The fight against tuberculosis
In Romania and Belarus, tuberculosis is still killing people – many people, while in Sweden or the Netherlands, deaths from TB are a rarity. Why, when the scourge of the Belle Epoque and the killer of La Traviata was all but eradicated from Europe until recently, are people still dying from it in large numbers? And in even larger numbers around the world – more than a million a year. There is a contrast here that might be expected to prompt a European response on purely humanitarian grounds. And because infectious diseases – and tuberculosis is infectious – do not stop at borders, there is also an underlying threat to European health security. But it has yet to provoke an effective concerted response.

Success – and a critical failure

For over half a century, antibacterials have been able to control TB. In the last two decades, millions have been cured and TB mortality cut by 45%, through a standardised regimen of systematic diagnosis and treatment endorsed by the World Health Organization (WHO).

But the treatment is arduous and unpleasant. A combination of antimicrobial drugs must be taken for six months, to overcome the extraordinary survival capacity of this disease, which can reactivate itself fully if only the tiniest fragments of it elude successive chemical bombardments. Health workers typically support and supervise patients, to ensure they take the medicines consistently – hence the term for this standardised treatment: ‘directly-observed treatment short course’, or DOTS.

It doesn’t seem a short course to patients, and many do not complete their DOTS – for reasons ranging from fatigue to administrative complications. These drop-outs are still infected, and capable of infecting others, which constitutes an obvious health hazard. But even more dangerously, these prematurely-ended treatments give the underlying pathogen the opportunity to evolve into new and more deadly strains. These are variants that the standard approach cannot cure – and they are known by the broad term ‘drug-resistant tuberculosis’ (DRTB). In many cases, nothing else can provide a cure for these variant strains either, and patients die. DRTB is an entirely man-made phenomenon, and since it was first described in the 1990s, its impact has magnified. Some half a million cases worldwide were identified in 2012.

As a result, TB is back – and often worse than before. It is
not just a problem in poor and remote countries. Europe has failed to hit its targets for TB reduction, and some European countries have very high levels of DRTB. The WHO 2013 report on Priority Medicines for Europe and the World identifies TB as “an important disease in some European countries”, and Zsuzsanna Jakab, WHO regional director for Europe, speaks of the need “to act urgently to prevent and combat the alarming problem of DRTB”. Warnings are multiplying that without adequate action, European countries will be at risk from an epidemic they are simply not prepared to meet. Mario Raviglione of the WHO says uneven performance across Europe means that “TB is a persistent threat”, pointing to recent local outbreaks in Milan and London as evidence that western Europe is susceptible to the disease. Fanny Voitzwinkler of the TB Europe Coalition and Global Health Advocates says: “The need is huge for Europe to prepare for the risk of the spread of DRTB.” Helle Asgaard of Médecins Sans Frontières (MSF) speaks of “urgency for the EU to push TB up the political agenda”.

Prospects – and tough challenges

The situation carries real peril, but is not without prospects of a solution. Additional tools intermittently become available to tackle the problem: new therapies are appearing – after a gap of 40 years; new diagnostic techniques are on the market; and work is under way on vaccines to widen prevention of the disease. Techniques for surveillance and data collection, essential to combat the disease, are improving. The links with social and economic causes are more widely recognised. And many health authorities are putting in place mechanisms that make on-the-ground prevention and treatment more effective.

Nevertheless, progress is far from satisfactory. Treatment remains profoundly uncomfortable, modern diagnostics are still not widely used, any effective new vaccine is at least a decade away, disease monitoring is still imperfect, and there is hardly a country in the world where health and social infrastructures are not under strain. Meanwhile, the disease hacks away remorselessly at life, health and prosperity, finding new channels of transmission through cross-border travel and more frequent migration. Until recently, there had been realistic hopes of eliminating the disease entirely, but now there are even questions about the possibilities of merely controlling and containing it.

It is against this background that Europe faces a decision about how it is to tackle a new version of an old challenge.

The scale of the challenge – in suffering and in spending

Many cases

In 2012, an estimated 8.6 million people around the world developed TB, and 1.3 million died from it. In Europe, 3.37 million cases were notified in 2012, and the disease killed over 60,000 people. Eight EU member states are failing to meet WHO targets for reducing the incidence of TB, and some report high rates of infection, with DRTB and co-infection with HIV. Romania has one of the worst epidemics in Europe and central Asia, with 20,000 TB cases a year. TB cases and resultant deaths in Hungary have increased “at a frightening rate over the past years”, according to Hungarian MEP Csanád Szegedi. Identified DRTB cases are running at around half a million cases worldwide, and the average cure rate is only around 50% – and 35,000 of these cases are in Europe. The highest rate of DRTB is in the WHO European region, which contains 12 of the world’s 14 most affected countries. On the doorstep of the European Union, more than one-third of the cases in the capital of Belarus are DRTB. MSF points to high rates of DRTB in Estonia, Latvia and Lithuania. And it is not just eastern Europe or the Baltics where the disease is flourishing: London has the highest overall TB rate of any capital city in western Europe. MSF estimates that DRTB is at epidemic levels globally, and only 19% of people infected are receiving treatment.

