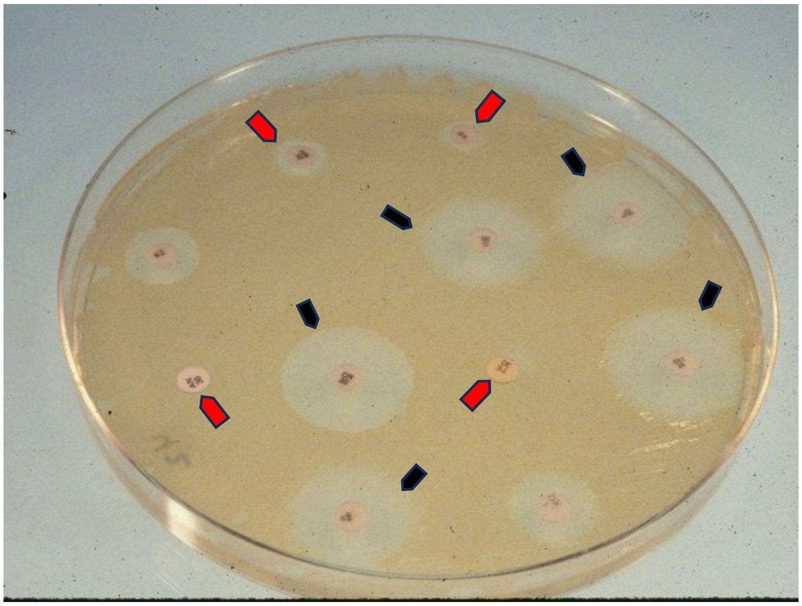
Antimicrobial Resistance Gallery

One Health: Antimicrobial Resistance in the Clinic, on Land and in the Sea

(Felipe C. Cabello and Henry P. Godfrey)



Antimicrobial resistance in *Staphylococcus aureus*. Disks containing antimicrobials placed on an agar plate first spread with *Staphylococcus aureus* cultured from an infected patient and incubated overnight at 37°. Wide halos (black arrows) indicate inhibition of bacterial growth by some antimicrobials. Narrow or no halos (red arrows) indicate growth of bacteria resistant to the antimicrobial being tested. (Photo courtesy of Dr. M.E. Aguero-Rosenfeld)

Antibiotics are "wonder drugs." Antimicrobials stop the growth and kill all kinds of "bugs" (bacteria, fungi and other microorganisms), including those that cause disease in people, animals and plants: the pathogens. Although commonly referred to as antibiotics, these drugs are more broadly referred to as antimicrobials.

Antimicrobials: sources and uses. Antimicrobials were initially synthesized by chemists (sulfa drugs) and later isolated and produced from fungi and bacteria by microbiologists. Later developments led to modification of their antimicrobial activity in many ways and decreased their toxicity in patients. The use of antimicrobials led to rapid decreases in deaths and complications from infections that used to routinely kill many children and grown-ups. These infections included streptococcal sore throat (which often led to rheumatic fever), diarrhea, pneumonia, blood poisoning/septicemia (sepsis), infections of the membranes lining the heart (bacterial endocarditis), infections of the membranes of the brain (meningitis) and tuberculosis. Antimicrobials also began to be used to prevent infections in patients undergoing medical procedures, such as elective surgery (for example, hip replacements), biopsies, cancer chemotherapy and organ transplantation.

First signs of the importance of antimicrobial resistance. Soon after antimicrobials began to be widely used in patients, they became less effective. This was recognized very early. In 1945, the year he won the Nobel Prize for discovering penicillin, Alexander Fleming warned that abuse of antimicrobials would select for antimicrobial-resistant bacteria. Antibiotic resistance in bacterial pathogens, such as *Staphylococcus aureus,* was detected first in hospitals (illustrated above) and health care facilities, and eventually in the population at large. This resistance increased complications, led to longer hospitalizations, and increased deaths from infections. It meant more expensive antimicrobials had to be used to treat infections by these resistant "super bacteria". It also affected many medical procedures where these drugs were used to prevent infections.

