The Health Provider's Role in Antibiotic Stewardship

Confronting Global Antibiotic Resistance

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The Unravelling of the 'Antibiotic Miracle'

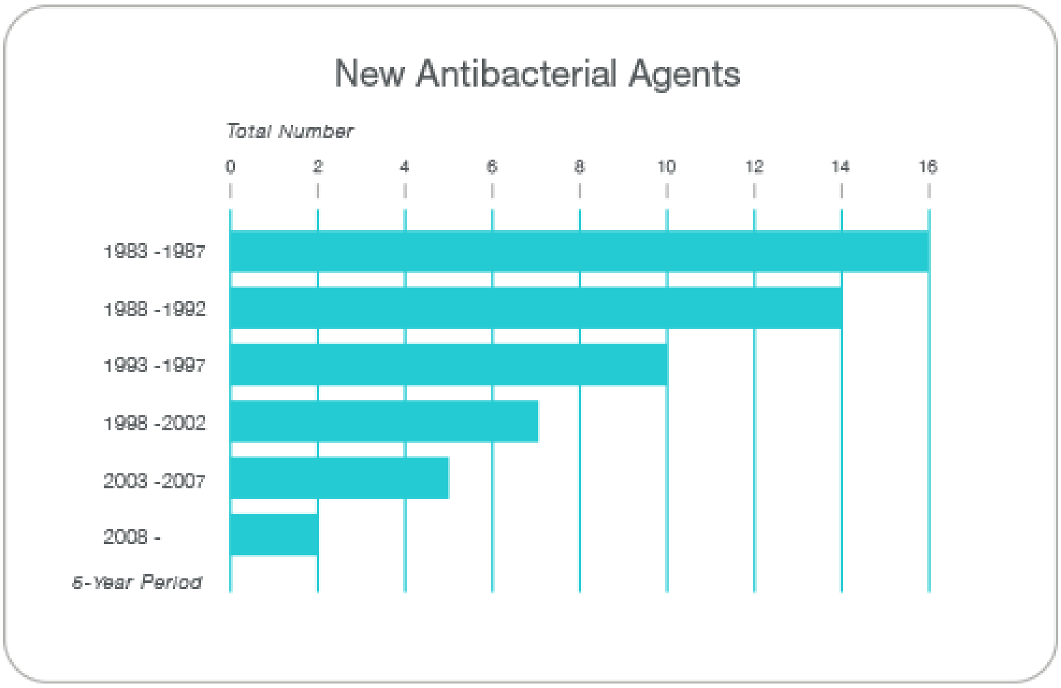
Today's global crisis in antimicrobial resistance should never have come as a big surprise. In 1945, 17 years after Alexander Fleming announced his monumental discovery of penicillin (1928), he wrote:

"The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out….In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted." — *Alexander Fleming*

70 years of antibiotic use have borne out his dismal prediction. Today, antibiotic resistance has risen to one of the top three global health problems, and with it, substantial healthcare and economic impacts[1,2] – the consequence of decades of imprudent antimicrobial use in hospitals, clinics, farm food animals, aquaculture and agriculture.

In addition, the developing world is burdened by rampant self-medication from unregulated over-the-counter sales. One by one, we have watched the gradual undermining of multiple classes of antimicrobial drugs, starting with the sulfonamides and followed by the penicillins and tetracyclines. With a serious deficit of new antimicrobials emerging from the antibiotic pipeline, some researchers predict an ominous return to the pre-antibiotic era.[3] (Fig. 1)

