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MICROBIOLOGY

Sources of Antimicrobial Resistance

Mark E. J. Woolhouse and Melissa J. Ward

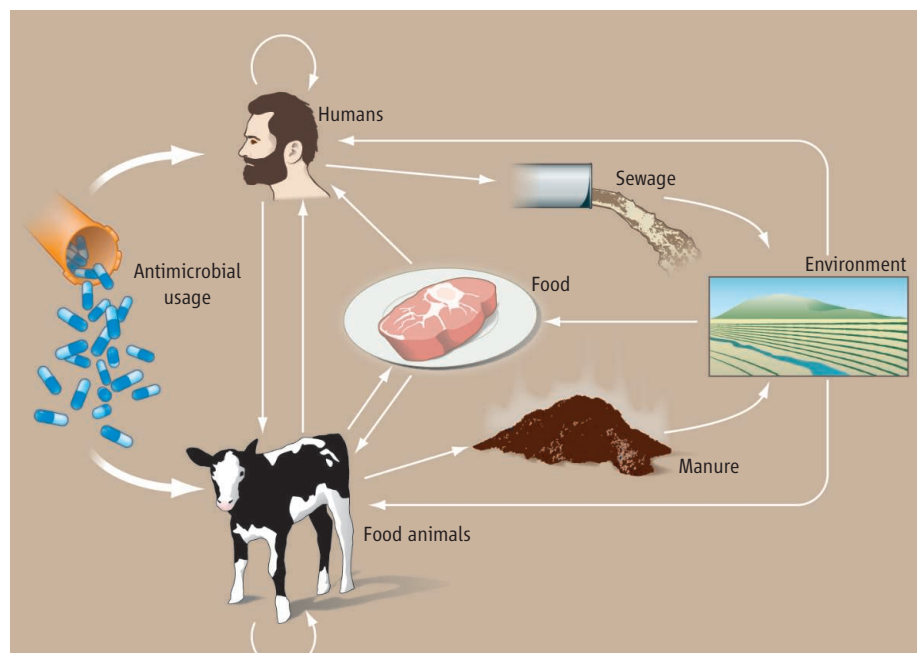
The relentless rise in levels of antimicrobial resistance is an unfolding global public health crisis (1). Resistance to frontline antimicrobials such as fluoroquinolones, third- and fourth-generation cephalosporins, and carbapenems is a particular concern, as is multidrug resistance. The antimicrobial resistance problem is not confined to human medicine: Comparable quantities of antimicrobials are used in livestock production, and resistance is rife in that setting, too, even on organic farms that restrict drug usage (2). Such observations have led to debate about whether antimicrobial resistance in farm animals is an important source of antimicrobial resistance in humans (3, 4). On page 1514 of this issue, Mather *et al.* (5) shed light on this important question in the context of *Salmonella* Typhimurium DT104 in humans and cattle in Scotland.

Antimicrobial resistance can spread from food animals to humans through a number of routes (see the figure). Direct contact with livestock is an important route of exposure for agricultural workers, but the most likely sources of exposure for the general population are thought to be resistant bacteria in livestock-derived food products and animal waste, which is used as a fertilizer of crops and can contaminate water supplies. Yet, antimicrobials are used in very large quantities in the human population, and bacteria carrying resistance genes can spread directly within human populations or indirectly through sewage contamination of food, water, or the wider environment. It is not clear how important the livestock-derived routes are compared with the human-derived routes.

In the 1990s, there was a global epidemic of *S. Typhimurium* DT104. These bacteria are multidrug resistant and are regarded as zoonotic, circulating in the domestic cattle population and acquired by humans mainly by way of food products from cattle—apparently a clear example of the animal-derived route. Mather *et al.* tested this idea for DT104 in Scotland. They conducted whole-genome

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Genomic data help to elucidate the role of food animals in the spread of antimicrobial resistance in humans.



Pathways to antimicrobial resistance. Antimicrobial resistance may spread through multiple direct and indirect pathways to humans and food animals (arrows). The relative strength of these pathways will differ greatly not only for different bacteria and different kinds of resistance but also in different locations and environments. Mather *et al.*'s study contributes to the development of a quantitative understanding of this complex process.

sequencing on more than 200 isolates collected by the Scottish Salmonella Reference Laboratory. The isolates were from both humans and livestock, collected over the same 20-year time period and from the same geographical region. Such well-structured samples are rare and valuable resources for epidemiological research.

The genetic sequence data were analyzed using a state-of-the-art approach to elucidate the histories of DT104 in human and animal hosts. The results suggest that the human and livestock epidemics were largely independent, though with some jumps in both directions between the two populations. These findings apply to the DT104 bacterium itself, but antimicrobial resistance can move by horizontal transfer between bacteria. Mather *et al.* therefore investigated the distribution of different multidrug resistance profiles across the DT104 phylogeny. They found more than 30 unique combinations of resistance to individual antimicrobials. The diversity of antimicrobial resistance profiles was at least as high in

the human isolates as in the livestock isolates, and there was little relationship between individual profiles and the phylogeny of the bacteria or the origin of the isolates.