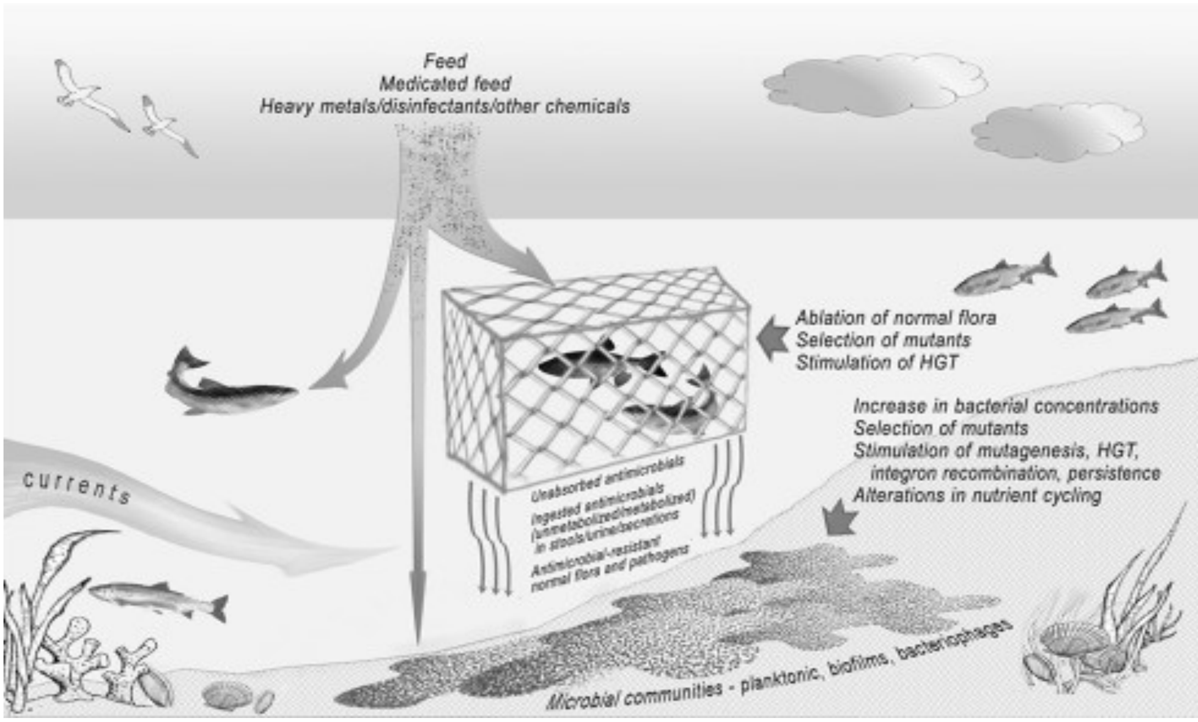
Antimicrobial use in food animal production. A few years after the introduction of antimicrobials for treating people, scientists discovered that adding small amounts of them to pig, cattle, and poultry feed increased the animals' growth rates. The resulting increase in economic returns led to antimicrobial supplementation becoming standard in farming practice. Roughly 70% of all antimicrobials sold are used in agriculture. Antimicrobials also began to be sprayed on fruit trees in orchards to prevent bacterial diseases that decreased fruit production.

Unfortunately, these practices selected for bacteria that could resist their effects. Some of the antimicrobial-resistant bacteria that arose and flourished under these conditions, such as *Salmonella*, *Campylobacter* and *Staphylococcus*, are zoonotic pathogens that can cause infections in both animals and people. More recently, farming of fish and other aquatic animals for human consumption (aquaculture) has rapidly increased, with antimicrobial use in these farms increasing in parallel. This has added the aquatic environment as a new source of antimicrobial resistance on the planet. The multiple effects of this resistance on the aquatic environment and ultimately on our planet's entire environment are illustrated below.

