Tackling resistance: bacteria, humans, animals and the environment

An Interview with Stuart Levy, Professor at Tufts University School of Medicine and President of the Alliance for the Prudent Use of Antibiotics

EMBO reports (ER): In September, the CDC reported that, by the most conservative estimate, each year 23,000 Americans die of an untreatable bacterial infection due to antibiotic resistance. In the EU, it is 25,000 deaths per year. You have been warning of this problem for nearly 40 years now. Why is apparently nothing changing?

Stuart Levy (SL): Things move slowly, and I think Europe moves faster than the USA. There are so many different issues and steps to go through to introduce change here. We face the problem of how antibiotics are being misused for people; how they are being misused in animals. People demand them, doctors over-prescribe them, veterinarians and non-veterinarians include them in animal feeds and they all end up in the environment. It's not as if you use an antibiotic for an animal, and suddenly "poof!" it destroys itself. These drugs stay around relatively stable in the environment. In many ways, antibiotics can be regarded as societal drugs. They have an effect not only on the person or the animal taking the drug, but also, directly or indirectly, on others sharing the geographical locale in which they are used; this could be a whole farm. If you look at the local bacterial flora, you'll find that as antibiotics are introduced, the flora changes to become drug-resistant. There's a societal and ecological effect of antibiotics, which is not true of any other medication.

Why are things not moving faster? It comes down to policy, influence, money. One believes addressing antibiotic resistance is going to improve the health of the people of the world, but you can't get the message

out, because it's not what the public believes about antibiotics. They are miracle drugs and should be available to everyone. The problem of resistance is now causing us to pause and reflect on the historic view of these drugs.

ER: So do you think it will get worse, or that it has to get worse before things begin to change?

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SL: Ironically, yes, that would influence change. Still we see that resistance continues to mount globally, thwarting successful treatment of many different bacterial diseases. Most importantly, addressing resistance requires more sustained change involving how antibiotics are provided and used both with the lay public and health professionals. My students now leave my laboratory realizing that antibiotics are precious drugs, and that they should not be misused. I have been lecturing to the dental school, to the veterinary school, to the medical school: it's the same message and now the younger generation is picking up the cue. Yes, I am optimistic that there's going to be a change, not only in how drugs are prescribed, but particularly their use for growth promotion in food animals.

ER: The CDC report warned about the so-called CRE [Ed: Carbapenem-resistant

Enterobacteriaceae] bacteria, which are resistant to nearly all antibiotics. In 2011, 53 people died during an epidemic in Germany caused by an EHEC [Ed: Enterohemorrhagic *E. coli*] bacterium. It does seem to be getting worse.

SL: How much worse does it have to get before more concerted action is seen? Does one have to have whole communities affected? No, I think that the data are already there, as seen in the CDC report. Additionally, the issue is strengthened when a large charitable trust like PEW puts funds behind removing antibiotics from animal feed. You've got some practical influence in terms of funds focused on eliminating the practice.

ER: So we have to wait for someone like Bill Gates to pick up the cause?

SL: That would be great, but unfortunately the Gates Foundation does not see drug resistance as one that it would like to take on. We had a grant though through the Gates Foundation for work in Zambia and Uganda. We could document misuse of antibiotics and widespread resistance. The Gates Foundation liked the report, but did not find that resistance merited the attention currently given to vaccines and designated infections, like TB, HIV and malaria. It is curious, since drug resistance plagues these diseases and others. There is at least action going on through European efforts. Different groups, such as the international Alliance for the Prudent Use of Antibiotics are working in Africa. With all the new ways of communicating, such as social networks, we can inform a lot more people more easily.

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naturally occurring in people. But they're not able to get around natural barriers in the bacterium. They're not very powerful or useful, even if they look good in the laboratory. There isn't any antibiotic really, except maybe alcohol or peroxide, that bacteria are not able to resist. What you really want is an antibiotic that works and then self-destructs so it is not able to select for resistance mutations. You'd have a drug that would be always useful.

ER: You mentioned that pharmaceutical companies are not developing new antibiotics. What would be needed to get them on board again? They developed all the original antibiotics in the 1950's and 60's, and they have the means to tackle the problem.

