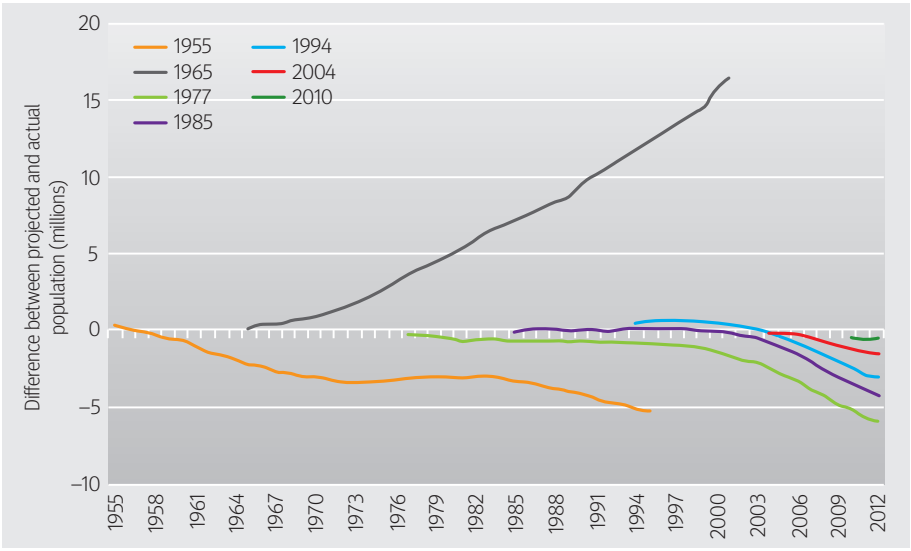

Fig 3| Difference between projected and actual population in UK[2]

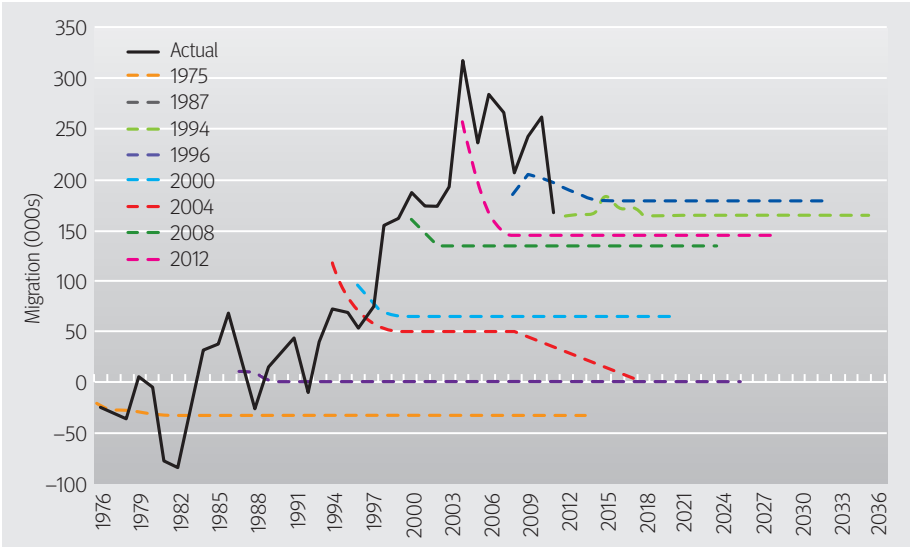

Fig 4| Actual and projected net migration for UK[2]

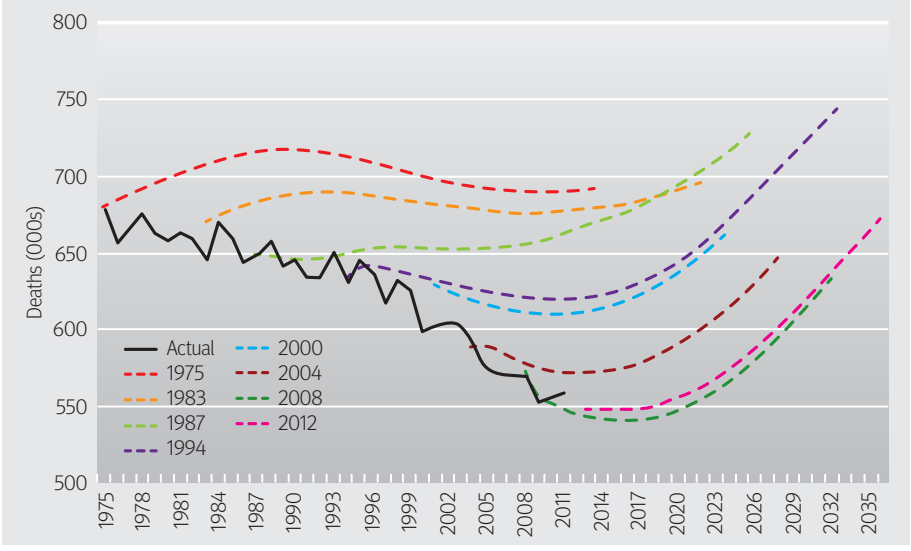

Fig 5| Actual and projected mortality in UK

What is particularly striking is how consistently wrong projections of deaths have been

the 1960s would continue. The most successful seem to be those made in 1985, being pretty much spot on up to 2001 and then veering off to an underestimate of 4.2 million (around 7% of the actual population) by 2012.

