Antibiotic resistance and the resulting risk for ineffective treatment of infections are serious and growing problems. The national and international efforts by governments and nongovernmental organizations are many and high-powered. For example, the Transatlantic Task Force on Antimicrobial Resistance was established by joint presidential declaration in 2009 by the European Union and US presidencies. It issued recommendations in 2011 for collaborative efforts to fight antibiotic resistance. In the US, the federal Interagency Task Force on Antimicrobial Resistance updated its “A Public Health Action Plan to Combat Antimicrobial Resistance” document in 2011. Despite these and many earlier efforts, antimicrobial resistance continues to increase, as does public awareness of the issue. In this Q&A article, 5 experts with different roles have been asked to address several questions about antibiotic resistance, including questions focusing on how to best combat this growing problem.

We frequently see frightening reports about antibiotic resistant bacteria in the media. How serious is the problem of antibiotic resistance?

David Hooper: Antimicrobial resistance in bacteria is a serious problem in healthcare today. Although most patients with infection will not necessarily have a resistant one, bacterial resistance can occur in a substantial minority of infected patients and particularly those who have other underlying health conditions, frequent hospitalizations, or recurrent exposures to antimicrobial agents. Methicillin-resistant Staphylococcus aureus (MRSA) is widespread in patients in hospitals and is sufficiently common in the community that for patients with serious infections, alternative antimicrobial agents, such as vancomycin, must be part of treatment until specific microbiologic data about susceptibility are known. Resistance to vancomycin also occurs commonly in Enterococcus species, another common hospital pathogen. Perhaps most concerning is the emergence in some patients of multidrug-resistant infections with gram-negative bacteria, for which few or no active therapies are currently available.

Alfred DeMaria: I agree that antimicrobial-resistant pathogens are a serious clinical and public health problem worldwide. The problem is not that antimicrobial-resistant organisms are “super bugs” in the sense of virulence (causing more severe disease), but rather it is in the sense of causing infections more difficult to treat effectively and thereby having more serious consequences. Infections are worse because they may not be promptly treated with effective agents because the drugs used empirically (pending susceptibility testing) are not effective. The development of new antimicrobial agents has been much less robust than in the past. The most effective and safe agents have already been developed, and newer effective agents often have more toxicity and other drawbacks, including higher cost. The problems associated with antimicrobial resistance are not limited...
to bacteria. The issue has become critical in the treatment of infection due to viruses, fungi, and parasites as well.

What are the factors contributing to the problem of antibiotic resistance?

Brandi Limbago: I think there’s really only one factor driving this problem: antibiotic use. Even when antibiotics are used appropriately, their use can select for resistant bacterial populations. But widespread abuse of antibiotics, including overprescribing in humans and use in animal feed, accelerates the problem by promoting antimicrobial resistance to many different agents among both pathogenic and nonpathogenic bacteria. This pool of resistant organisms can serve as a reservoir for new resistance mechanisms in pathogenic organisms. People infected or colonized with drug-resistant pathogens can then transmit these organisms. This is particularly problematic in healthcare settings, because hospitalized patients often have risk factors that make them susceptible to serious infections, which in turn necessitates more antibiotic use and provides more opportunity for transmission. It’s a vicious cycle.

Thomas F. O’Brien: When use of each new antibiotic began, laboratories rarely found bacteria resistant to it, but genes encoding such resistance already existed. They existed as unselected mutants, which use of the antibiotic would then select for, or in obscure bacteria, from which resistance traits would mobilize and be transferred to bacteria that would infect people. Every step in the process of selection, mobilization, or eventual global spread was driven by the enormous amplification of antibiotic selection.

The extent of antibiotic resistance at any time can be seen as some function of how many bacteria had until then encountered an inhibitory concentration of an antibiotic. If fewer had, then resistance would be less advanced or would have taken longer to become this far advanced—giving more time for a rescuing antibiotic to arrive. This factor can be divided into subfactors altering routes or rates of spread, such as personal hygiene and food safety, but all depend on selection.

David Hooper: Bacteria are very versatile and adaptable, and in the case of antimicrobials that are natural products produced by other microbes, resistance is likely to have emerged in nature. Thus, environmental and commensal bacteria represent natural reservoirs of resistance determinants. Bacteria can transfer resistance genes among themselves, often on plasmid DNA that contains multiple resistance genes leading to multidrug resistance. In the context of this dynamic reservoir of resistance, factors that contribute to resistance in human pathogens include (1) use of antibiotics, which may select for and amplify preexisting resistant bacteria, and (2) spread of resistant pathogens from person to person.

Where do people acquire infections by antibiotic-resistant bacteria?

