The world's deadliest diseases: The WHO priority list of antibiotic-resistant bacteria

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Penicillium chrysogenum
Source: en.wikipedia.org/wiki/Penicillium_chrysogenum.

We all take it for granted that if we get a cut or scratch or go into hospital for an operation, we won't die from an infection. But that's literally what often used to happen less than a century ago – a toothache could kill you! Antibiotics are the main weapon against bacterial infections. And yet antibiotics are losing their power to kill bacteria – and save our lives! – because bacteria are becoming increasingly antibiotic resistant. This article reports on a project by the World Health Organization (WHO) and experts around the world to create a priority list of antibiotic-resistant bacteria to guide research and development (R&D) into new antibiotics.[1]

A VERY HAPPY ACCIDENT!

One of the world's greatest discoveries occurred by accident in 1928 when Scottish scientist Alexander Fleming noticed something weird in his untidy laboratory: the bacteria in a petri dish that had become contaminated with a mould were dead! Here's how Fleming modestly described his discovery of what he originally called "mould juice" and that became known as *Penicillium chrysogenum* (Brown 2005):

One sometimes finds what one is not looking for. When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionise all medicine by discovering the world's first antibiotic, or bacteria killer. But I guess that was exactly what I did.

Over the next two decades, chemists purified the mould and developed the drug Penicillin as an antibiotic or bacteria killer. Penicillin kills a large number of bacterial infections in humans – e.g. pneumonia, anthrax, sexually-transmitted diseases, mouth infections, diphtheria and cellulitis – without harming humans themselves.

Fleming shared the 1945 Nobel Prize in Physiology or Medicine with Howard Florey and Ernst Chain – "for the discovery of penicillin and its curative effect in various infectious diseases." (Nobelprize.org 2018). Since then, many kinds of Penicillin's have been developed, and also many other kinds of antibiotics too. Hundreds of millions of lives have been saved around the world as a result.

NOW FOR THE BAD NEWS ...

Because bacteria are continually evolving they are becoming increasingly resistant to antibiotics. This evolutionary process has been exacerbated by decades of overuse and misuse of antibiotics on human, animals and plants. As a result, antibiotics are not as effective at killing bacteria as they used to be; bacteria are regaining their power to kill humans.

According to Ed Whiting, director of policy at the Wellcome Trust, "drug-resistant infections already kill 700,000 people a year globally" (quoted in Boseley 2017). This number could increase to 10 million people a year by 2050 (The Guardian 2017).

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[1] This article is based on recent research involving the author that is fully reported in Tacconelli et al (2017) and Weyer et al (2017).

Here is the how the WHO (Weyer et al 2017) summarises the menace posed by "antimicrobial" – including antibiotic[2] – resistance:

Worsening antimicrobial resistance could have serious public health, economic and social implications. The threat of antimicrobial resistance is also becoming a key consideration for programmes addressing maternal and child health, sexual and reproductive health, foodborne diseases, water and sanitation, and infection prevention and control. The World Bank has warned that antimicrobial resistance could cause more economic damage than the 2008 financial crisis. And although the 21st century is being shaped by technology and innovation, humans could soon find themselves in an era where simple infections once again kill millions every year.

THE CUPBOARD IS BARE

Notwithstanding the massive threat posed by antibiotic resistance, R&D into new antibiotics has lagged behind. Too few new antibiotics are in the pipeline because of the expense and complexity involved in developing them.

Hence, in 2016 the WHO was asked by its member states to create a priority list of antibiotic-resistant bacteria to guide R&D into new antibiotics by pharmaceutical companies, research institutions and universities.

A LOT TO CONSIDER

Ranking diseases according to their priority for R&D involves considering multiple considerations or criteria simultaneously – e.g. to mention but three such criteria here: the number of people killed by each disease, the extent of its antibiotic resistance and the number of new antibiotics in the 'pipeline'. The WHO chose to use Multiple Criteria Decision Analysis (MCDA) to handle the inevitable trade-offs between the criteria involved.