TB is bad, and resistant TB is worse. But it gets even worse than that. Strains resistant to two of the first-line drugs are known as multi-drug resistant – MDR-TB. But one in ten DRTB cases are classified as XDR-TB – extensively drug-resistant, meaning that many of the current possible treatments simply do not work on these variants of the disease. More than eight out of ten victims of XDR-TB die. According to drug firm Lilly, XDR-TB has been found in more than 50 countries, including the UK, Italy and Norway. In eastern Europe, 14% of MDR-TB patients have been diagnosed with XDR-TB. And an additional concern is that
cases of DRTB – in all its forms – are now being acquired via infection. In other words, this near-fatal form of the disease affects not only DOTS drop-outs, but can be transmitted to healthy people too. Marc Sprenger, director of the European Centre for Disease Prevention and Control (ECDC), admits that 2013 data show DRTB is “a serious challenge in the attempt to eliminate TB across Europe”. Only seven countries reported a decline for MDR-TB, and “overall, Europe does not have a good track record”, with treatments failing to cure two-thirds of these patients, and only a quarter of patients with XDR-TB. “This failure to treat MDR-TB patients successfully not only puts the patients’ life at risk but also facilitates development of XDR-TB,” he says.

In the view of the ECDC, drug resistance represents a major threat that hampers Europe’s progress in TB control. The problem is all the more disturbing because TB often goes undiagnosed and ignored – or even concealed, for fear that patients will be stigmatised. The WHO estimates that 3 million people around the world who fell ill with TB are unreached every year. Many victims remain outside healthcare systems – in poorer developing countries where access to care is scanty, but also in the developed world among segments of the population that are marginalised. Vulnerable populations are often at risk because of living conditions that are conducive to transmission (such as poor nutrition and overcrowding), and because even when cases are diagnosed, lifestyles can hamper the compliance necessary for successful treatment. The ECDC expects the economic crisis to have an impact on European healthcare systems “and on factors that affect the epidemiology of TB” – notably reduced services for the needy.

In addition, millions of people carry latent TB, which is likely to become active and infectious when people’s immune systems are compromised – as is notably the case with HIV patients. Voitzwinkler says current estimates inevitably underestimate the situation since data collection is poor, many diagnostic tools are inadequate, and at-risk populations are frequently inaccessible. Europe’s monitoring record is far from homogeneous at country level.

Many costs
Treating TB can be expensive. Recent studies suggest treatment of straightforward cases of TB – (known as drug-susceptible TB – DSTB) costs around €7,000 per patient in Germany – and treatment for MDR-TB costs more than €50,000. The costs of treating one case of XDR-TB are put – in drugs alone – at more than €100,000, and can be as much as €300,000. But not treating TB can be even more expensive. TB is already inflicting annual direct costs of more than €500 million on the European region – but is estimated to be responsible for more than €5 billion in lost productivity. WHO/Europe bases its current five-year plan for combating DRTB on forecast savings of €50bn.

Professor Koen Andries of the University of Antwerp, a key figure in the development of bedaquiline, one of the new hopes for therapy, says: “The costs of inaction are enormous. Governments that fail to invest in their healthcare system and TB treatment programmes now will undoubtedly end up paying more in future.”

Problems – and the search for solutions
If there are so many cases, such high costs, and such success in the past in dealing with TB, why is today’s problem still not solved? There are many aspects to the challenge, and some of them are new. The newest challenge is the evolution of the disease. TB is demonstrating an extraordinary capacity to outsmart science, and the intrinsic complexity of the disease is making the search for effective therapies, diagnostics, and vaccines long and hard.

Another modified characteristic of the disease is its distribution. The poorest countries in the world, where health provision is scarce and treatment options most limited, still have by far the highest number of victims. But in the developed world, there is a recrudescence of the disease too – and its incidence is highest among populations in the most precarious circumstances: migrants, intravenous drug users, ethnic minorities, the urban poor...

The distribution of the disease in turn complicates the provision of successful responses. The essential elements of efficient screening, diagnosis, ensuring compliance with treatment and follow-up, data collection and public health monitoring are all impeded among populations that are often on the fringes of society’s structures.