How do microbes become resistant? There are several ways bacteria can become resistant to antimicrobials and become "super bacteria" One is by developing mutations in their DNA. This allows them to adapt to the presence of antimicrobials in their environment. Another is by direct transfer of genes from antimicrobial-resistant bacteria to sensitive ones. This is called horizontal gene transfer (HGT) and allows the recipients of these genes to resist the effects of antimicrobials.

Because the drugs used to treat bacterial infections are becoming less effective, some experts think the millions of deaths caused each year by these resistant bacteria may indicate a return to a pre-antimicrobial era in patient care.

Early studies of antimicrobial resistance. Antimicrobial resistance was initially studied by many scientists. Mary Barber, Richard Novick and Mark Richmond dissected the mechanisms of antimicrobial resistance in *Staphylococcus aureus*. Ephraim S. Anderson, Naomi Datta and H. Williams Smith characterized resistance in zoonotic pathogens such as *Salmonella* and *Escherichia coli*. Stanley Falkow and Stuart B. Levy analyzed the genetics and modes of spread of resistant bacteria and resistance genes from animals to humans. All these researchers called attention to the detrimental role played by excessive antimicrobial use in farming of animals and plants on human health (for more information about these warnings, see *The antimicrobial resistance crisis: a history of unheeded warnings*, by Felipe C. Cabello and Henry P. Godfrey, in this Gallery).



Pathways and effects of administration of antimicrobials in salmon farming. (Figure published in Lancet Infectious Diseases, Vol 16, F. C. Cabello, H. P. Godfrey, A. H. Buschmann, H. J. Dölz, Aquaculture as yet another environmental gateway to the development and globalization of antimicrobial resistance, pp. e127-133, Copyright © Elsevier Ltd 2016).

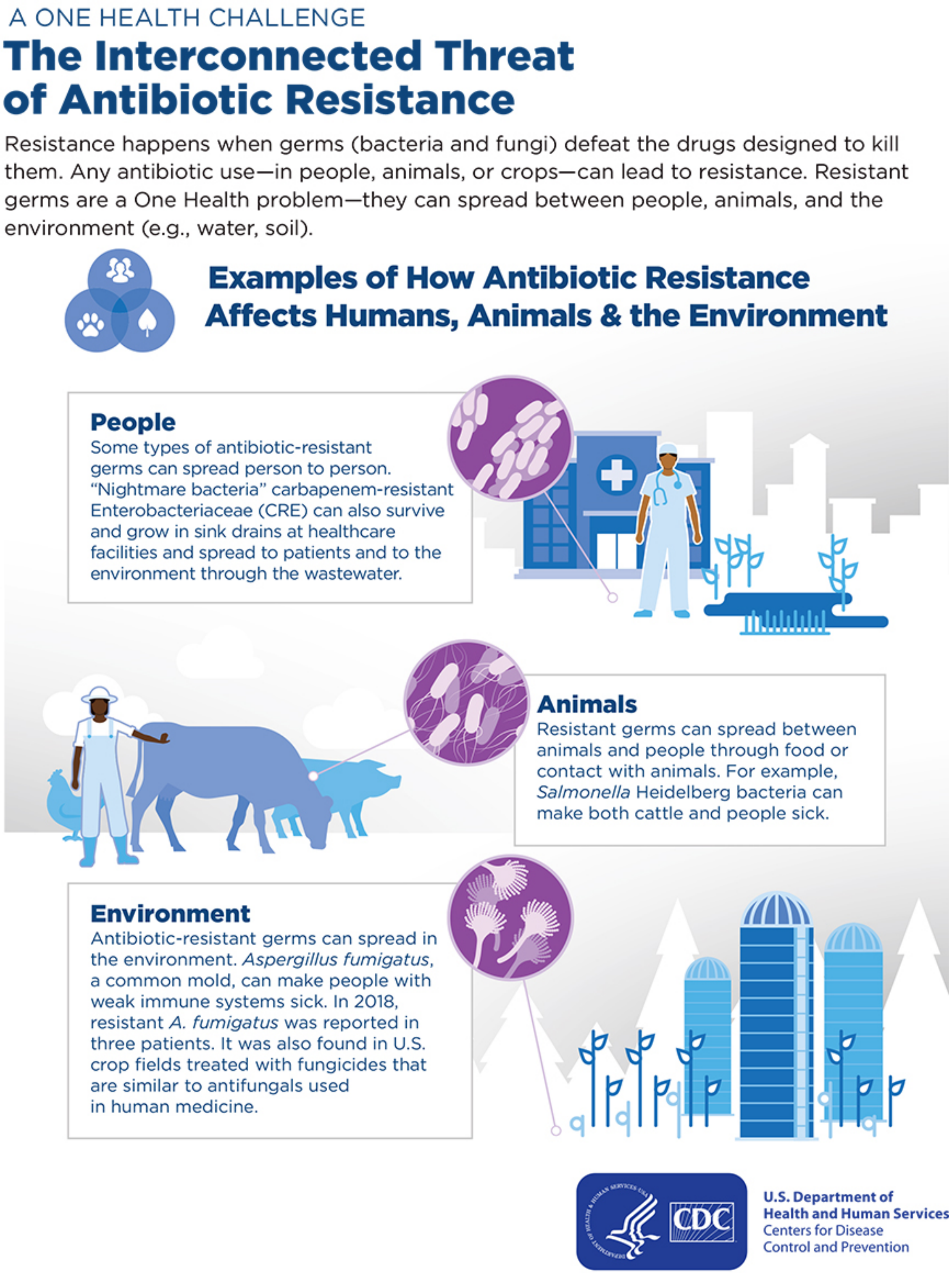
Industrial scale non-clinical use of antibiotics in the raising of food animals. Industrial farming on land, in fresh water, and in the ocean raises large numbers of animals under highly confined conditions. These animals are more likely to develop infections because of the stress of confinement and physical closeness to other animals, conditions which also favor transmission of infections.