MCDA is a systematic approach to prioritisation usually supported by specialised decision-making software[3] that is increasingly used in the health sector. In the present context, MCDA involves evaluating diseases' priority for R&D according to multiple criteria, based on the judgments of experts in infectious diseases, clinical microbiology, public health and pharmaceutical R&D.

The WHO project, led by Professor Evelina Tacconelli of Tübingen University and supported by 1000minds software (1000minds. com), involved these four steps:

1. Selection of the antibiotic-resistant bacteria to be prioritised, and identification of relevant criteria for prioritising them.

2. Collection and synthesis of evidence to assess the bacteria and rate them on the criteria.

3. Determination of weights on the criteria, representing their relative importance, based on surveying 70 experts from around the world.

4. Priority ranking the bacteria based on the criteria and weights, and checking the ranking's robustness.

These 10 criteria, in decreasing order of importance,[4] were used to prioritise the bacteria: (1) treatability, (2) mortality, (3) health-care burden, (4) 10-year trend of resistance, (5) prevalence of resistance, (6) transmissibility, (7) community burden, (8) preventability in the health-care setting, (9) pipeline, (10) preventability in the community setting.

DRUM ROLL PLEASE!

The WHO published its priority list of 12 antibiotic-resistant bacteria to guide R&D – stratified into three tiers: critical, high, and medium priority – as presented in Table 1 (reproduced from Willyard 2017). In addition, multidrug-resistant tuberculosis was classified as a global priority for R&D too.

Table 1: WHO priority list of antibiotic-resistant bacteria for R&D into new antibiotics

Threat list

Bacterium or bacterial family (and antibiotics it resists)	Typical effects
Priority: **critical**	
1. *Acinetobacter baumannii* (carbapenem)	Hospital infections
2. *Pseudomonas aeruginosa* (carbapenem)	Hospital infections
3. Enterobacteriaceae (carbapenem) ESBL-producing	Hospital infections
Priority: **high**	
4. *Enterococcus faecium* (vancomycin)	Hospital infections
5. *Staphylococcus aureus*	Skin infections (methicillin, vancomycin), pneumonia, bloodstream infections
6. *Helicobacter pylori* (clarithromycin)	Infection can lead to stomach ulcers and cancer
7. *Campylobacter spp.* (fluoroquinolone)	Diarrhoea
8. Salmonellae (fluoroquinolone)	Diarrhoea
9. *Neisseria gonorrhoeae* (cephalosporin, fluoroquinolone)	Gonorrhea
Priority: **medium**	
10. *Streptococcus pneumoniae* (penicillin-non-susceptible)	Pneumonia
11. *Haemophilus influenzae* (ampicillin)	Childhood pneumonia, meningitis, bloodstream infections
12. *Shigella spp.* (fluoroquinolone)	Diarrhoea

ESBL, extended-spectrum β-lactamase. Bacteria that produce this enzyme are resistant to certain classes of antibiotics.

Source: Willyard (2017).

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2   Antimicrobials are chemicals that kill or inhibit the growth of microscopic organisms such as fungi, alchaea, algae, bacteria, etc. Antibiotics kill or inhibit the growth of bacteria.
3   For recent MCDA software surveys, see Weistroffer and Li (2016) and Oleson (2016).
4   Weights are available from Tacconelli et al (2017).

Colonies of Pseudomonas aeruginosa and Staphylococcus aureus (yellow pigment) on tryptic soy agar

Source: en.wikipedia.org/wiki/Pseudomonas_aeruginosa.

CONCLUSION

Antibiotics have protected humans (and other animals and plants too) for the last 70 years, but their potency is waning due to antibiotic resistance. The priority list created by the WHO is intended to help prioritise R&D into new antibiotics by pharmaceutical companies, research institutions and universities. Let's hope such R&D is successful!

FURTHER READING

The research this article is based on is fully reported in Tacconelli et al (2017b) and Weyer et al (2017).

QUESTIONS TO THINK ABOUT

1. Why have many diseases become resistant to antibiotics?

2. Some people consider that if effective antibiotics were no longer available to fight infections, it would be like returning to the Dark Ages. Do you agree? How would your life change, do you think?

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