# Post-Antibiotic Era is Business as Usual

Jack A. Heinemann and Brigitta Kurenbach
School of Biological Sciences
University of Canterbury, Christchurch
New Zealand

The post-antibiotic era[1] is more than the loss of existing antibiotics; it is the entrenchment of systems that threaten the effectiveness of new antibiotics and transition to a post post-antibiotic era. These systems include unprecedented reliance on manufactured chemical substances, where most of the ~8 million in commerce have neither been adequately evaluated for effects on human health[2] nor for effects on microbes. Another is a social priority to use profit-generating inventions to direct both public and private sector research and development.[3]

The common response to the crisis of antibiotic resistance is renewed commitment to invention of new ones. Invention of new therapeutics as a solution to the problem of infectious disease has been the dominant paradigm since the dawn of the modern antibiotic era. Yet it has for much of this history failed to keep pace with need.[4-6] Another path lies in the adoption of social structures that ensure the effectiveness of existing and new antibiotics, through stewardship. This path, however, is poor at rewarding invention of social value through capture of financial rewards.

*"The same powerful socio-legal and industrial institutions will resist changes needed to help us exit the coming post-antibiotic era."*

In the post-antibiotic era, as in the present,[7] each new antibiotic will be quickly countered by resistance. It becomes tempting to hypothesize that resistance is a pre-determined outcome of use. In which case, stewardship has no promise. If any use would be too much, then would prudent use ever sustain efficacy?

The direct link between the evolution of antibiotic resistant bacteria of medical importance and the scale of use of antibiotics in medicine and agriculture is sound. It is not just that antibiotics *kill* that causes resistance. It is also how we manage their development and use.[3,8] Stewardship requires us to face the social, not just biological, causes of resistance.

**Chemical habitat**

Industrialized societies have enormous capacity to manufacture and intentionally spread commercial chemicals,[2] including antibiotics. For example, concentrated animal feeding operations use large quantities of antibiotics to support dense animal populations.[9] Much of the antibiotic consumed by farm animals is unabsorbed and transferred to the soil.[10] The air becomes contaminated with aerosolized antibiotics, selected microbes and antibiotic resistance genes, thereafter distributed by wind and inhaled or ingested.[11] Run-off from farms also causes contamination of waterways.[9] Even concentrations too low to kill bacteria select resistance.[12] Antibiotic-resistant bacteria in animal manure may find their way to food by direct transfer or by using insect vectors.[13]

Antimicrobial compounds such as heavy metals are added to paints.[14] Antibacterials such as triclosan are in household products such as soaps.[15] Despite evidence that triclosan use increases resistance to clinical antibiotics and nasal colonization by *Staphylococcus aureus,*[16,17] hundreds of tons are released through household products and accumulate in the waste stream.[15] Other biocides are incorporated into food packaging and cosmetics.[18,19]

There may be many more manufactured chemicals not intended to affect microbes but do.[20] Characterization of chemicals in commerce rarely includes testing for antimicrobial activity. On the bright side, unintended antimicrobial effects are occasionally pursued as a source of potential new antibiotics.[21]

Salicylates, including those used in aspirin, induce multiple antibiotic resistance in bacteria.[22] Herbicides also have been shown to induce multiple drug resistances. Observed effects were fast and required no pre-exposure to the herbicide.[23]

As with the salicylates, herbicide exposures increased the concentration needed by some antibiotics to inhibit bacteria, and decreased or had no effect on the concentration needed by others. The response pattern depended on species and herbicide, suggesting that the multiple antibiotic resistance response was due to changes in production of efflux pumps and/or porins. This was confirmed by restoration of wild type response patterns when the bacteria were treated with the efflux inhibitor PaβN.[23]

The herbicide concentration required to achieve the effect was generally above legal maximum residue limits in food and most animal feeds. However, it was significantly below recommended application rates.[23] Herbicides are among the most commonly released products in both urban and rural environments (Table 1). Worldwide, 3 billion pounds of active ingredient are used annually.[24] The U.S. accounts for 25% of global use on nearly 800,000 farms and in 52 million households.[24] Relevant rural exposures could occur in farm animals grazed on treated pastures or within spray drift areas. Relevant human and pet exposures in urban areas might occur in private lawns or public parks, where herbicide use is not controlled, leaving people and pets to be exposed as they travel through them (Figure 1).