So why are the projections generally wrong? Leaving aside problems with actually counting people to get an accurate baseline to make projections, populations change for three reasons: births, deaths, and migration. Predicting how these will change has proved hard. OBR's analysis suggests that net migration (fig 4) has been particularly hard to predict, and for projections made from 1977 to 2004 migration estimates accounted for the majority of the error in the projected population for 2011. Also, earlier projections of fertility rates tended to overestimate births whereas later projections underestimated rates.

What is particularly striking is how consistently wrong projections of deaths have been—and all in the same direction, overestimating the number of deaths (fig 5). The 1975 based projection, for example, overestimated the number of deaths in the UK in 2011 by 132 000—nearly a quarter of the actual number. All mortality projections show a turning point where the number of deaths starts to rise, reflecting the 1950s-60s baby boomer bulge working its way through the population. But that turning point has moved with each projection.

Future projections will inevitably remain uncertain. As the OBR does, the best thing is to recognise this and construct various alternative futures.

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1 Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat. World population prospects: the 2012 revision. 2014. http://esa.un.org/unpd/wpp/index.htm.
2 Office for Budgetary Responsibility. Fiscal sustainability report. 2014. http://cdn.budgetresponsibility.org.uk/41298-OBR-accessible.pdf.

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Read MSF's response to this article
http://www.bmj.com/content/349/bmj.g4665/rapid-responses

Incentives for neglected disease drugs: a good idea gone wrong?

It was a perfect example of "creative capitalism"; a scheme to encourage for-profit companies to invest in treatments for neglected diseases. But nearly seven years on, **Peter Doshi** asks, has this concept flopped?

Bill Gates believes—or at least believed—that government led market incentives could solve the fundamental conundrum in developing drugs for neglected diseases. For-profit companies see little economic justification to invest in treating diseases that affect the poor, but "creative capitalism," as Gates put it, could lure companies into solving some of the world's most pressing problems by bringing to market new treatments for endemic tropical diseases.

At the 2008 World Economic Forum in Davos, Gates highlighted a new US Food and Drug Administration (FDA) law that rewards sponsors of drugs for tropical diseases with a voucher that entitles the bearer to a "priority review" of another new drug application. "If you develop a new drug for malaria your profitable, say, cholesterol lowering drug could go on the market up to a year earlier," Gates explained. And under the law, the voucher can be sold. "This priority review could be worth hundreds of millions of dollars."

Gates was not the only one to be excited about the idea. Originally proposed by Duke University economist David Ridley and colleagues in the health policy journal *Health Affairs*,[1] the concept was quickly championed by a republican senator from Kansas who, along with two democrat senators, successfully introduced the priority review voucher program into US law. The vouchers are fully transferable between companies and might be worth around $300m (£175m; €220m).

Who is benefiting?

But more than six years later, has this promising concept flopped? Ridley does not think so. "Drug development takes many years (7+) so the impact of the voucher is not immediate." He points to companies that have taken up the charge: "NanoViricides was focused on HIV and flu before learning about the voucher, and now they're developing a drug for dengue."

Nevertheless, the FDA has awarded just three priority reviews vouchers since the law was introduced in 2007: for combination artemether-lumefantrine (Coartem) for malaria, bedaquiline for multidrug resistant tuberculosis, and, most recently, for miltefosine to treat leishmaniasis.

A leishmaniasis patient. But did the Gates-backed incentive scheme stimulate drug treatment?

But far from spurring research into new treatments for neglected diseases, two of the three drugs were developed and registered outside the US well before the voucher system was established, meaning that, at least in these cases, the scheme did little to encourage the development of new drugs for neglected diseases.

Miltefosine, for example, has been around for decades. Originally identified as an anticancer compound in the 1980s, the drug came to be used for treating leishmaniasis. Visceral leishmaniasis, the most serious of the three presentations of the disease, kills around 59 000 people a year, making it the "world's second biggest parasitic killer after malaria," according to the World Health Organization.[2] Miltefosine is included in WHO's essential medicines list.

Since 2004, miltefosine has been marketed for the treatment of leishmaniasis in Germany (home of its original manufacturer) and India (where most cases of visceral leishmaniasis occur).[3 4] Before its 2014 approval in the US, miltefosine was also registered in several countries in South America.[5] Licensing and rights to the drug passed through numerous hands over the years: from AstaMedica to Zentaris (which later became AEterna Zentaris). Then in 2008, AEterna Zentaris sold the drug to Paladin, a small Canadian company that was purchased by Endo International for $1.6bn in late 2013.