And the scale of the challenge – scientific, social, logistic – demands deployment of corresponding resources, to fund better tools and systems, and to finance wide access to treatments among the multitude of patients who are least able to pay. In a period of economic downturn and austerity in public financing, those resources are harder to find.

So it is important to run a status check on progress – and setbacks.

Progress – and pitfalls
The science of medicines
It is science that must produce the tools for responses in the field. The WHO 2013 report Priority Medicines for Europe and the World calls for increased research and development in TB diagnostics, medicines and vaccines.

Approaches to treatment are all based on combinations of four or more drugs, which in the current state of science are
necessary to overcome the pathogen's capacity to evolve, to elude attack, and to develop resistance. According to Dr Evan Lee, a vice president of Eli Lilly & Company, even with new drugs there is a need to mix multiple regimes for many months. “It’s not one drug for TB that is needed – you need multiple compounds that work as cocktails, that don't interact and don't have multiple side-effects.”

But side-effects are at present an inescapable reality for all treatments for TB. And for DRTB the treatments are even more demanding. They involve as much as two years of highly toxic and debilitating drugs, including at least six initial months of daily injections and about 15,000 pills. The liver, the skin and the sensory organs can suffer severe side-effects. And there is no guarantee of a cure – at best a 50/50 chance of survival.

For those tackling TB on the ground, the deficiencies are all too obvious. Dr Francis Varaine, leader of MSF's TB Working Group, sees the principal handicap as “the complexity and cost of current treatments for health programmes, and patient intolerance”. Current treatment regimens for DRTB are “entirely insufficient to mount an effective response to the disease,” says MSF. “We, the medical staff who provide medical care for people with drug-resistant tuberculosis, find it unacceptable that the only treatment options that we can offer people cause so much suffering, especially when the chance of cure is so low... We want to save many more lives, but we desperately need shorter, safer and more effective treatment to do so.”

Some new treatments are in the offing. At the end of 2013 the European Medicines Agency (EMA) issued favourable opinions on two new medicines for treating MDR-TB: Deltiba (delamanid) from the Japanese firm Otsuka, and Sirturo (bedaquiline) from Janssen, the pharmaceutical division of Johnson & Johnson of the US. Formal authorisation decisions are expected from the European Commission by April. The recommendations are only for conditional approvals, since they have completed testing only up to phase 2b of clinical trials (customarily, data from phase 3 trials are required for authorisation). And the opinion specifies only second-line use, as part of combination therapy. But these will be the first approvals for 40 years for new medicines to treat TB, and the EMA recommendations prompted some enthusiastic expressions of satisfaction at breakthroughs after decades of stagnation.

Nonetheless, Richard Bergström at the European Federation of Pharmaceutical Industries and Associations (EFPIA) takes a cautious view. “Any suggestion that this shows there is a pipeline of new treatments is misleading,” he says. Behind these two products there is not much else coming through “to replace nasty treatments”. MSF has also highlighted the paucity of the development pipeline for TB medicines. It contrasts the half-dozen compounds currently in clinical trials for TB with the 40 or more candidate medicines in the pipeline for hepatitis C. The president of the Global Alliance for TB Drug Development, Mel Spigelman, is equally dismayed at the lack of candidate drug compounds that are in late pre-clinical testing and early clinical trials.

It is the tough nature of the science that has led to repeated failures of vaccine trials, or difficulties in diagnosis, or disappointments in medicines. And this is part of the reason that many companies have abandoned the field. Commercial developers actually reduced investment in TB drug research between 2011 and 2012. Pfizer withdrew from anti-infectives research entirely, Otsuka decreased its drug discovery budget, and AstraZeneca announced closure of its last remaining TB research facility in late 2013. As MSF acknowledges, “the market for TB regimens is far less lucrative than for other diseases and is marked by chronic underinvestment”.

Without medicines that can combat TB quickly and with fewer side-effects, the chances of extending treatment to wider populations are poor. As Varaine of MSF says, until there are simpler, shorter and more effective treatment regimens, “the scope is limited for the scale-up of programmatic treatment for DRTB, which will continue to spread, and to cause suffering and death”. Those responsible for developing and regulating medicines agree. “There is an urgent need to develop shorter, more effective treatment regimens to tackle this deadly disease,” says Michel Goldman, executive director of the EU’s public-private partnership in early stage research, the Innovative Medicines Initiative (IMI). And the EMA lists treatments of pulmonary multi-drug-resistant tuberculosis as an area of high unmet need.

As long as combinations of drugs are the only option, the development of treatment regimes - even with new medicines - is correspondingly complex and slow, because of the number of variables to be evaluated. Scientists are trying
to devise ways of speeding up this process. IMI is running a project - know as PREDICT - that responds to “an urgent need to develop a more potent, yet patient-friendly, combination of drugs to tackle TB”.