Fig. 1 New antibacterial agents approved in the United States, 1983–2013

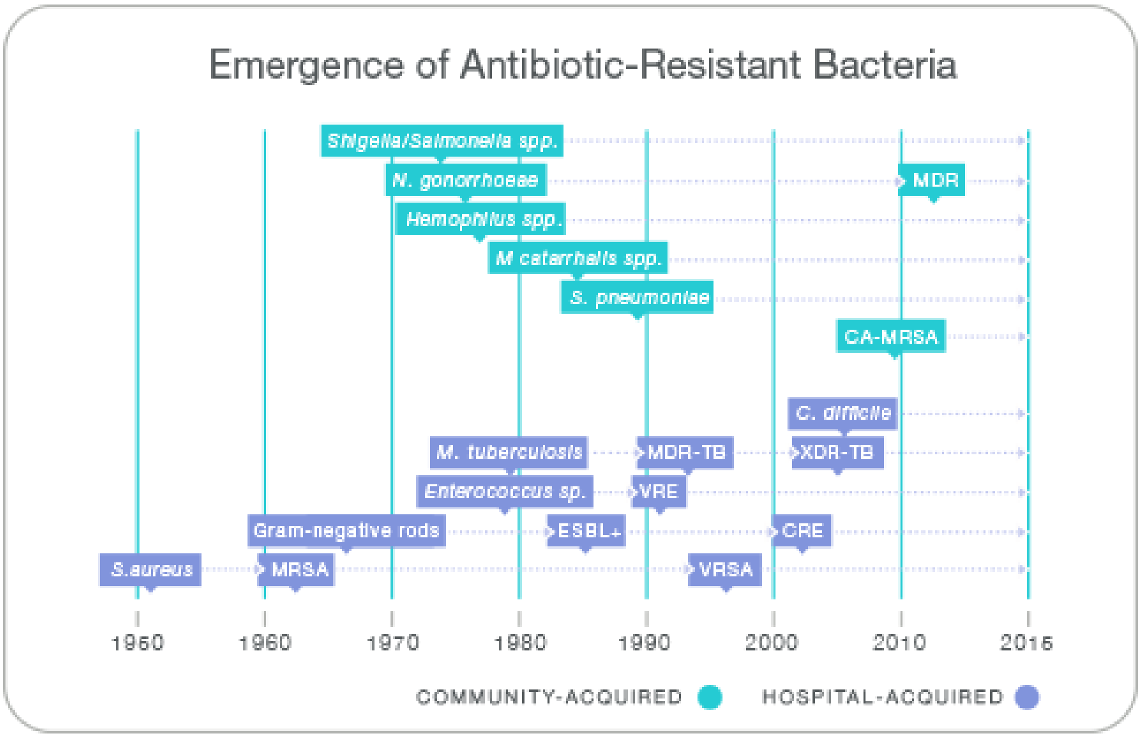


Source: adapted from Spellberg, B. *et al*. (2008) The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clin infect Dis* 46:155-64.[1]

As of 2011, the estimated annual sales of antimicrobials was ~36 million pounds (lbs.) in the US alone (28.9 million sold for animals and 7.3 million for treating sick people), 70% of which is not utilized for disease treatment, but rather for purposes of growth promotion and prophylaxis in farm food animals.[4]

This use, in conjunction with the major driving force of overuse and misuse in humans has given rise to an era of "superbugs" – organisms that are resistant not only to multiple drugs, but in some cases, to every, or all but one, "last resort" antibiotic (Fig. 2). Life-threatening, antibiotic-resistant infections have even forced a reversion to the use of older drugs that were largely abandoned because they were considered too toxic for regular use.

Fig. 2 Emergence of resistance in hospital- and community-acquired pathogens0



MRSA: methicillin-resistant *Staphylococcus aureus*; VRSA: vancomycin-resistant *S. aureus*; ESBL+: extended-spectrum beta-lactamase producers; CRE: carbapenem-resistant *Enterobacteriaceae*; VRE: vancomycin-resistant enterococcus; MDR-TB: multi-drug resistant *M. tuberculosis*; XDR-TB: extensively drug-resistant *M. tuberculosis*; CA-MRSA: community-acquired methicillin-resistant *S. aureus*.

Source: adapted from Cohen, M. *et al.* (1992) Epidemiology of drug resistance: implications for a post-antimicrobial era. *Science* 257:1050-1055.[2]

According to the World Health Organization (WHO), there are no global data on the number of cases or fatalities due to highly resistant pathogens. These gaps in knowledge regarding the economic and human cost of resistant bacterial infections are due to the lack of any coordinated global surveillance system.

In the U.S. alone, superbugs affect more than 2 million individuals and contribute to 99,000 deaths each year.[5] In the European Union, at least 25,000 patients die every year from multidrug-resistant pathogens[6]; two-thirds of these are due to gram-negatives. Once confined almost exclusively to the hospital environment, superbugs such as MRSA and *Clostridium difficile* are now emerging in the community setting.

