

REVIEW ARTICLE

Antimicrobial drug resistance and infection prevention/control:
lessons from tuberculosis

J. Peter Cegielski^{1*} , Carrie Tudor^{2,3}, Grigory V. Volchenkov^{3,4} and Paul A. Jensen^{3,5}

¹JP Cegielski Consulting, LLC, Atlanta, GA, USA; ²International Council of Nurses, Geneva, Switzerland; ³End TB Transmission Initiative, Stop TB Partnership, Geneva, Switzerland; ⁴Vladimir Regional TB Control Center, Vladimir, Russian Federation; ⁵Division of Global HIV and TB, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, GA, USA

Abstract

Antimicrobial drug resistance (AMR) is increasing rapidly worldwide, causing an estimated 700,000 deaths annually over the past decade, en route to becoming the leading global threat to public health by 2050 with an estimated 10 million deaths per year (more than heart disease, cancer, and stroke), while reducing global wealth by US\$100 trillion. Yet AMR has not received the attention and action required to change this trajectory. Appropriate infection prevention and control (IPC) measures are needed to prevent transmission of infections to healthcare workers (HCWs), other patients, families, and the general public. In this review, we discuss a notable case study of AMR: highly drug-resistant tuberculosis (TB) has emerged repeatedly over the past 70 years as new drugs have been introduced, leading to new diagnostics, therapeutics, funding, public health strategies, and, in high-income countries, effective IPC measures that curtailed transmission. We review current efforts to control and prevent AMR using the example of drug-resistant tuberculosis to highlight important themes including laboratory systems, surveillance, control and prevention of healthcare-associated infections (especially among HCWs), better coordination across disciplines and diseases, and powerful advocacy/social change initiatives grounded in social and behavioral sciences. These strategies are the foundation of an effective response to the AMR threat to public health.

Keywords: antimicrobial resistance; infection control; tuberculosis; surveillance; healthcare associated infections; healthcare workers

Received: 24 September 2020; Revised: 31 March 2021; Accepted: 24 May 2021; Published: 28 July 2021

The global advance of pathogenic microbes with resistance to all or nearly all antimicrobial drugs is a major threat to public health. Starting with penicillin and sulfonamides less than 90 years ago, antimicrobial drug resistance (AMR) has emerged among so many pathogens to so many drugs that it has become a foundational principle of modern microbiology and medical therapeutics (1–4). More than one-third of countries report widespread resistance among common pathogens (5), and 35% of common human infections are resistant to available medicines in many countries (5). In some low- and middle-income countries (LMICs), resistance rates are as high as 80–90% for some antibiotic-bacterium combinations (5). Resistance to the last remaining agents against many common bacteria, fungi, protozoa, and certain viruses is projected to almost double between 2005 and 2030 (5). Today, highly drug-resistant tuberculosis (TB), healthcare-associated infections (HAI), gonorrhea,

malaria, and human immunodeficiency virus (HIV) have been reported repeatedly in many countries, causing an estimated 700,000 deaths annually (5, 6). One-third of these deaths, an estimated 230,000 each year, are due to multidrug-resistant (MDR) TB alone, more than any other pathogen (7). On our current trajectory, by 2050, AMR will be the leading threat to health, causing over 10 million deaths per year (more than cancer, heart disease, and stroke) and reducing global wealth by US\$100 trillion (5, 8). One sees the realistic possibility of a post-antibiotic era; indeed, the leading edge is already here.

Pharmaceutical research into new antimicrobial compounds shrank dramatically after the 1980s, and the development of new compounds into commercial products shrank in tandem by the early 2000s (1, 2, 6, 8–16). Antibacterial drug discovery all but ended in the 1980s with oxazolidinones, monobactams, and cyclic lipopeptides, the last truly novel chemical cores, although their

development into commercial pharmaceuticals continued for 20 more years creating the false impression of a robust pipeline (1, 14). The newest antifungal agents, the triazoles and echinocandins, were discovered in the 1970s, patented in the 1980s, and entered clinical use by the 1990s (17). Resistance to azoles and triazoles is now common, and highly resistant *Candida auris* has become a global menace to the point of front-page news in the *New York Times* (18). The newest antimalarial drugs – mefloquine, halofantrine and its derivatives, and artemisinin and its derivatives – were discovered in the 1960s and 1970s (19). Resistance to these agents is already well established (20). Antiretroviral drugs came later because HIV was unknown before 1983. From the first antiretroviral drugs (1987), HIV has developed resistance rapidly, undermining the effectiveness of global HIV/acquired immunodeficiency syndrome (AIDS) control programs, increasing their cost and complexity (21). HIV is not alone among drug-resistant viruses. Acyclovir, the first specific antiviral drug (1982), and all the cyclovirs are compromised by widespread resistance among herpes group viruses and cytomegalovirus (22). Influenza resistance to oseltamivir (1999) was reported widely during the 2009 H1N1 influenza epidemic (23, 24).