Alfred DeMaria: The most important source of infection with resistant organisms in people is other people. While antimicrobial resistance may, as would be expected, emerge in an organism colonizing or infecting an individual being treated with an antimicrobial agent, more often people acquire resistant organisms from others or a contaminated environment. The opportunities for such exposure were always higher in healthcare settings, with juxtaposition of vulnerable patients and high utilization of antibiotics. At one time, multidrug-resistant organisms were mostly a problem in acute-care hospitals, but now because of the broad spectrum of care settings and movement of patients, the problem is wider, inclusive of home, transitional, rehabilitation, and long-term care settings.

Brandi Limbago: Most infections with antibiotic-resistant bacteria happen in healthcare settings, due to the selective pressure created by high antibiotic use and the presence of both drug-resistant donor organisms and very susceptible patients. Colonized and infected patients often transition between hospitals and long-term care facilities, which can facilitate the spread of resistant organisms among many facilities in a region. This is one reason that it is important to have situational awareness of the extent of the antibiotic resistance in a given region.

How do you interpret the 2 studies that come to apparently different conclusions about the value of interventions to prevent transmission of MRSA in hospitalized patients [N Engl J Med 2011;364:1407]
(Huskins et al.) and N Engl J Med 2011;364:1419 (Jain et al.)?

David Hooper: The reasons for the differences in the outcomes of these 2 studies are likely multiple, including differences in trial design, compliance with the planned intervention, and overlapping interventions, as discussed in a 2011 editorial in the New England Journal of Medicine by Richard Platt. As tests of the effectiveness of broad surveillance of patients for carriage of MRSA, these studies leave unresolved the controversy about the value (in improved outcomes balanced against operational and other costs) of such a surveillance strategy and highlight the importance of future evaluations. The effectiveness of the several interventions in the study by Jain et al. deserves further evaluation to understand the relative contributions of each of the components of the employed bundle of infection-control practices to the improved outcomes. In my experience related to a program resulting in substantial and sustained improvements in hand hygiene before and after patient contact that were followed by major reductions in hospital acquisition of MRSA, I think system-wide approaches with buy-in and participation of a broad range of care providers and senior management are particularly important for interventions to be effective in complex healthcare environments.

Betsy McCaughey: Numerous studies confirm that you cannot control the spread of MRSA unless you know the source. Screening incoming patients is key to prevent patients from shedding drug-resistant bacteria on bedrails, wheelchairs, floors, or wherever they go. So why did the 2 studies yield such different results? The study by Huskins et al. had a fatal flaw: delay in delivering the culture results to the intensive care units (ICUs). Patients were cultured within 2 days of admission, allowing plenty of time for colonized patients to shed bacteria. Worse, the mean time from taking the culture to reporting the result was 5.2 days. For the majority of patients, their ICU stay was more than half over. Had patients been preemptively isolated until their culture results came back, that problem could have been avoided.

Delay can defeat the purposes of screening. A 2008 study in the Journal of the American Medical Association by Harbath et al. grabbed headlines when it purported to prove that screening is ineffective. But the study had the same flaw. Many patients did not receive their test results until halfway through their hospital stay, and 31% of MRSA-positive patients had already had their surgeries before getting their test results.

The study by Jain et al. may exaggerate the impact of screening at typical acute-care hospitals. An astounding 13.6% of incoming Veterans Affairs patients were carrying MRSA, far higher than the general US population. Therefore, screening identified many more carriers than it would in a more typical hospital setting.

Thomas F. O’Brien: The study by Huskins et al. seems complicated by the need to manage a large number of variables, many of them involving estimates of caregiver compliance to the protocols. The discussion thoughtfully points out possible reasons for the study’s failure to find an expected reduction in rates of colonization for the more stringent precautions, including slow culture turnaround time that extended the unprotected time before initiation of precautions. The study by Jain et al., a multi-intervention effort to prevent MRSA infections across the whole Veterans Affairs healthcare system seems more clear-cut, positive, and convincingly successful. The substantial reduction in infection rate reported would be exemplary—even if the antecedent rate were higher than average.

Do you think that hospitals should be required to report their rates of hospital-acquired infections by antibiotic-resistant bacteria to public health authorities? Should this information be made publicly available with identification of the specific hospitals?

Betsy McCaughey: Yes. Secrecy allowed the problem of hospital infections to fester for too long. The Committee to Reduce Infection Deaths has aggressively campaigned for disclosure of hospital infection rates. There is no reason to restrict reporting to drug-resistant infections. Reporting should include Clostridium difficile, for example.