"More people now die each year of hospital acquired infections than of AIDS, traffic accidents and the flu combined."
- Center for Disease Dynamics, Economics & Policy (CDDEP)[5]

The total medical and societal costs of treating these resistant infections have escalated dramatically and are now estimated at $16.6-26 billion in the U.S.[7] and at least €9 billion in the EU.[8] For *Clostridium difficile* infection alone, the annual excess hospital healthcare cost is estimated at $1.1 billion in the U.S. and €3 billion in the EU.[9]

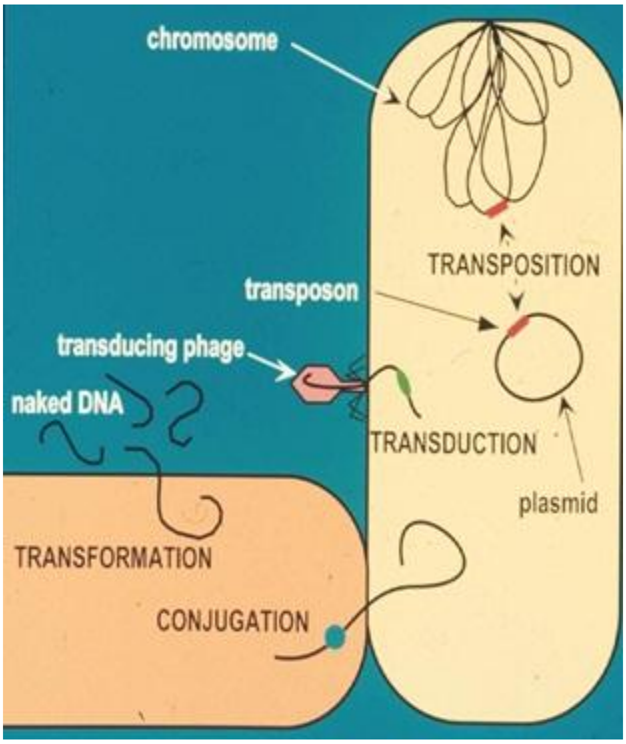
The Societal Effects of Antibiotic Use

Antibiotics are 'societal drugs'—that is, their effects are not solely confined to the individual that consumes them.[10] They are unlike other pharmaceuticals designed for non-infectious illnesses of the individual, such as diabetes, heart disease, and cancer, for example.

Antibiotic selective pressures are far reaching, and result not only in the transmission of pathogens from individual to individual, but in the promiscuous transfer of mobile, intracellular genetic elements that code for antibiotic resistance.

While some bacteria are naturally resistant to certain classes of antibiotics (i.e. chromosomal-mediated resistance), others may become resistant – either by genetic mutation or by acquiring resistance genes from another bacterium (Fig. 3).

Fig. 3 Mechanisms of DNA exchange between bacteria



Source: adapted from Levy, S.B. (2002) The Antibiotic Paradox - How the misuse of antibiotics destroys their curative powers. Perseus Publishing. p84.[10]

Multiple mechanisms readily permit the transfer of genetic elements carrying resistance genes (colored shapes) between bacteria. Transformation allows the uptake of external naked DNA, while bacterial viruses (phage) inject foreign DNA via transduction. Conjugation, a bacterial "mating" process, permits transfer of a linearized plasmid and its resistance gene(s) across juxtaposed bacterial cell walls. In transposition, a resistance gene (transposon) "hops" from a plasmid and becomes incorporated into the bacterial chromosome, where it can stably pass to successive generations.

In both cases, the resistance traits may spread through bacterial populations either 'vertically', by passing them to new generations, or 'horizontally', through the exchange of gene segments with other bacteria. Over time, assorted resistance genes may congregate and package themselves into DNA 'cassettes' that confer multiple resistances and can transfer horizontally en mass to similar, or even very different bacterial species.

Additionally, the escalating pollution of the environment with low-level antibiotic residues in soils, water, sewage and sludge is operating as a selective force to trigger mutations and to promote gene exchange and proliferation of resistant cells that have acquired these genetic elements. A dramatic case-in-point for this accumulation of resistance genes is demonstrated by the gram-negative bacterium *Acinetobacter baumannii*. 30 years ago, this organism was totally susceptible to antibiotics. Today, through promiscuous horizontal gene transfer, this species has amassed forty-five genes from a variety of bacterial genera and expanded its genomic island by 66Kb—emerging as a serious multi-drug resistant pathogen causing 2-10% of gram-negative nosocomial infections in the U.S. and Europe.[11]

Antimicrobial Stewardship: The need for a holistic approach

While many reports paint a gloomy outlook for the future of antibiotics, others are more optimistic that innovative research and careful drug management can reverse, or at least slow the negative trends—if global efforts are focused on recognizing and controlling the antibiotic resistance problem. In its broader holistic sense, antibiotic stewardship is the careful and responsible management of antibiotic resources in the interest of long-term sustainability.