Miltefosine, however, did not come along for the ride to Endo. By this point Paladin's new drug application to the FDA was well under way and it was expecting approval of miltefosine along with a priority review voucher. Paladin's chief

executive, Jonathan Goodman, put a separate price tag on miltefosine, which the company had acquired for $C9m, ($8.5m; £5m; €6.3m) and the expected voucher of more than $100m. Endo refused to pay and so Goodman's new company, Knight Therapeutics, retained the drug. In March 2014, the FDA approved miltefosine, making Knight Therapeutics the fourth company to be awarded a priority review voucher.

Following the miltefosine money

But did the voucher go to the right party? Was it right that a drug co-developed with public money and already licensed in key countries should attract such lucrative incentives? The international medical aid organisation Médecins Sans Frontières (MSF) thinks not.

> Was it right that a drug co-developed with public money and already licensed in key countries should attract such lucrative incentives?

"The PRV [priority review voucher] for miltefosine is not rewarding true innovators," says Julien Potet, a policy adviser at MSF. "Paladin/Knight's efforts have been strictly on regulatory affairs, and we argue that Paladin/Knight should not be rewarded for some preclinical and clinical risks that they did not take."

MSF points out that not only was miltefosine developed well before the voucher program was conceived but neither Paladin (which currently manufactures and markets miltefosine) nor Knight Therapeutics (which holds the licensing rights) even underwrote the drug's research and development. Instead, they note that the clinical trials were funded by a mixture of public and private sources.

Miltefosine has been celebrated as a success story of public-private partnerships.[6] Its development and ultimate registration as a drug to treat leishmaniasis was the product of a near decade-long partnership between industry (first Asta Medica, then Zentaris) and Unicef, the United Nations Development Programme, World Bank, and WHO's Special Programme for Research and Training in Tropical Diseases (TDR). TDR brought knowledge of disease control programs, field experience, and contacts to help build capacity to run the trials as well as money. Industry brought expertise in drug development and money. Together, the partnership resulted in the first oral, single drug treatment for leishmaniasis.[4] While miltefosine's activity against *Leishmania* was known early on, without interest from TDR, the drug would arguably have remained as just a cancer treatment. TDR's involvement in the development of miltefosine achieved the same goal as the FDA's priority review voucher—bringing to market treatments for neglected tropical parasitic diseases.

Pricing

One of the goals of this public-private venture was to ensure miltefosine was an affordable drug. But it is unclear that this goal has been achieved. According to MSF, Paladin charges €2636 (£2080; $3570) for an adult treatment course (€842 for children). It also offers substantially reduced prices (€45-€55 for an adult course) for bulk orders of at least 3500 courses. This, however, presents a problem for MSF.

"It may be possible for a large and highly endemic country like India to reach this quantity, but it is nearly impossible for smaller organisations to reach this quantity. Recently MSF and DNDi [Drugs for Neglected Diseases initiative] had to buy a whole batch together, although this quantity actually exceeded our needs. We are now seeking to donate the drugs that we have bought in excess to third parties. It would be a shame if these drugs expired unused on our shelves," explains Potet.

> "If you develop a new drug for malaria your profitable, say, cholesterol lowering drug could go on the market up to a year earlier," Gates explained

But Goodman was unsympathetic. He said that MSF "needs to weigh the benefits of the discount against the risk of over-supply."

Reforming the priority review voucher system

Today, Knight Therapeutics is a company with a single product (miltefosine), two employees, $255m in cash, and a priority review voucher. While at Paladin, Goodman bought miltefosine for $9m CAD, which included clinical trial data. FDA approval cost another $10m. And now, Knight hopes to sell the voucher for "a ton of money."

For MSF, Knight's story shows how the priority voucher scheme is a good idea gone wrong. While it strongly agrees with the need for mechanisms to speed development of new treatments for neglected diseases, it questions the wisdom of the law, which allows companies like Knight Therapeutics to singly reap the benefits of the voucher despite the significant public investment in miltefosine's development.

Goodman, however, defends the history. "I find it ironic that MSF would take issue with the PRV program as it is specifically designed to help the same people that MSF is passionately trying to help by encouraging the development of innovative, new therapeutics for neglected tropical diseases."

A spokesman for the Bill and Melinda Gates Foundation said that although the program has not yet delivered on its original promise, "it's clearly a step in the right direction." He pointed to some theoretical benefits from the law other than novel drugs. "If we do get new formulations, if we do get new manufacturers . . . I think we would see those as benefits as well."

Of the three vouchers issued, none has been sold. And only Novartis has used its voucher—for an application the FDA ultimately did not approve. Even Duke University's Ridley would like to see some changes in the law. While "it's not entirely bad to reward good deeds," he told *The BMJ*, "I favor some changes, including precluding award to drugs approved outside the US several years ago."

Such a change would have kept Knight from its voucher.

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References are in the version on thebmj.com.
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