But combination therapies also present challenges of a more commercial nature. Companies that have developed potential therapies – invariably at great expense – are reluctant to allow third-parties to run tests on them, even when they are not actively exploring the potential themselves. Medicine campaigners complain that company policies keep them out of assessments of new medicines in new combinations. MSF says this translates into slow or stalled scientific progress, as promising candidate drugs can languish for lack of a business case. MSF’s Jennifer Cohn says that what is needed for rapid results is “open collaboration to test new multi-drug regimens”. Her colleague Katy Athersuch underlines the frustration. “How do we use bedaquiline and delamanid?”, she asks. “We haven’t had a chance to get to them or try them; everyone is working in their own silo.”

MSF proposed a pilot project to the WHO last year to open up joint development. “We need to have companies willing to work together and share information, because these drugs need to be developed in combination,” said the project’s sponsor, Grania Brigden. The project aimed to deliver affordable and effective new regimens for TB more quickly, through open collaboration incentivised by grants, financial rewards for achieving agreed research objectives, and pooling of intellectual property. But in December, the WHO decided not to back the proposal.

The recipe for the science is easily expressed. MSF says: “New drugs must be developed specifically to treat DRTB, while research must continue into combinations using new and existing drugs to respond to the wide range of drug resistance. Research and development must be financed to rapidly develop not only effective and safe new drugs, but also easy-to-use, accurate and affordable diagnostics, as well as development of a vaccine to prevent the spread of TB.”

But matching those imperatives is not so easy. This is why the WHO 2013 report Priority Medicines for Europe and the World argues that for TB, “funding is needed for additional investment in R&D for diagnostics, medicines and vaccines”.

The science of diagnostics

TB is notoriously hard to diagnose accurately. As Lee of Lilly, who is in charge of global health programmes and access, puts it: “There isn’t just a simple blood test.” A slow and cumbersome laboratory test of sputum samples that was developed over 100 years ago is still widely used, even in Europe, and frequently fails to detect TB. Inadequate diagnostic capacity is one of the principal reasons that so many cases go undetected – more than 90% of the estimated global burden of MDR-TB, according to the WHO. The delay involved in getting results from this type of test has also contributed to the spread of TB, because doctors are faced with an invidious choice. They can wait for as much as two weeks for a result before starting any treatment, with the consequent risk of infection being spread. Or they can start treatment straight away, before the pathogen has been precisely identified, with the consequent risk of using – and then having to change or stop – a treatment that proves to be inappropriate.

Since 2010, the situation has improved, with a WHO-endorsed diagnostic that is more sensitive, gives a result on the spot in just two hours, and can also identify not only TB but also the likelihood of DRTB. With rapid diagnosis, the chances are higher of rapidly starting infected patients on the right treatment. Faster turnaround also means treatment can start straight away with patients who might not be prepared – or able – to come back in two weeks for a result.

But making better tools available does not automatically mean they will be used. As Mario Raviglione says: “It is a real advance to be able to get results in hours rather than weeks, and it should be available everywhere in the EU – but isn’t.” Professor Frank Cobelens of the Amsterdam Institute for Global Health and Development notes: “This is not yet universally implemented, either in the EU or in neighbouring countries in eastern Europe and the Caucasus.”

One of the reasons for slow take-up is cost. Philippe Jaco, a representative of the European Diagnostic Manufacturers Association, argues that the higher price of newer tests needs to be weighed against the cost-savings from abandoning more labour-intensive older methods. Tense negotiations over prices are under way with health ministries and donors. But Jaco says that responsibility also lies with health authorities that are hesitant to embrace change – and to deal with the implications for staff.
them up for several years. As Cobelens remarks, this is “an
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Cobelens points to some of the “major technical hurdles to
vaccines.”

The more advanced molecular technology in these new
tests has opened the door to a series of improved diagnostics
that Cobelens hopes will bring down costs, allow use
anywhere, and, crucially, provide earlier identification of
suspected infection. ECDC’s Sprenger says: “Health systems
in EU/EEA countries need to be able to diagnose and treat
latent TB infection,” and he points out that current
diagnostics are not specific enough and treatment options
are too long and cause too many side-effects. As
understanding of the disease advances, there will be a
continuing need to reassess diagnostics too. “We need to
understand better what to test for”, says Jacon.

The science of vaccines
“The DOTS strategy has proven insufficient to reduce
transmission”, says Cobelens, “probably because in settings
with poor living conditions most transmission has already
taken place before an infectious patient is diagnosed and
started on effective treatment. The only way TB can really be
controlled, at least in resource-poor settings, is by a vaccine
that provides protection against adult pulmonary TB.”