Aggressive stewardship at international, national and institutional levels is imperative for preserving antibiotic efficacy, improving healthcare outcomes, and reducing healthcare costs. While grass roots activists work to bring legislation that will reduce antibiotic use in food animals[12,13] and thereby lower antibiotic contamination of the environment, it is imperative that hospitals, community healthcare workers and the public access the knowledge for rational use of antibiotics, and more importantly, initiate and consistently implement interventions and practices that will reduce the unnecessary use of antibiotics, now estimated at >50%.[8]

Numerous countries have championed national stewardship programs—with diverse strategies and varying degrees of success. Belgium's experiments in mass media campaigns resulted in a 36% decline in antibiotic prescriptions. This prompted France to initiate its own successful *Antibiotics are not Automatic Anymore* campaign, which is directed at the public and general practitioners, particularly in the implementation of rapid strep diagnostic tests for upper respiratory infections.

Other programs, e.g., Sweden's effective *STRAMA* initiative, the newly evolving *Vietnam Resistance Program (VINARES)*, South Africa's *Best care…Always!* and the EU's ABS International, focus primarily on hospital-based stewardship efforts. In contrast, the *Get Smart: Know When Antibiotics Work* campaign in the U.S. is an example of an ongoing, multi-faceted approach that targets the general public, as well as healthcare facilities.[14-19]

Within the healthcare facility, antimicrobial stewardship refers to measures that promote the selection of an antimicrobial drug regimen that will achieve the best clinical outcome. Optimal drug regimens require accurate decisions on dosing, duration and route, and at the same time, attempt to minimize toxicity to the patient, as well as curtail the selective pressure that creates antibiotic resistance.

Ideally, an antimicrobial stewardship program (ASP) should be comprehensive and encompass the full chain of care-givers. This would include the pharmacist, laboratory technologist, attending physician, nurses, and housekeeping and infection control teams. The concerted efforts of all players, working with approved guidelines and often aided by a state-of-the-art information technology system, can have highly beneficial outcomes. Multiple studies have demonstrated how effective stewardship teams can reduce the incidence and prevalence of nosocomial infection, decrease hospital costs and favorably impact hospital resistance profiles.[20,21]

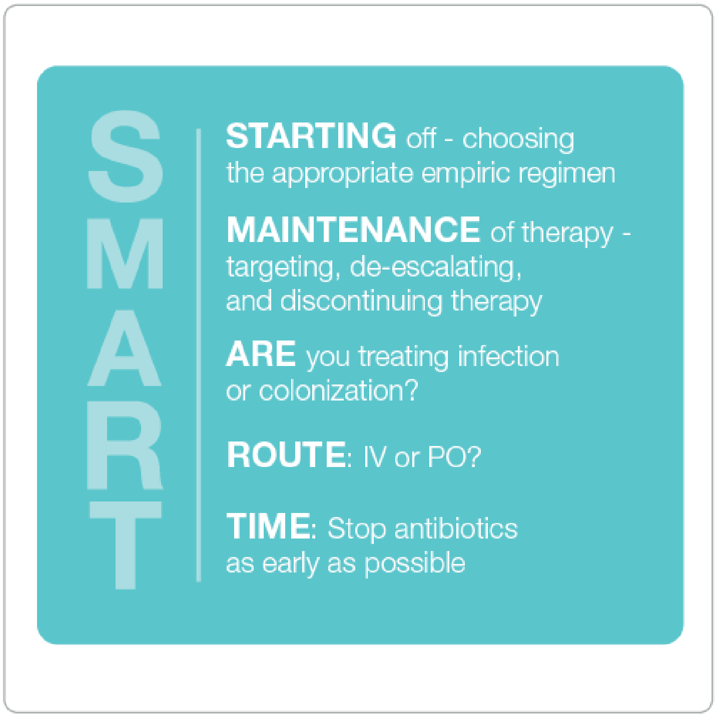
However, a 2009 survey of 3,500 practitioners in various hospital settings found only 48% of U.S. hospitals had an antimicrobial stewardship program in place, and these were more common in teaching hospitals than non-teaching ones (78% vs. 17%). As more than 80% of registered U.S. hospitals are the latter, the great majority does not have an ASP, but some do have certain components in place, such as an antibiotic formulary (66%), or required approvals from ID physicians (28%) or clinical pharmacists (21%) before dispensing.[22]

Building an antimicrobial stewardship strategy

Prevention of infection is always the best measure to reduce antibiotic use. Thus, education on optimal hygiene is essential and cannot be overemphasized, both in the community and the hospital.[23,24] Hand hygiene is effective at reducing diarrheal and respiratory infections, and when integrated with environmental hygiene measures and other infection prevention interventions, has been shown to prevent potentially fatal infections from spreading among patients, and between patients and healthcare workers.[24,25]

When infection does arise, however, it is first and foremost essential to know when antibiotics will work. Antibiotics are only effective in treating bacterial infections and use for any viral infections such as colds or flu is inappropriate and will only breed resistance. Disseminating this knowledge among the public is important for reducing demand on clinicians to prescribe antibiotics inappropriately. The basic tenets of an appropriate antimicrobial selection can be summarized in the sample acronym SMART (Fig. 4).