SL: They have the money, but they don't have the teams to work on it anymore. The reason is that the return on investment is not there for antibiotics as it is for other medicines, which are being used chronically. But many, including myself, argue that doesn't mean that there isn't a niche, with a good financial return, for developing new antibiotics.

ER: Do you think they should get additional incentives for developing new antibiotics?

SL: Yes, definitely. You need incentives to get the companies to reinvest in this area. And we can do that: lengthen the time for patent protection, remove certain regulatory impediments leading to a more rapid approval from the FDA. The FDA is already doing this by relying on certain studies to speed up approvals. But they may be taking a risk that the drug needs more studying. The public gets what it needs, namely new antibiotics, clinicians get what they need, and the company gets what it needs.

ER: On the one side is the development of new antibiotics, on the other side is the prevention of misuse. As you said, it is the misuse in animal farming but also the misuse in hospitals. How do we tackle this problem?

SL: Misuse is not just a hospital problem, it's even more prevalent in the community. And we have no easy way to track these incidences. You come to the doctor with a scratchy sore throat and you get an antibiotic designed to kill a bacterium, when in fact the culprit is a virus. The hospital sees more overuse or perhaps use of the wrong antibiotic, which is why we should stress the

ER: About 10–15 years ago, there was a lot of interest in new antibiotics, such as cationic peptides, which seem to be evolutionarily very old mechanisms, and bacteria had not

developed any resistance. None of these ever made it into clinical use. So what happened?

SL: They don't last long enough. We did work on cationic peptides, which are

need for new ways of diagnosing the cause of the illness—bacteria, virus, parasite. If we can make the diagnosis early, we can treat more appropriately, and we won't be treating a viral disease with an antibiotic that will be doing nothing for the patient except creating resistance. We found in Zambia and Uganda that clinics were using co-trimoxazole for respiratory tract infections, and they had not realized that the pneumococcus was already resistant to this drug combination. So there are a lot of simple ways to improve our use, but in order to improve our use, we need to improve our ability to diagnose.

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ER: Do you see any progress there? With genomics and sequencing technologies it should theoretically be much easier and faster?

SL: Either you do the whole genome sequencing, or you do portions of the genome if you're concerned about whether a penicillin-resistant staph is an MRSA or not. You need to have a method, which is both sensitive enough to pick up the gene, but also exacting enough so that you don't make a misdiagnosis. You need to bring this technology to the bedside, so as to make the diagnosis quickly enough to treat appropriately. If you step back and think about it, more education on how to use antibiotics effectively, rapid diagnostics and an understanding by clinicians about how to use them would improve the situation.

ER: Do you see a role for academics, like you and others, to be more active and pushing for change?

SL: Even better, you educate your students on the proper use of antibiotics and you hope that they take that message with them when they graduate. When I lecture veterinary students, I very strongly emphasize the misuse in providing antibiotics in animal feed for growth promotion. But it's a giant step when these students enter the field of veterinary medicine, where you get faced with the idea that you

have to give an antibiotic for growth promotion because that's part of the industry standard. Maybe I'm overly optimistic, but if we can eliminate this huge abuse of an estimated 70–80% of all antibiotics that are being used, that should reduce the frequency of resistance.

ER: You already mentioned the environmental factor in antibiotic resistance. There is this One Health concept that looks at the interplay of humans, animals and the environment. Do you think that applying this concept would help to understand and tackle the problems of virulence and antibiotic resistance?

SL: I'm touched by the whole concept because the *Mar* locus in *E. coli* and other related bacteria, which we discovered, and the *MarA* regulatory protein control resistance as well as the ability to cause infection—this is the link between environment and health. If you remove this gene, which codes a protein that regulates the expression of 90–100 different genes, you prevent infection itself. So if one can build an inhibitor of the *Mar* protein, which we have done, we end up with an organism that is not able to cause an infection. There are of course other virulence genes that companies have made antibodies against, especially for MRSA. So there's interest, there are new ways, there's new thinking to address antibiotic resistance and bacterial infection.

ER: It's interesting to look at this link between resistance and virulence, because this was a problem of the EHEC strain: if you tried to treat it with antibiotics, it began to release shiga toxin into the bloodstream, which then led to kidney failure.