But no new vaccines have been introduced to prevent TB
for 80 years – and the best estimates are that the earliest
anything really effective could become available is 2024. The
venerable BCG vaccine, although widely used, has only
variable efficacy in preventing pulmonary TB in adults. “To
eliminate the disease we need a better vaccine, and we do not
have that yet,” says Giovanni Migliori, secretary-general of the
European Respiratory Society (ERS), “We are behind in
vaccines.”

Here again, the intrinsic science is difficult, even daunting.
Cobelens points to some of the “major technical hurdles to
overcome”, citing the disappointing results last year from a
keenly watched vaccine trial in South Africa. This “not only
showed that this vaccine showed no protective efficacy, it
also indicated that our current markers for selecting
promising vaccine candidates are entirely insufficient”, he
said. The trial dashed hopes that a valid system was
emerging for identifying likely successes. In consequence,
the only way to check whether a candidate vaccine works is
to run field trials on tens of thousands of people and follow
them up for several years. As Cobelens remarks, this is “an
investment that industry and research funders may be
increasingly reluctant to make”.

Raviglione also notes the scientific challenge. “We still
need basic science to understand the pathogenesis of the
disease – and the necessary investments.” Goldman at IMI
adds that classic vaccine approaches, using antibodies, may
not work for TB, in the same way as they have proved
insufficient for developing a vaccine against HIV. “We just
don’t have the science for that at present,” he admits.

Critics of current attempts to overcome these challenges
say that there is too much fragmentation, with research
initiatives operating in parallel, with their own focus. The
absence of a co-ordinated strategy means missed
opportunities to make the most effective use of resources, or
to share information promptly.

Applied science
Even if science can provide better tools for prevention,
diagnosis and treatment, the battle against TB cannot be won
without big changes in the way the tools are deployed and
managed. According to Andries: “The development of new
treatment and diagnostic options is only one piece of the
puzzle. We also must ensure these medicines are used
correctly.” Migliori insists on the importance of strong health
systems, and strong national programmes, ensuring that
cases are diagnosed early, and when diagnosed are treated
and cured without defaulters, to prevent emergence of further
drug-resistant mutants. “Good clinical services are not
enough, we need strong public health to avoid losing the new
drugs in less than the time it took to develop them,” he says.

Gaps are repeatedly identified in screening, treatment,
follow-up, monitoring and data collection. TB “is not a well-
recognised priority in all European countries, and some
tackle it better”, says Raviglione, pointing to parts of western
Europe where micro-epidemics are not managed properly,
because of “a lack of national co-ordination or follow-up to
counter the risk of spread”, he says. Italian MEP Elisabetta
Gardini has suggested that “the responsibility for DRTB
increasing in Europe lies with the centres that treat it”,
because they fail to comply with international guidelines for
management, with errors in prescribing and in the doses
administered, and in failure to provide final clinical reports
on discharged patients. Polish MEP Artur Zasada says that
in the countries of central and eastern Europe there are
deficiencies in training doctors, data collection systems, and
the performance of healthcare institutions. In Romania,
DOTS coverage has been impaired by general practitioners
refusing to supervise treatment because of insufficient
financial incentives. Adrian Thomas, head of Janssen’s
Global Public Health Group, speaks of the absence in many
EU member states of “epidemiological analysis and cluster
identification to get TB under control”. Lee of Lilly insists on
the need for systematic monitoring of treatment of MDR-
TB, to verify if therapy has been effective – and this, he
points out, depends on adequate health infrastructure.

Migliori says if the EU wants to tackle DRTB it should
invest more at all levels, including public health, at its
borders. “Investing in research in the EU is not enough. TB
control and elimination are like a war. We need aviation,
land troops and navy. If we miss just one component we lose
the war.”

Investments in public health need to take account of the
special conditions that increase the risks of infection and of the development of resistant strains – and this means attention to specific segments of the populations. Hungarian MEP Lívia Járóka insists that “the fight against TB must walk hand in hand with the fight against poverty and social exclusion”. Prisons, often with a disproportionate number of intravenous drug users and HIV patients, are centres of infection in many eastern European countries. Migrants, asylum seekers and refugees also require special attention. Roumyana Petrova-Benedict of the International Organisation for Migration highlights the need to ensure identification of infection and continuity of care, in immigration detention centres and throughout the reception process, and adequate follow-up as migrants disperse – to avoid poor treatment adherence and high default rates. It is not just a question of migrants from distant countries, as John Stillo, who has studied TB in Romania for many years, emphasises. Romania’s TB epidemic is a major public health threat, and if it is not controlled, it poses a danger to other EU nations where so many Romanians are now working, he says. European Commission health officials also point to the special needs that risks groups have for community-based integrated treatment services.