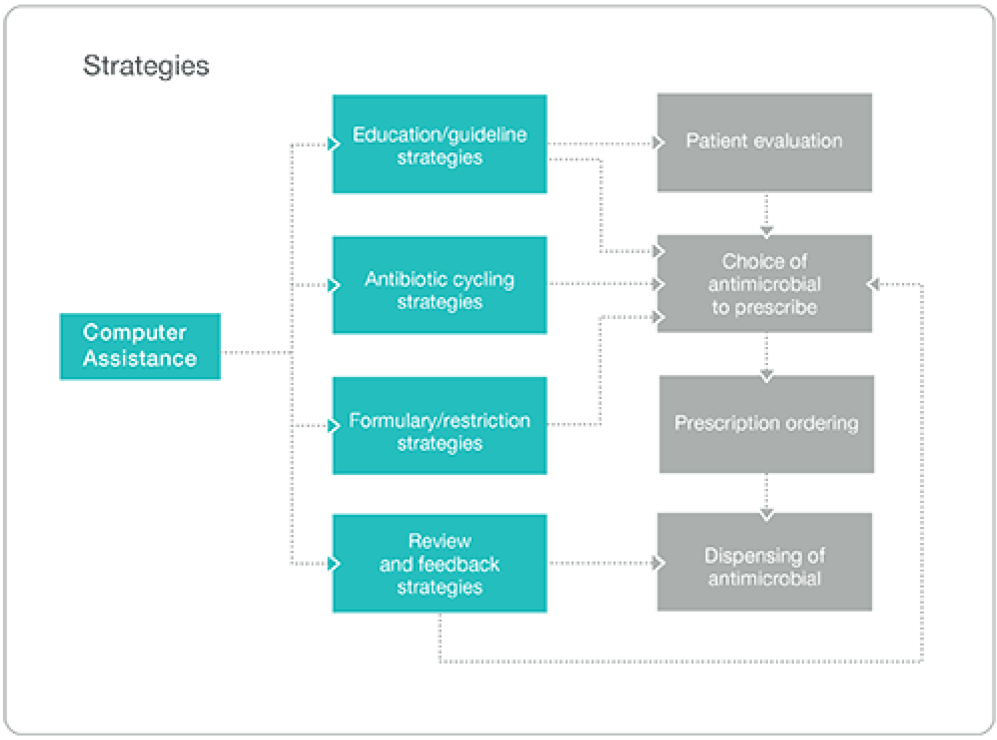
Fig. 4 "SMART": an example of a healthcare acronym for guiding appropriate antimicrobial therapy in a healthcare facility



Source: adapted from Doron, S. and Raman, K. (2013) Get SMART: Optimizing antibiotic use in the hospital. Available at:http://www.whitehatcom.com/Alere/Antibiotic_Stewardship_Alere_APUA_111412.pdf [Online] Accessed: 2nd May 2014. [26]

Supplemental strategies that facilitate these activities can include formulary restriction by the pharmacy; education, guidelines and clinical algorithms; antimicrobial order forms; and computerized decision support (Fig. 5).

Fig. 5 Antimicrobial stewardship strategies for impacting the stages of patient treatment



Source: adapted from MacDougall, C. (2006) Antibiotic Stewardship Programs: proven strategies to preserve medicine's "magic bullets". *APUA Newsletter* 24(1):1-3.[27]

The Role of Diagnostics

The 'test' element of the Test Target Treat™ paradigm is a critical link in the physician's response to an infected patient and one that is sometimes overlooked in stewardship discussions and models. Rapid diagnostics for distinguishing between viral and bacterial infections greatly facilitate the decision of whether or not to prescribe antibiotics. Recent advances in this field have brought much-needed products to aid physicians in the arenas of bedside, clinic and field diagnosis, but much more can be done to rapidly match disease agents with appropriate therapies. Cost and limited access still present major roadblocks to much of the developing world.

