Box 1 Action points to counter antibiotic resistance

In its September report, "Antibiotic Resistance Threats in the United States, 2013," CDC officials identify four core actions to combat the public health threat from antibiotic resistance.

- **Preventing infections, preventing the spread of resistance.** Avoiding infections reduces the amount of antibiotics that have to be used and the likelihood that resistance will develop. Drug-resistant infections can be prevented by immunization, infection-prevention actions in healthcare settings, safe food preparation and handling, and general hand washing.
- **Tracking.** CDC gathers data on antibiotic-resistant infections, causes of infections, and whether there are particular reasons (risk factors) that cause some people to get a resistant infection. With that information, experts can develop strategies to prevent those infections and prevent the resistant bacteria from spreading.
- **Improving antibiotic use/stewardship.** Perhaps the most important action needed to greatly slow the development and spread of antibiotic-resistant infections is to change the way antibiotics are used. Up to half of antibiotic use in humans and much of antibiotic use in animals is unnecessary. The commitment to always use antibiotics appropriately and safely—only when they are needed to treat disease—and to choose the right antibiotics and administer them in the right way in every case is known as antibiotic stewardship.
- **Developing drugs and diagnostic tests.** Because antibiotic resistance occurs as part of a natural process in which bacteria evolve, it can be slowed but not completely stopped. Therefore, new antibiotics will always be needed to keep up with resistant bacteria, as will new tests to track the development of resistance.

The full CDC report is available at http://www.cdc.gov/drugresistance/threat-report-2013/.

and to drive up costs for their care by as much as $45 billion.

Blocking toxins or virulence factors "makes sense as an approach," says Lynn Silver, a consultant to several biotech companies working on antimicrobial products, who is based in New Jersey. "As to commercialization, it depends upon the prevalence, severity and lack of other treatments for the particular bug." And the model for evaluating efficacy is "also very important and whether the virulence factor is present in all members of the species. But, chosen well (and maybe chosen semi-empirically) the approach has promise."

"It's a high-risk strategy with no proof of principle from animal models," says David Shlaes, principal of Anti-Infective Consulting in Stonington, Connecticut. "So the first time that you will see if it's working will be during phase 2 trials. That's the problem." Synagis, which targets respiratory syncytial virus, is used to prevent, not treat established infections, he adds. "It doesn't work for therapy in people but does in animal models [because] RSV is not an animal virus so it's a poor model…and with treatment the virus just goes away faster. So, the overall idea of targeting bacterial virulence factors in theory is fine, but it's high risk without a predictable pathway for applying it."

In the case of *S. aureus*, three mAb-based products are under active development—one by Aridis of San Jose, California, licensed from Kenta Biotech in Zurich; a second by Alopexx of Cambridge, Massachusetts, in partnership with Sanofi-Aventis of Paris; and a third by MedImmune that completed a phase 1 clinical trial. For *P. aeruginosa*, four antibody-based, toxin-targeting products are under development: one from Aridis/Kenta; a second from Kalobios of S. San Francisco, California, in collaboration with Sanofi-Aventis that is in phase 2 clinical testing; a third product consisting of a mixture of up to ten mAbs from Symphogen of Copenhagen, working with Meiji of Tokyo, that is preclinical; and a bispecific mAb from MedImmune that also is in preclinical development.

More generally, there is a shift towards pathogen-specific antimicrobial drugs, after decades in which antibiotics with broad-spectrum activity were dominant and pretty much favored by doctors and thus sought by pharma. This more recent trend to acknowledge the value of conventional candidate antibiotics with narrow activity could prove helpful as highly targeted anti-infective mAbs come before FDA and other regulatory officials in Europe or elsewhere.

Even so, new regulatory guidance, including for the design of clinical trials involving such mAbs will likely be needed, particularly when evaluating those mAbs whose clinical effectiveness will benefit from being paired with conventional antibiotics, according to Ken Stover, a senior director at MedImmune. Advantages in using such mAbs include their specificity of action, safety—including no drug interactions—and their lack of resistance or cross-resistance with other antimicrobials, he says. Further, they can be "engineered" to have long half-lives or to exert effects, say, on host immune-system cells. Earlier efforts to develop such anti-infectives failed because investigators chose "bad targets, and the antibodies weren't very good," he adds.

IN brief

GM crop protection act fizzles

A legislative provision designed to protect growers of biotech crops from the whims of US courts expired in late September, following an overblown public relations attack from special interest groups. The provision allowed farmers to continue growing a genetically modified (GM) crop whose approval might be subsequently invalidated by a US court (*Nat. Biotechnol.* **31**, 479, 2013). The law followed two high-profile cases—Roundup Ready alfalfa and sugar beets—in which US courts halted planting of the deregulated crops after finding that the US Department of Agriculture's (USDA) environmental review was insufficient. Growers were left in limbo while the USDA completed its court-ordered environmental impact statement, which took years and concluded in both cases that there was no environmental impact. The temporary provision was intended to avoid such situations in future and provide continuity for farmers, who make planting decisions several seasons in advance. But special interest groups launched a public attack on the law, dubbing the provision the "Monsanto Protection Act," as the crops in the court cases were products of the St. Louis–based agbiotech company. The attackers declared victory when the provision, section 735 of a temporary spending bill passed in March this year, was allowed to expire with the bill at the end of September. These groups blew the issue out of proportion, says Jon Entine, director of the Genetic Literacy Project at George Mason University in Fairfax, Virginia. "This became a public relations gambit by anti-GMO activists," he says. "It's a symbolic issue rather than a real one." Besides, the USDA already possesses the power detailed in the controversial provision. In the sugar beets case, USDA allowed the crop to be grown on a limited basis while the agency finished its environmental review. It's not worth the battle to try to get the provision attached to another bill, says Greg Jaffe, director of biotech at the Center for Science in the Public Interest in Washington, DC. "I would hope the provision just goes away since all it did was cause controversy." *Emily Waltz*

IN their words

"Mine is not a fantasy look at the future. The goal isn't to imagine this stuff. We are the scientists actually doing this." Craig Venter describes his latest invention, the Digital Biological Converter (described in his new book, *Life at the Speed of Light*), a device that could create vaccines and other DNA-based therapeutics on demand. (*The Guardian,* 12 October 2013)

"We get people in, they almost take the ring, they're at the altar, and then they realize they have to divest everything." Janet Woodcock, head of the FDA's Center for Drug Evaluation and Research. In response to speculation that she might retire in the next few years, Woodcock describes how the requirement that employees refrain from investing in FDA-regulated companies makes recruiting difficult. (*Reuters,* 10 October 2013)