**Paying for science and its applications**

Acquiring better tools and upgrading health systems to use them more effectively do not come free. Innovation has costs. If it is commercial innovation, that also means prices. And even where it is innovation in the public sector, the resources must be found from increasingly hard-pressed government budgets and increasingly strained donor communities.

Lee of Lilly is confident that therapeutic solutions are technically possible – but he says that realising the potential is impeded by the costs of clinical trials and other obstacles. With the increasing pressure on companies to maximise shareholder value, the margin for manoeuvre continues to shrink, and taking on projects without a prospect of return becomes an unacceptable luxury. Raviglione says: “There is a need for new mechanisms to incentivise industry.”

For diseases that largely affect poor people, the question arises of who pays. “If there was a viable market there would be market forces exerting pull mechanisms”, says Lee. But it is “a challenge going forward – how are you going to pay for medicines, and how are you going to make them available?”

For MSF, the overarching aim is “to delink the cost of drug development from the price at which the drug is sold”. But that requires some fundamental rethinking of the economic model for drug development – and is likely to put more of a burden on public spending, at a time when public spending is least able to respond.

Already TB is something of a poor relation in terms of public funding. NIH spends €170m on TB, much less than for other conditions, and the Bill and Melinda Gates Foundation does not at present give it top priority. As Raviglione points out, there is limited research on TB compared to the burden of the disease. He instances the approach of most of the world’s top funders of health research that do not invest in TB as they invest on other issues, despite the burden considerations.

The Tuberculosis Vaccines Initiative, partly-sponsored by the EU’s research programmes, estimates that global control of TB (including developing improved vaccines) will require a total of more than €30bn, but less than half of this is available. The Treatment Action Group, a campaigning organisation for fighting HIV, calculates that funding for TB research dropped by €21.9m in 2012 to €452.4m, which is only 30% of the WHO’s $2billion (€1.4 billion) annual target.

Funding is necessary not just for research, but also for programmes to ensure that medicines are available and that patients can get access to them. Here too, Europe’s efforts have come under critical scrutiny.

Cobelens says the current international funding landscape for TB control “is hugely dominated by USAID”, the United States federal government agency responsible for administering civilian foreign aid, which is particularly dominant in the Caucasus and Central Asian republics. USAID is a highly effective donor, but is not being backed up by parallel action from European governments, he says. “The need for concerted European support of effective TB control in the former Soviet countries, in particular with a view to curbing the MDR-TB epidemic, is essential for limiting its further spread to other European regions,” argues Cobelens.

Within the EU, Stillo has documented numerous funding gaps that create shortages in medication, inefficient diagnostics, and inadequate patient support programmes in Romania. Public spending on TB was only €4.3m in 2010 for more than 20,000 patients, less than a third of what much smaller and poorer Moldova invested in 5,434 patients, and barely a quarter of the €16m per year required for Romania to reach WHO goals on containing DRTB by 2015.

Access depends on the price of drugs too, and Janssen is currently engaged in negotiations with national agencies about the price it might charge for its new drug in different countries. A spokesman for the company has said: “We will offer a pricing framework that includes three groups: resource-limited and special effort countries, upper middle-income countries, and high income countries.” Even so,
Don’t know means don’t care

Raviglione says the low level of funding for TB research and TB programmes is because the disease is not seen as a problem. “There is no political backing to push the allocation of resources.” He sees some complacency in Europe. “People have adapted to the notion of having TB at the door. That may have been reasonable when we had drugs and diagnosis. The EU has also funded research and supported international donors. The European Commission is one of the world’s largest funders of TB research. Under its most recent research programme it spent €80m on TB vaccines, drugs and diagnosis. The EU’s new research programme, Horizon 2020, aims to increase political and public awareness, support and strengthen EU member states’ efforts, and to contribute to control ‘TB in the EU’.

A role for the European Union?