In the hospital, an efficiently operating stewardship program will quickly identify resistant infections. This is a function of how rapidly the microbiology laboratory can identify the problem organisms and determine their antibiotic susceptibility profiles. Diagnostic uncertainty is a limiting factor in optimal stewardship and drives the overuse and misuse of antibiotics as clinicians attempt to 'second guess' and provide a much-anticipated remedy to a sick patient.

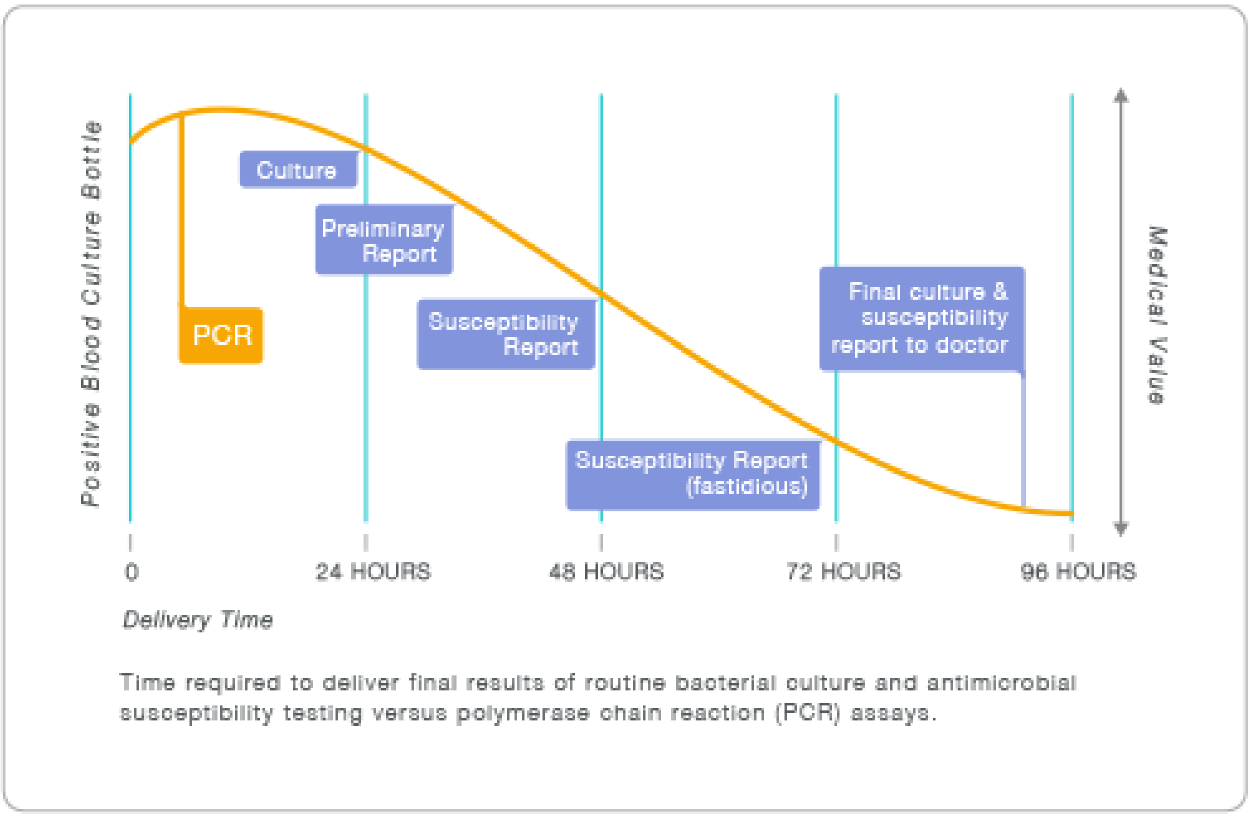
'Gold standard' methodologies, which involve the culturing and susceptibility testing of isolated organisms, are sensitive and low-cost, but can result in delays of up to 96 hours (4 days). The more useful tests employ patient samples, rather than culture isolates. While a patient awaits optimal antibiotic treatment, there is a high risk for nosocomial transmission of a resistant organism to multiple patients.

With the advent of newer rapid diagnostics, these time frames can be reduced dramatically.[28] For example the introduction of molecular techniques utilizing PCR (polymerase chain reaction) can dramatically reduce reporting times from several days to just a few hours (Fig. 6).

However, such tests are generally costly and require considerable technical expertise. The advent of reliable point-of-care diagnostic tests (POCTs) have reduced dependency on the laboratory and highly trained staff and have greatly facilitated field testing in both the community and in resource-limited settings of the developing world.