Relevant exposures might also result from combination exposures. Some herbicides could combine with aspirin to reach an inducing concentration.[23]

The increases in resistance to various antibiotics, including ciprofloxacin, ranged from two- to six-fold. This is relevant because two- and four-fold changes in resistance to ciprofloxacin were enough to cause 21% and 75%, respectively, of patients to get a lower-than-target dose.[25]

If each antimicrobial activity could only be countered by a biochemistry unique to it, then prudent use of future antibiotics might sustain efficacy. However, the biochemistry of resistance is overlapping, sometimes in surprising ways.[26, 27] When a non-medicinal chemical has antimicrobial activity, resistance often first arises from a change in gene expression. Removing the inducer eventually restores susceptibility. However, these adaptive changes increase the potential for acquisition of spontaneous mutations or horizontal gene transfer leading to genotypic resistance.[7,28]

**Innovation Environment**

Prevailing intellectual property rights instruments reward anti-

**Table 1. Herbicide use by sector in millions of pounds* of active ingredient.**

| Active ingredient | United States | |
|---|---|---|
| | **Agriculture** | **Other**** |
| glyphosate | 280 | 13 |
| 2,4-D | 35 | 13 |
| atrazine | 69 | not reported |
| pendimethalin | 11 | 6 |
| dicamba | 5 | 2 |

* Based on mid range of estimates for 2012.

**Home and garden combined with government and industry.

Source: Ref. 24

biotics with the largest market rather than a long useful life.[29] It influences what kinds of drugs are commercialized and offers few incentives for innovation in stewardship.[3, 30, 31]

Innovation in stewardship has other impediments too, especially where unrelated industries using chemicals that induce resistance may also have to change behavior, and possibly profit margins.

The post-antibiotic era comes from business as usual. The same powerful socio-legal and industrial institutions will resist changes needed to help us exit the coming post-antibiotic era. Antibiotics are precious global resources. Future innovation should treat them as such.


Figure 1. A day in the life of a pram. Hagley park is a large public area in the center of the city of Christchurch, New Zealand. It is used for exercise by people and their pets, as well as by hospital patients and their visitors.

**References**


1. Reardon S 2014, WHO warns against 'post-antibiotic' era. http://www.nature.com/news/who-warns-against-post-antibiotic-era-1.15135. Accessed: 15 April 2017 [Online.]

2. Egeghy PP, Judson R, Gangwal S, Mosher S, Smith D, Vail J, Cohen Ubal EA. 2012. The exposure data landscape for manufactured chemicals. Sci. Total Environ 414:159-166.

3. Amabile-Cuevas C. 2016. Society must seize control of the antibiotics crisis. Nature 533:439.

4. CDC. 2014. Antibiotic resistance threats in the United States, 2013. Centers for Disease Control and Prevention.

5. Neu HC. 1992. The crisis in antibiotic resistance. Science 257:1064-1073.

6. WHO 2015, Antimicrobial resistance. http://www.who.int/mediacentre/factsheets/fs194/en/. Accessed: 7 July 2015 [Online.]

7. Levy SB, Marshall B. 2004. Antibacterial resistance worldwide: causes, challenges and responses. Nat. Med. 10:S122-S129.

8. Davies J, Davies D. 2010. Origins and evolution of antibiotic resistance. Microbiol. Mol. Biol. Rev. 74:417-433.

9. EPA. 2013. Literature review of contaminants in livestock and poultry manure and implications for water quality 820-R-13-002. US Environmental Protection Agency.

10. Chee-Sanford JC, Mackie RI, Koike S, Krapac IG, Lin Y-F, Yannarell AC, Maxwell S, Aminov RI. 2009. Fate and transport of antibiotic residues and antibiotic resistance genes following land application of manure waste. J. Environ. Qual. 38:1086-1108.

11. McEachran AD, Blackwell BR, Hanson JD, Wooten KJ, Mayer GD, Cox SB, Smith PN. 2015. Antibiotics, bacteria, and antibiotic resistance genes: aerial transport from cattle feed yards via particulate matter. Environ. Health Pers. 123:337-343.

12. Andersson DI, Hughes D. 2014. Microbiological effects of sublethal levels of antibiotics. Nat Rev Microbiol 12:465-478.

13. Zurek L, Ghosh A. 2014. Insects represent a link between food animal farms and the urban environment for antibiotic resistance traits. Appl Environ Microbiol. 80:3562-3567.

14. Flach C-F, Pal C, Svensson CJ, Kristiansson E, Östman M, Bengtsson-Palme J, Tysklind M, Larsson DGJ. 2017. Does antifouling paint select for antibiotic resistance? Sci. Tot. Envir. 590–591:461-468.

15. Bedoux G, Roig B, Thomas O, Dupont V, Le Bot B. 2012. Occurrence and toxicity of antimicrobial triclosan and by-products in the environment. Environ Sci Pollut Res 19:1044-1065.

16. Aiello AE, Larson EL, Levy SB. 2007. Consumer antibacterial soaps: effective or just risky? Clin. Infect. Dis. 45:S137-S147.

17. Syed AK, Ghosh S, Love NG, Boles BR. 2014. Triclosan promotes *Staphylococcus aureus* nasal colonization. mBIO 5:e01015-01013.


*References continued on p. 12*