Since 1990, the WHO has had the target of eliminating TB, and there are plenty of European statements of intent about tackling the disease. In a formal declaration in 2007, all WHO Europe member states committed themselves to respond urgently to the re-emergence of TB in the region and properly address DRTB. It acknowledged weaknesses in unfavourable treatment outcomes, poor implementation of internationally accepted control strategies, inadequate use of quality-controlled diagnostics and treatment strategies, and insufficient attention to control in high-risk groups such as migrant populations, the homeless, prisoners and other socially vulnerable groups. In 2008, the ECDC published an action plan for control and ultimate elimination of TB in the EU, foreseeing an important role for the EU as a catalyst for action. Since then, successive plans and strategies have emerged from the EU, from ECDC and from the WHO, all with similar recipes focused on prompt and quality TB care for all, uninterrupted supplies of medication, strengthened health systems, development of new tools, and the building of partnerships and international collaboration. The European Monitoring Centre for Drugs and Drug Addiction and ECDC have issued joint guidance on prevention and control of TB among people who inject drugs. The EU has also funded research and supported international donors. The European Commission is one of the world’s largest funders of TB research. Under its most recent research programme it spent €80m on TB vaccines, drugs and diagnosis. The EU’s new research programme, Horizon
that has boosted TB expertise in Africa.

Developing Countries Clinical Trials Partnership (EDCTP)

States. And the EU is the prime mover in the European and

Institute, a leading public-private organisation in the United

new treatment regimens for TB with the Critical Path

EU's IMI last year agreed to co-ordinate the development of

research, fresh funding that may permit some real action. The

is providing, through the EU’s plan to promote antimicrobial

2020, has already offered €25m for TB vaccine research, and

and collaboration have not developed far. “There is scope

leadership, according to former Romanian MEP Cristian

problems. According to former Romanian MEP Cristian

philanthropic bodies, civil society organisations, the EU

leadership could come from senior people in distinct

to work together.

Balasegaram urges ministries of health and drug regulators

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that are best used against DRTB.” And MSF's Manica

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Great expectations

Plenty of people have expectations of Europe – to fund research, to finance delivery programmes, and to show leadership. According to former Romanian MEP Cristian Silviu Buşoi, it is “Europe's duty to look for viable, innovative methods to guarantee the funding for research in order to combat tuberculosis.” Aagaard of MSF agrees: “With one of the biggest research programme budgets in the world, the EU surely has an important role to play in the fight against TB – especially by prioritising funding of research and development for better drugs.” Aaron Oxley, of a UK TB charity, Results, says the EU should be filling gaps where current donors reduce their funding: “This is an issue where the EU has a unique opportunity to demonstrate leadership and to ensure these vulnerable populations are not abandoned.”

The EU’s influence is highly regarded – but many believe it is under-exploited. Patrick Bertrand of Global Health Advocates France says: “Diseases do not respect borders, and to address global health issues such as TB and HIV, the EU must pay attention to what is happening both within its member states and its neighbours.” Voitzwinkel says effective political action in Europe means involving the EU, which she sees as the only body with real political leverage. It should, she says, have the courage to act at regional level to counter the threat of cross-border transmission of DRTB, and to co-ordinate action to combat it, perhaps through a task-force that could encourage countries to take ownership of the problem. For her, the EU can also be a major promoter of civil society organisations to ensure that bottom-up pressure complements top-down policymaking. And for Jacon the EU could encourage member states to adapt to more modern diagnostic techniques and overcome resistance to change among vested interests.

Thomas of Janssen also has expectations because of Europe’s position as “a thought leader in health”, with a track record in tackling disease. “It has political weight as a member of the G8, and a strong voice. To move from acknowledgement of the problem to action, Europe has to take a position that others can react to,” he says. He also underlines the urgency, “Europe cannot afford to sit on the sidelines, and there is no better way than for Europe to show the lead.”

Need for collaboration

There are also plenty of recognitions of the merits of collaboration. According to Andries: “Collaboration is critical if we are to make a meaningful difference to the lives of people with TB.” Aagaard of MSF says the research collaboration required to bring new regimens to market will not take place without government-led policies and incentives in place to encourage this, “and the EU needs to step up”. For Lee, collaboration helps in terms of generating the necessary cocktail of treatments: “TB drug development is so complex that no single company or institution has the resources or expertise to do it alone.” Cobelens shares the view: “Concerted efforts are needed to bring together trial capacity and funding in order to find the drug combinations that are best used against DRTB.” And MSF’s Manica Balasegaram urges ministries of health and drug regulators to work together.

But collaboration is not automatic. Cobelens recognises “this is not easy to achieve, since funders as well as researchers and implementing agencies tend to have their own agendas and preferences”. Lee favours “a consultative process”, but recognises that different parties have differing views. However, the input of health campaigners “can stimulate dialogue in situations where there is no easy answer – such as on costs”. Bergström sees a solution being impeded by “too much fragmentation” among the many parties concerned by the problem of TB.

No one is being starry-eyed about the prospects. As Lee points out, creating fruitful collaboration requires a deep level of trust between individuals and organisations, which is challenging because each institution – companies, academia international groupings, governments, donors, civil society organisations – has its own level of accountability. “Establishing trust necessarily entails a willingness to take on a level of accountability that may be outside traditional boundaries.” Recent history is littered with examples of lack of trust and even mutual suspicion and hostility between some of the key players. Bergström accepts that “there is a lot of concern in the global community about what industry is up to” – but, he says, it is time to develop new narratives.