These tests permit treatment without delay and can likewise avoid antibiotic overtreatment where not needed.[29] It has been estimated that the use of POC tests having at least 95% sensitivity and 85% specificity to identify febrile children who need an antibiotic could save more than 150,000 lives annually in Africa and markedly reduce overtreatment in Asia and South America.[30]

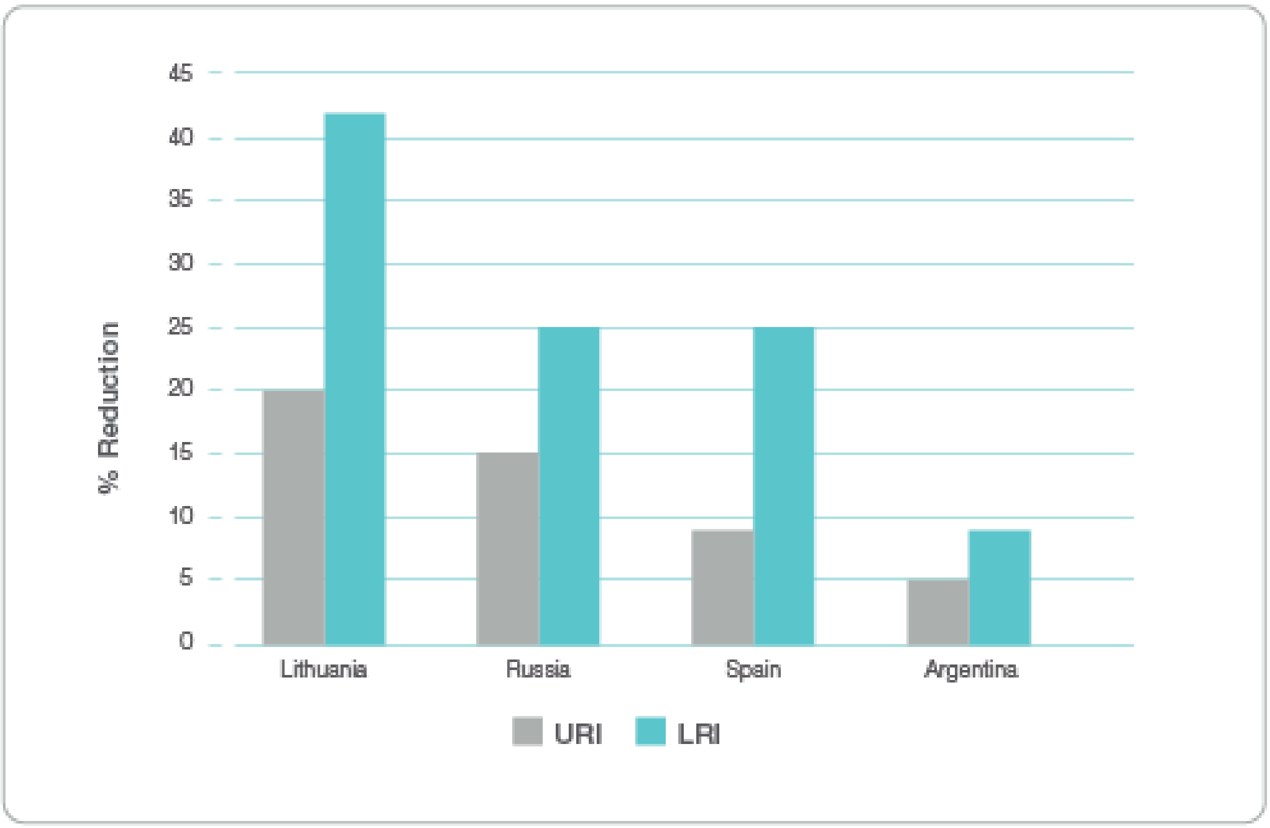
Fig. 6 Impacts of rapid diagnostic testing in optimizing antimicrobial selection



Source: adapted from Goff, DA et al. (2012) Using rapid diagnostic tests to optimize antimicrobial selection in antimicrobial stewardship programs. *Pharmacother* 32(8): 677-687. [31]

The potential benefits of a community-based stewardship intervention program were demonstrated in a 2009 multinational study that focused on implementing training in the use and interpretation of point-of-care diagnostic tests (Strep A and C-reactive Protein), but also utilized clinical guidelines, posters for waiting rooms, and patient information brochures in the treatment of respiratory tract infections. The intervention led to a marked reduction in the rates of antibiotic prescribing in four of the six countries, which represented diverse healthcare systems and prevalence of resistance (Fig. 7).

