SCRIP
CITELINE COMMERCIAL

16 May 2016 |

Expert Round Table: Can We Beat AMR?

by Eleanor Malone

On the fringes of the 26th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) in Amsterdam in April 2016, four eminent players in the fight against antimicrobial resistance (AMR) came around the table with Scrip to discuss the current state of play and where the most pressing needs lie.

Joining moderator Eleanor Malone, editor of *Scrip*, were

- Professor Mike Sharland, Professor of Paediatric Infectious Disease at St George's University Hospital and chair of an expert advisory committee on AMR for England
- Professor Roman Kozlov, Chief Specialist of the Ministry of Health of the Russian Federation in Clinical Microbiology and Antimicrobial Resistance, and a Director at the Institute of Antimicrobial Chemotherapy at the Smolensk State Medical University
- Professor Matteo Bassetti, head of the Infectious Diseases Division of the Santa Maria Misericordia University Hospital in Udine, Italy, and professor Infectious Diseases at the School of Medicine and Postgraduate School of Infectious Diseases at the University of Udine
- Dr John Rex, Senior Vice-President and Chief Strategy Officer for AstraZeneca's antibiotics business unit

Q **Eleanor Malone: *Jim O'Neill's Review on Antimicrobial Resistance* predicts that by 2050 the cumulative negative effect on the global economy of antimicrobial resistant infections will be $100trn. It has also been predicted that 10 million people will be dying of AMR each year by that time. Are we doomed?**

A Mike Sharland: Like any estimate one needs to be aware of confidence intervals, but this estimate has been very helpful in providing political focus on AMR as a global

problem. The UK's O'Neill Commission has done an excellent job in highlighting that this is going to be an extremely serious problem that will actually impact on the conduct of healthcare. Doomed is a complex word, but if you ask is AMR impacting on healthcare and will it impact increasingly on routine healthcare provision, then the answer is 'yes'.

A John Rex: The O'Neill estimates were about what it would cost if we did nothing. There's a lot we can do, and the O'Neill estimates have given impetus to the idea that you need to put effort into being good stewards of the drugs we've got already. However, the scary part is the global development pipeline. If you look at the current pipeline of drugs in Phase I, II and III trials, that is everything you are likely to see in the clinic in the next decade. Nothing else will emerge in the next 10 years that I can't already put my finger on because that's how long it takes to develop drugs. Looking at that collection of drugs, there are 39 things. But then you start asking 'how many are for Gram negative infections?'; 'how many are novel?'; 'how many are likely to actually make it?'. A good guess is that there are six drugs for Gram negatives but none of those is novel. In terms of getting out ahead of resistance, novelty is the way to do that, and I don't see novelty. Novelty is really rare and the pipeline is inadequate to keep up with the growth of resistance unless we become really good stewards and really good infection control practitioners.

A Roman Kozlov: What the O'Neill review has done is provide an excellent background for political action. Everybody in this field knows that AMR is a problem but it has been limited to the sidelines of congresses. Political decision makers need a clear picture of what will happen from the point of view of human death, material losses and so on to make a political commitment. We're now starting to see that political commitment within the EU, the US and the Russian Federation. Now is the time for action and without the support of politicians this would never be achievable. Now there is a chance to achieve at least intermediate goals.

A Matteo Bassetti: I think the situation in Italy and southern European countries is of particular concern because we are the leader in Europe in terms of resistance rates. AMR already costs the EU around €6bn a year, and I think that in some European

countries the politicians are still not ready to address the problem. It's still a problem being discussed by physicians and scientific societies but it's not yet discussed at a very high political level. In Italy we started our stewardship program, we made some steps, but we're still not doing what I think we have to do. And we need to focus attention on the public, because in Italy there are still a lot of people that go to the pharmacy and demand antibiotics, and take them like aspirins or anti-inflammatories. I know it's similar in many other countries: there's no conception of antimicrobial resistance.

"I guess I'm crossing my fingers because if it doesn't work we've got a big problem" - John Rex

Q **So there's a lack of public awareness, there's a lack of pipeline, there's existing impact on routine healthcare. How has the situation been evolving and where do you think we're headed?**

A MS: In countries like Europe with relatively standard surveillance programs over a period of time, we've seen a steady increase in antimicrobial resistance rates which have generally been associated with a steady increase in antimicrobial prescribing rates. We know how to do monitoring programs reasonably well but what hasn't been done very well so far is intervention. One example of a formal intervention that we've introduced in England very recently is the release of quality indicators to reduce both community and hospital antibiotic prescribing. We have a community quality indicator that asks for a net reduction of around 3% of antibiotic prescribing in primary care, and it requires cephalosprins, quinolones and co-amoxiclav to be no more than 10% of prescribing in primary care. We've also released quality indicators to reduce hospital prescribing overall and for particular drugs like meropenem, carbapenems and piperacillin-tazobactam, again by very defined, exact metrics. It is possible to produce national policies with very clear quantitative metrics and a

clearly defined ambition for reducing both primary care and hospital prescribing.

A MB: But there is a discrepancy between the size of the problem and the peak of the intervention. In countries with the highest incidence of resistant strains in Europe, they don't have any stewardship approaches.

A RK: The WHO has been severely criticized for saying a lot but doing nothing. But at the May 2015 World Health Assembly – which is a much higher level than WHO – a record number of countries endorsed the *WHO's Global Action Plan on Antimicrobial Resistance* and in so doing committed to developing national action plans to combat AMR. Although I think too many declarations have been signed previously, I think this is more positive because in this declaration countries promised to develop national action plans with do-able actions by May 2017. I am optimistic because there is a clear-cut message that you have to develop a do-able plan and report to the World Health Assembly on what you did to at least delay the development of AMR. And if we have at least a minor story of success – for example where a plan was developed which allowed the spread of carbapenem-resistance enterobacteriaceae in a number of hospitals to be stopped – that could lead to further successes. I don't want to focus on the negatives! Small positives will spur further advances.