There has not been political mobilisation for TB as there was for other major infectious diseases, notably HIV, Bergström points out, and as a consequence, co-ordination and collaboration have not developed far. “There is scope there, but it needs leadership,” he says. He suggests that leadership could come from senior people in distinct organisations – company chief executives, major philanthropic bodies, civil society organisations, the EU institutions – including the European Investment Bank.
Evidence of collaboration
Some scepticism still colours relationships between the different constituencies of academics, industry, civil society organisations, regulators, and governments. But there are signs of a more collaborative response to pressing need. Drug firms are increasingly signing up to partnerships with non-governmental organisations such as the Tuberculosis Drug Accelerator, the TB Alliance, the Critical Path to TB Drug Regimens, the Stop TB Partnership, and the Global Drug Facility, to accelerate research and widen access to treatment.

ECDC plans to conduct stakeholder and expert consultations and develop guidance to assist EU member states with the introduction of new tuberculosis drugs. ECDC and the European Respiratory Society (ERS) jointly developed European standards for the care of TB, with recommendations aimed at reducing its spread by boosting screening, testing and treatment. And the ERS recently set up a broad-ranging think-tank to “refocus and optimise control strategies” for TB, inspired by what it sees as positive prospects.

Voluntary organisations are increasingly involved in easing strained social conditions and remediying deficiencies in health infrastructure, says Cobelens, highlighting some Dutch groups that work with TB victims in the Netherlands and in the developing world.

Even Voitzwinkler, who laments the continuing lack of adequate vaccines, point-of-care diagnosis, or effective short cures, recognises that “there has been a slight and encouraging change over recent years”.

At the level of international organisations, the WHO is on the brink of adopting a new TB strategy for post-2015. The World Health Assembly in May is scheduled to sign off on a framework for prevention, care and control, with ambitious milestones for 2035, alongside a recognition of the social implications of the disease, in the shape of a goal of “preventing families facing catastrophic costs due to tuberculosis”.

On paper at least, this plan ticks most of the boxes. It gives priority to “government stewardship and accountability”, along with monitoring and evaluation, and “a strong coalition with civil society organisations and communities”. It urges early diagnosis, universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups. It aspires to treatment of all TB cases and patient support, and preventive treatment of persons at high risk, and advocates frameworks to ensure case notification. It also urges “engaging a much wider set of collaborators across government, communities and the private sector”, and notes that “failure to do so will carry serious individual and global public health consequences”.

The European Commission is exploring a new concept for a global TB vaccine partnership. This would be a collaborative effort to accelerate development through sharing technical, financial and market risks in a novel balance of commercial and public-sector interests. This approach has engaged the EIB, the Bill and Melinda Gates Foundation, and the EDCTP, and it could be launched later in 2014 when the new Commission takes office.

The European drug industry is increasingly open to new approaches, to funding research and financing drugs, and to maximising the potential of molecules that might otherwise be neglected. Bergström is creating a post in EFPIA for a ‘vacuum cleaner’ to hoover up candidate drugs lying fallow, and is exploring novel approaches to intellectual property. Lee says he is ready to look at projects for collaborative research and development proposed by civil society organisations, such as the MSF’s concept that was rejected last year by the WHO.

Whatever solutions emerge, they will not be and cannot be just European solutions. As Bergström says: “Health is global health, threats are global threats.” “TB is a global killer, and it will take global solutions to defeat this insidious disease,” says Martha Brumfield of C-Path. The Commission too takes the view that “TB is a global problem and the responsibility to support research activities should be shared.”

But Europe may be groping its way towards closer collaborations that could allow it to step up its response to TB. It has a double interest in doing so in protecting its own population from a disease that should not kill, and in contributing, for humanitarian reasons, to easing health burdens in poorer countries beyond its borders.

Conclusion

There is a perceptible sense of impending change in attitudes to TB, across much of the health community in Europe and beyond. Senior figures in industry, research, civil society organisations and the international community – including the EU institutions – are increasingly ready to talk of greater collaboration, and even speak without embarrassment or irony of a possible leadership role for Europe in effecting change, at home and at global level. Some tangible steps have been taken in new collaborations, and more are under active discussion and likely to emerge in 2014. But Europe has always been good at talking. What is still missing is a trigger to fuse the multiple expressions of goodwill and good intentions into action. It would hardly be a satisfactory breakthrough if the impulse was to be the sudden spread of extensively drug-resistant TB across the continent.

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