To prevent and treat these infections, farmers are using larger and larger amounts of antimicrobials. The use of such large amounts may even favor development of infections because they reduce population sizes of some members of the normal bacterial flora of skin and mucous membranes in these animals. This normal surface flora constitutes a second skin that serves as a barrier to colonization by pathogens and plays an important defensive role against infections. Antimicrobial-provoked disturbance of the normal surface flora generates an imbalance (dysbiosis) - chinks in the armour - which allows entry of pathogens and helps bring about infections.

The use of large amounts of antimicrobials in the production of food animals also selects for antimicrobial-resistant zoonotic pathogens that can also infect people and hence promotes the transfer of difficult-to-treat infections from animals to humans. Such pathogens can contaminate the meat, eggs, milk, and fish which can then infect people handling them. Food handlers can also transmit food-borne infections to others. Since cooking kills most pathogens, infections can either result from eating contaminated raw food such as beef tartare, sushi or shellfish, or from poor hygiene (pathogens transferred to someone preparing food who then contaminates uncooked ingredients or already cooked food).

Antimicrobial resistance and One Health. Because antimicrobial use in farm animals can be cost effective, its damaging aspects were originally denied by the farming and food industries. They were only generally accepted after being confirmed by molecular methods involving DNA sequencing. Both antimicrobial-resistant bacteria and antimicrobial resistance genes are now seen as circulating freely between animals, humans, plants, and the environment. This means bacterial resistance arising in any single place (hospital, terrestrial farm, freshwater, and ocean aquaculture) can impact the entire biosphere.

The environment is a reservoir of bacteria with new and unknown antimicrobial resistance genes that may pass by horizontal gene transfer to human and animal pathogens. The interdependence of all living things (humans, animals, plants, microorganisms) and the environment underlies the concept of One Health. Animals therefore must be raised under conditions that protect their well-being to avoid excessive use of antimicrobials if the health of humans and the environment is to be preserved.



The interconnected threat of antibiotic resistance.
(https://stacks.cdc.gov/view/cdc/120252/cdc_120252_DS1.pdf)