Fig. 7 Reductions (%) in the rates of antibiotic prescribing for respiratory tract infections following implementation of an antibiotic stewardship program in 6 countries. (Reductions were negligible in Denmark and Sweden)



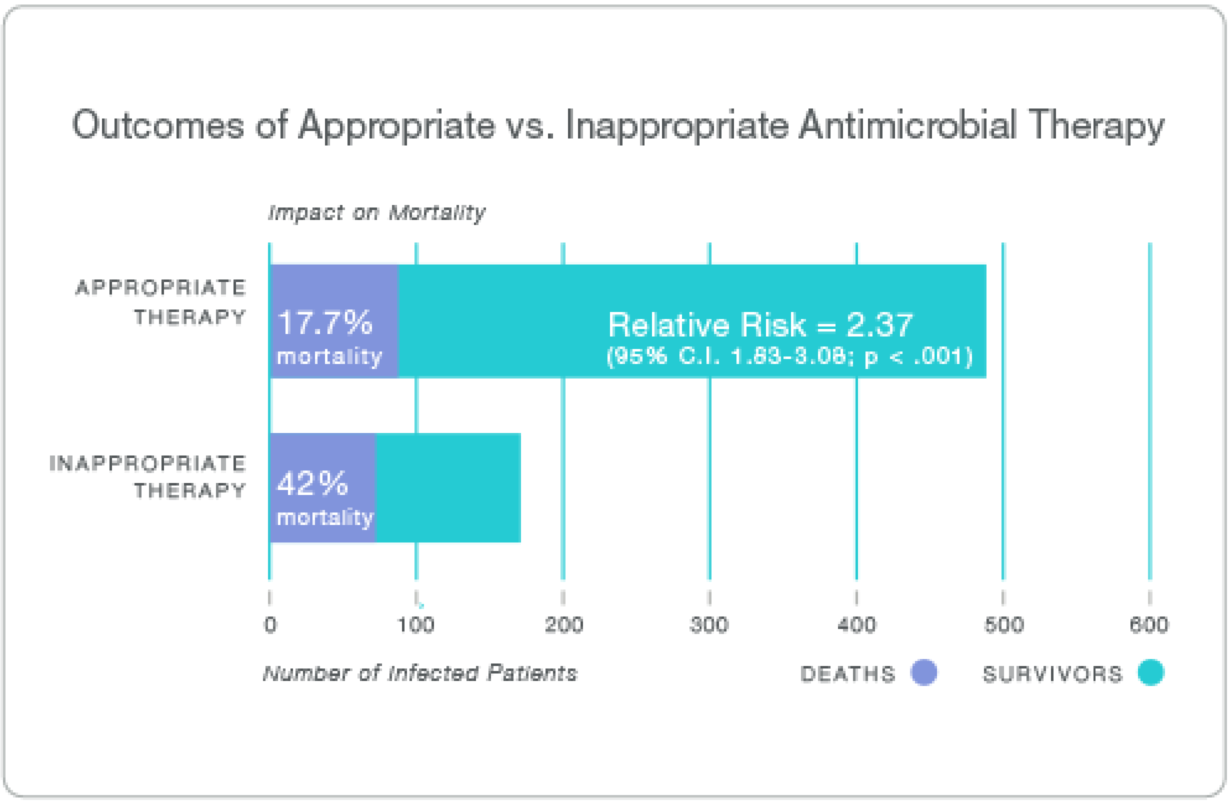
Source: adapted from Bjerrum, L. *et al*. (2011) Health Alliance for prudent antibiotic prescribing in patients with respiratory tract infections (HAPPY AUDIT) -impact of a non-randomised multifaceted intervention programme. *BMC Family Practice* 12:52-60. [32]

Conclusions

There is general consensus that antibiotic resistance development and spread can be curtailed by limiting antibiotic use, discouraging misuse, and reducing the burden of infectious disease.[34] An optimally functioning antimicrobial stewardship program is instrumental in accomplishing these goals.

It can have significant positive impacts on morbidity and mortality, (Fig. 8) and potentially reduce healthcare costs in the range of 20-35%.[21,35] Importantly, it plays a critical role in broad-based, larger scale efforts to help preserve our antibiotic resources for future generations.

Fig. 8 Decreased mortality through appropriate antimicrobial therapy



Source: adapted from Kollef, M. *et al*. (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 115:462-74 (cited by the CDC, 12 Steps to Prevent Antimicrobial Resistance: Hospitalized Adults) [Presentation] [33]

To find out more about the APUA and to discover more stewardship tools and information please visit **apua.org**

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