A JR: The echo chamber has gotten bigger, which is very helpful. It used to be just the medics that worried about AMR but now there are some at the political level who get it: there's the O'Neill economists, and some health ministers are becoming really active in this area, a few governments. One step leads to another. I guess I'm crossing my fingers because if it doesn't work we've got a big problem.

Q **How about at an industry level, are companies doing enough?**

A JR: The thing I've found exciting is that the number of small companies active in this area has really gone up. The small companies are where the really good innovation comes from: historically you just need lots of little companies trying a lot of crazy ideas to come up with an interesting new drug. But there are still relatively few large companies involved, and they're the ones who can deliver the drug into markets

around the world.

Q **Let's talk about progress, what recent advances have been effective in the fight against AMR, maybe we can start with you, John, on talking about that R&D pipeline?**

A JR: You can see antibiotics as a three-part problem. It's hard to discover antibiotics, it's hard to develop them and the economics aren't very favorable. We've seen a lot of progress on the first two of those problems. We've seen significant investment from governments – the US through the NIAID and BARDA; the European Commission through the IMI New Drugs for Bad Bugs program, etc – and from big public funders like the Wellcome Trust. There's been a significant amount of money made available at the academic, early discovery, early development phases. The regulatory agencies have spent close to a decade talking about the problem of how you develop an antibiotic in advance of the epidemic spread of resistance. It's hard work but we do have some answers and it is possible to do this. The fact that we are now discussing the economics of antibiotics at political levels – it was on the G7 agenda, it's going to be on the G20 agenda, it's going to get discussed by non-techies! Ten years ago you could not have gotten people to talk about this because there was so little understanding. The problem was real but we hadn't yet developed the tools with which to discuss it. But, the discovery and development pipeline is inadequate mathematically to address the needs. For example, in TB, the rate of spread of multi-drug resistant TB is absolutely outpacing our ability to control it and produce new drugs to treat it.

A RK: One figure that strikes me from the O'Neill report is that in the current system, it takes 23 years to get a return on investment from the development of new antimicrobials.

Q **One area you are particularly involved in John is the problem with the financial models for commercializing antibiotics and also for developing them. You've talked about an insurance model: can you outline that?**

A JR: Antibiotics are effectively the fire department of medicine. If you think about a fire department, you think about your community, you've got fire stations and fire trucks and trained fireman and the water supply to the city, and now if we think about all that infrastructure we ask a couple of questions like 'how often should we pay the firemen a salary – is it only per fire or should we actually agree to pay them on a monthly basis?' And if you get to the end of the year and there have been no fires, is your reaction 'well that was actually a waste of money on the fire department, we didn't use it so we obviously don't need it anymore'? Or do we actually say, 'wonderful job done with the fire prevention, let's actually keep doing that'? And it's obvious what the correct answer is; the correct number of fires is zero and we need the fireman out there to help us prevent fires.

"The antibiotic has two values: one is when you use it to put out a fire and the other is knowing you could put out a fire that makes it safe to go into the hospital" - John Rex

A If you translate that into medicine, in effect we currently pay for antibiotics on a per fire basis and that's not very rational and we're also overlooking the fire extinguisher value of an antibiotic. On the wall there's a fire extinguisher and if a little fire starts –you're cooking at home and a little grease fire gets started – you put it out with your fire extinguisher and you have to order takeout because you've ruined your dinner but if you don't have a fire extinguisher and your kitchen burns down or the apartment building burns down you can actually have an enormous economic impact on many others around you. I once closed a surgical ICU for nearly two weeks because of an outbreak of an untreatable infection. I effectively closed ORs because they didn't have a place to send their patients: it was a huge impact, for lack of a fire extinguisher. The antibiotic has two values: one is when you use it to put out a fire and the other is knowing you could put out a fire that makes it safe to go into the hospital. So we have to think about economic models that deal with both of those

> uses because in fact the correct number of carbapenem-resistant antibacterial infections in any one of our hospitals next year is zero and yet you still want to have a drug in the pharmacy. That requires a really different economic model and you need to think about the antibiotic as being like the fire extinguisher, it's an insurance policy, you want to have it available. Just like with your life insurance: we've all paid our life insurance premiums and we're all really glad that our life insurance didn't pay off this year, nobody's mad that they didn't get their life insurance proceeds, they're delighted to still be here for another year ... We're actually talking about that model with some countries where the circumstances are right to explore a model in which the payment for the antibiotic is not related to how many infections you treat, it's related to the availability of the drug and the occasional use of it. Changing that is the big thing, because that will allow us to create a sustainable pipeline of new antibiotics by rethinking the economic models. It's going to take a lot of time, we're not close to a final answer on it but there are baby steps going on in some countries in Europe, particularly single payer state countries, it's a good test bed for developing some novel economic models. There was a *big declaration* on this that we released in parallel with the World Economic Forum in January of this year, so the industry really, really wants to engage with countries, country by country, to think about a model that would work in those countries for the sustainable use of antibiotics, pulling them into the marketplace even when we're trying to drive the rate of infections down, which is all a good thing.

Q **AMR is such a complex area but can anyone sum up the key priority in a word?**

A MB: Commitment. Just one word: it's commitment.

This is an edited version of the round table, which was sponsored by AstraZeneca. Scrip will publish the full audio recording of the discussion in five parts. To hear part 1, click *here*