David Hooper: To improve the quality of patient care, it is necessary to collect and analyze data and ultimately to hold healthcare workers and institutions accountable for their practices. Reporting can be an important component of accountability, and reports are most easily interpreted when they relate to compliance with established procedures that should be consistently followed. Reporting of outcomes such as resistant infections, however, is more complex because of variation in patient populations and the complexity of care provided that affect risks of prior carriage and new acquisition of resistant bacteria and the risks of hospital-acquired infections from them. Standardized reporting
of compliance with best practices to public health authorities and to the public is important. Outcomes reporting has a greater potential for misinterpretation because of modifying factors not necessarily under the control of the institution and should be directed to public health authorities, who are in a position to understand and evaluate the complexities. Public reporting of rates of antibiotic-resistant bacteria, however, has considerable risk of misinterpretation and unintended consequences that could impede the common goal of improving quality of patient care.

Alfred DeMaria: In many states, certain healthcare-associated infections are mandated for public reporting by facility, with data on infecting organisms. The Centers for Medicare and Medicaid Services require public reporting of a number of quality indicators, including infections, as a condition for participation and enhanced financial compensation. Such transparency can be a stimulus to enhanced quality improvement. States have attempted to do public health and population-based surveillance for antimicrobial-resistant organisms in various ways. This is difficult because of the multiple organisms that cause infection, the multiple antibiotics used in testing, and the multiple mechanisms of resistance. As electronic support for such surveillance becomes more robust, the opportunity for antimicrobial-resistance surveillance will expand, and useful and actionable information may be available for public health measures.

A report issued by the Institute of Medicine in 2003 (“Microbial Threats to Health: Emergence, Detection, and Response”) recommended that the “FDA ban the use of antimicrobials for growth promotion in animals if those classes of antimicrobials are also used in humans.” What should the US Food and Drug Administration (FDA) do to regulate the use of antibiotics used to promote growth of farm animals?

Alfred DeMaria: Scientific and medical organizations have advocated for decades for a ban on use of antibiotics for growth promotion in animals. Resistant organisms do emerge under nontherapeutic use of antibiotics in animals, but the contribution of this source of antibiotic resistance in human pathogens remains controversial. The FDA published a draft guidance (“The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals”) for comment in 2010, proposing limiting the use of antibiotics that are used in human medicine to preventive and therapeutic veterinary applications under veterinarian control. The FDA came close to banning penicillin and tetracycline agents in animal feed at the end of 2011, but backed off and closed hearings that had opened in 1977. They proposed banning nontherapeutic cephalosporins in early 2012. The Europeans banned antimicrobials used in human medicine from animal feed in 1998 and all antibiotics in 2006, with little economic impact (in part due to subsidy and consumer support) and some benefit in terms of reduced resistance. So it can be done and would be a sensible action to reduce antimicrobial resistance.

Thomas F. O’Brien: The FDA should ban them—finally—as has been recommended by many responsible groups for a very long time. The practice exposes enormous numbers of bacteria to varying concentrations of antibiotics indefinitely—the major driver of antibiotic resistance, as discussed above.

Brandi Limbago: I think that the use of nontherapeutic antibiotics in any setting is a bad idea. The only argument for the use of growth-promoting antibiotics is an economic one, and I don’t think higher returns for producers or lower meat prices are worth the public health cost of increasing antibiotic resistance. Resistance will develop even when antibiotics are used appropriately, but we can preserve the efficacy of our antibiotics by saving them for use against clinical infections.

What do you think are the most important things that can be done to reduce the problem of antibiotic resistance?

Thomas F. O’Brien: While things (hygiene, food safety, etc.) can be done to seclude individuals from colonization with resistant bacteria, the magnitude of resistance can be reduced or at least delayed only by reducing exposure of bacteria to antibiotics. Antibiotic-resistance genes spread through the world in successive irregular epidemics, so reducing antibiotic use anywhere would help, but reducing local use is likely to help more locally. Doing everything would include reducing unregulated usage in the developing world, where many of the epidemics seem to originate, and continuing to reduce unnecessary use in medical and agricultural practices.

Betsy McCaughey: Bacteria have been morphing since the beginning of time. We will not always win the race to produce more effective antibiotics. Therefore, it is critical to improve hygiene in healthcare settings to shield patients from infection.

Brandi Limbago: For too long people have viewed antibiotics as posing very little risk while promising to solve our infectious disease ills. I think we are beginning to understand that indiscriminate antibiotic use comes at a cost, and if we want these agents to be avail-
able in the future, we need to be more judicious with their use now. Patients and consumers can stop demanding antibiotics from their healthcare providers, physicians can ensure that antibiotics are necessary and can prescribe the most narrow-spectrum agents, hospital administrators can provide support and resources for infection control programs to limit the spread of resistant pathogens in healthcare settings, and we can all do a better job washing our hands.

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