SL: It's also been true of the so-called flesh-eating streptococci. You want to use protein synthesis inhibitors before you lyse the bacteria with something like penicillin, because you have an enormous release of toxin from the bacteria that is liable to kill the patient before you eliminate the infection. You have to know the organism so you can determine the treatment.

SL: I think they can be useful, but they're not all-purpose drugs. A commensal bacterium, for instance, can keep infectious bacteria at bay by crowding them out. Phage therapy is interesting, but I see more use in agriculture. Instead of spraying fruit for instance with tetracycline or streptomycin, you spray with a phage to kill unwanted

bacteria. Most interesting is the proposed use of phage therapy in intravenous therapy for patients with MRSA infection of heart valves; but I don't think phage therapy has reached its optimum yet or defined its approach. It is easier to see it as topical use for preventing infection because you don't have to worry about the person having an adverse immunologic reaction against the phage itself.

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ER: There is also interest in bacteriophage therapy, passive immunizations, and commensal bacteria to fight infections. How promising are these approaches?

ER: One beautiful characteristic of phages is that they co-evolve with the host; so even if bacteria start mutating, phages co-evolve; and as you said, it is an antibiotic that destroys itself once its job is done.

SL: I think it is worth pursuing as long as one keeps the practicality in mind; most notably if you're injecting phages into a person. Then the question arises, how do you get a license from the FDA for the phages when the exact composition of the treatment will be difficult to maintain? You're using a mixture of phages in the therapy.

ER: What should governments do more in order to address antibiotic resistance?

SL: One is, encourage the discovery of new antibiotics by offering incentives. And that's why Congress passed the GAIN Act [Ed: Generating Antibiotic Incentives Now]. We're in a decade where we've seen very little new antibiotics, and we must ask, do we want to enter another decade like this one? As new antibiotics are being introduced, they have to be thought of not necessarily in terms of what happens in the target organism, but what happens afterwards in terms of the risk of resistance among all bacteria in contact with the drug.

ER: How do you see the potential of rational drug design versus exploring biological diversity? Many classical antibiotics are biological products, which means bacteria have been exposed to them and have

developed and evolved means to evade them, if necessary.

SL: Trimethoprim combined with sulfamethoxazole, called Bactrim, is an example of a synthetic drug composition. Still resistance to each component appeared. Quinolones worked fantastically, especially against gram-negative bacteria. That should not have gotten resistance—it was right there. Carbon, nitrogen, oxygen and hydrogen have been around in different combinations and bacteria have seen them all. I think the only way to maintain a drug's efficacy is to use it appropriately and be aware of its environmental impact.

ER: Which means proper public health measures are the best strategy?

SL: Absolutely. The public has to be part of the answer. The public has got to learn that antibiotics are precious therapeutics, and that they should not be wasted. You need education to get the message out. The body is there to take care of itself. There are so many ear infections, which are mild, that don't require treatment, that would save the

environment from the contamination with antibiotics.

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ER: Lastly, it's a global problem, so even if Europe and the USA, Japan and Zambia move forward, you still have so many countries where antibiotics are sold over the counter, sold in street markets. There's the additional problem of counterfeit medicine. So how do you address the global perspective?

SL: You can address the problem with practical solutions. You perform a situation analysis as we did in Zambia and in Uganda. You find out the major problems, you address them. You go step-wise. You don't expect it to happen like that (snaps his fingers)

ER: So you remain an optimist, in the sense that we're not heading back to the 19th century in terms of public health?

SL: Yes, I'm an optimist down to my toes. I think that in this decade we're going to see some major changes. We won't see new antibiotics yet, but we will see changes in how they're being used. And I think that will make a big difference. The environment is a reservoir of antibiotic resistance and so we should really look at the reservoir in this particular city or country or region. The carbapenem-resistant organism in India was found in the environment. But we could have found it before, had we looked and put up some barriers so it did not get transferred all over the world. Antibiotics are societal drugs and need to be treated as a special drug category. Antibiotics come out of the environment as much as they go back into the environment.

ER: Dr Levy, thank you for the interview.

The interview was conducted by Holger Breithaupt.