Taken together, the results do not support the hypothesis that the human population of Scotland acquired all their diversity of multidrug-resistant DT104 directly or indirectly from Scottish livestock. So where did it come from? The source is likely to be different DT104s introduced from outside Scotland, particularly in imported food products, with some circulation of these introduced DT104s in the human population.

This expectation can, in principle, be tested in a similar study on a larger geographic scale. However, as Mather *et al.* point out, surveillance and isolate collection outside Scotland have been too patchy to attempt this. This problem is not confined to DT104. The lack of good-quality surveillance data and of access to biological material internationally limits further research on antimicrobial resistance more widely, too.

An interesting corollary of Mather *et al.*'s results is that some of the genetic and antimicrobial resistance diversity of DT104 in Scottish livestock could have been derived from the human population, the opposite of naïve expectation. Yet there is evidence that bacteria do spread from humans to animals. For example, it has been reported that one lineage of the human pathogen *Staphylococcus aureus* (ST5) spread from humans to poultry (6), and another (CC398) to pigs (7), and hundreds of other bacterial species are known to be shared between humans and livestock (8). Given that most antimicrobial resistance is encoded by mobile genetic elements that permit horizontal transfer between different species of bacteria, there is obvious potential for antimicrobial resistance to move quickly and easily in both directions.

The development of antimicrobial resistance cannot be stopped. It is a natural and

ancient phenomenon that originated independently of either modern medicine or industrialized agriculture (9) and is ubiquitous (10). But can the spread of antimicrobial resistance be slowed? Concerted action will be crucial. Antimicrobial resistance is not just a multidrug, multibug problem (3); it is a multihost, multicountry problem as well. The European Union has been pressing its member states to tackle this issue for many years. This year, in response, the UK Department of Health has published a 5-year antimicrobial resistance action plan (4) that will target veterinarians and farmers as well as clinicians and their patients.

This kind of integrated approach is very welcome. However, the epidemiology of antimicrobial resistance is complex (see the figure) and our understanding of it is largely qualitative (11), making it difficult to provide clear advice to policy-makers. We urgently need more comprehensive, rigorous, quanti-

tative studies such as that by Mather *et al.* to know where best to direct our efforts to deal with this pressing problem.

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MATERIALS SCIENCE

A New Route for Growing Large Grains in Metals

Eric M. Taleff and Nicholas A. Pedrazas

Most metallic materials consist of a network of small single crystals, or grains, connected by grain boundaries. This microstructure, which spans length scales from a few nanometers to hundreds of micrometers, controls many of the properties of the metal. Mechanical processing and thermal treatments can be used to alter this microstructure, but the evolution of grains during processing of a material is governed by phenomena that are so complex (relative to our present scientific understanding) that the outcome cannot be reliably predicted. On page 1500 of this issue, Omori *et al.* (1) describe a wholly unexpected microstructure that arises from synergies among multiple phenomena. They created very large grains in a copper-based shape-memory alloy—a material that will spontaneously recover large strains upon a temperature change—by thermal cycling across temperatures that produce solid-state phase transformations. The subtle mechanisms that apparently act together at elevated temperature to produce this microstructure include internal-stress plasticity

(2) and abnormal grain growth (3). This discovery has potential for technological applications that depend on long service lives of shape-memory alloys.

Particular grain structures are desired to achieve specific material properties. Fine grains are generally desired to increase yield strength (which usually will increase the load that the material can bear), but can also be useful for increasing fracture toughness (resistance to cracking) or enabling tremendous ductility at elevated temperatures through superplasticity (4). In shape-memory materials, incompatibility of deformation between grains undergoing the shape-memory transformation can lead to fracturing along grain boundaries and failure after just a few transformation cycles. This is one example of when extremely coarse grains, even single crystals, are desired. Service life may therefore be increased by eliminating the grain boundaries at which deformation incompatibilities might occur. Omori *et al.* created such a microstructure in the copper-aluminum-manganese alloy $\text{Cu}_{71.6}\text{Al}_{17}\text{Mn}_{11.4}$ through abnormal grain growth induced by thermal cycling, a unique discovery. This finding is just one example of how a better understanding of grain growth

Controlled thermal processing can create alloys with large crystalline grains that can lead to improvements in materials performance.

phenomena can enable the engineering of material microstructures for specific applications. Prediction, control, and design of microstructure is a linchpin of current efforts to implement integrated computational materials engineering strategies in manufacturing (5, 6).

Studies of grain growth have shown a natural division into normal and abnormal growth types (3). In normal grain growth, grain sizes increase uniformly throughout a material by the thermally activated migration of grain boundaries. In abnormal grain growth, one or a few grains grow much faster than others. The mechanisms that cause abnormal grain growth are not well understood, and a further complication is that both grain growth types can occur under static and dynamic conditions (7). Most theories of grain growth have been developed for the static case, in which there is not substantial plastic deformation during growth. The phenomena observed by Omori *et al.* suggest a dynamic situation with concurrent plastic deformation generated by internal stresses. The observation of subgrains—partitions within grains produced by the dislocation structures generated during plastic deforma-

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