Infectious diseases declined broadly in affluent countries throughout the 20th century in terms of major causes of morbidity and mortality. As a result, industry research and development shifted to chronic diseases that offered much more lucrative markets (14). To large pharmaceutical companies, the net present value of a new antibacterial drug is estimated to be approximately US\$42 million (12). This contrasts with new drugs for neurological or musculoskeletal disorders, where net present values range from US\$720 million to US\$1.2 billion (12). For the same investment, it was more profitable to focus on drugs that patients take life-long rather than for only 7–10 days. Of 18 major pharmaceutical companies, 15 have exited antimicrobial research and development (25, 26). Unlike any time since the 1930s, there are no new antibiotics, and the pipeline is anemic (10, 15, 25, 27).

Considering the gravity of widespread, severe AMR, why has it not received more attention from the public and from policy makers? *Mycobacterium tuberculosis* may have been the first major pathogen over the AMR cliff in the 1940s, and the response to it was anemic until alarming, highly lethal, widely publicized outbreaks started in the 1990s. Since then, the response has been modestly successful over the past 20 years. For other pathogens, we suggest the message never rose to the level of widespread popular attention and public alarm sufficient to motivate leaders and funders because, unlike the situation with TB, there were no sudden shocks, no major crises at the global level. Given the large numbers of different pathogens and antimicrobial drugs, we became inured to increasing

reports of progressive resistance among more and more specific pathogens to each class of drugs. Until recently, there were always alternatives, so there was no cause for alarm.

Physicians, nurses, microbiologists, and their professional societies began sounding the alarm about AMR in earnest in the early 2000s (6, 25–29). As a result, AMR was incorporated into the 2009 United States (US)-European Union (EU) Summit, leading to a resolution for action (30). The EU, US, United Kingdom (UK), and United Nations (UN) followed with extensive examinations of antimicrobial resistance, producing profound analyses, national action plans, and international guidance (2–4, 6, 8, 31–33). In 2016, the Political Declaration of the High-Level Meeting on Antimicrobial Resistance of the UN General Assembly represented a major milestone in confronting AMR globally, leading to an Interagency Coordination Group on Antimicrobial Drug Resistance that focused on human medicine, animal husbandry, veterinary medicine, research and innovation, the pharmaceutical industry, and antimicrobial contamination of the environment – a *One Health* approach to AMR (5, 11, 34–38).

We review global efforts to prevent and control AMR using drug-resistant TB as a case study to highlight crucial themes, including laboratory systems and surveillance, control and prevention of HAIs (especially among healthcare workers, HCWs), better coordination across disciplines and diseases, and powerful advocacy/social change initiatives grounded in social and behavioral sciences. These strategies are the foundation of an effective response to the AMR threat to public health.

Multidrug-resistant tuberculosis: A case study

Tuberculosis had the dubious distinction of being the first major infectious disease to become resistant to all known antibiotics. Anti-TB drug discovery research practically went dormant in the 1960s after the advent of rifampicin and 6-month chemotherapy because it was such a dramatic advance compared to what came before. Today, TB is the leading cause of death among all infectious diseases, with an estimated 10.0 million cases and 1.4 million deaths in 2018 (7). Tuberculosis evolved from an entirely curable disease in the 1960s, to more than 400,000 cases per year of MDR-TB in the 1990s to the worldwide emergence of extensively drug-resistant (XDR) TB in the early 2000s (28, 39). MDR-TB is defined as TB caused by *M. tuberculosis* that is resistant to at least isoniazid and rifampicin in standardized laboratory tests – the two most important anti-TB drugs. Until 2021, XDR-TB was defined as MDR-TB plus resistance to at least the two most important second-line drugs, fluoroquinolones and aminoglycosides (including capreomycin). As novel therapeutics were approved and became widely available, in 2021 XDR-TB was redefined by the World Health Organization (WHO)

as MDR-TB plus resistance to the fluoroquinolone plus either bedaquiline or linezolid, the two remaining first-choice drugs for MDR-TB. Today, drug-resistant TB kills approximately 230,000 people annually, one-third of all AMR-associated deaths.

Tuberculosis not only has a heavy toll in human suffering and death but also in healthcare costs. In South Africa, for example, one of the countries with high TB burdens, the per patient cost of XDR-TB was US\$26,392; MDR-TB, US\$6,772; and drug-sensitive TB, US\$257 (40). These costs consume a disproportionate share of each country's TB control program budget (40, 41). Deaths attributed to drug-resistant TB overall in 1 year cost the global economy at least US\$17.8 billion in future gross domestic product loss, mainly in LMICs (41). Lost productivity during the illness itself and treatment costs result in a further loss of at least US\$3 billion (41). These numbers, however, are underestimated because less than one-third of people with

drug-resistant TB receive a diagnosis and are recorded; of those, only one in four starts treatment (7, 41). Those untreated individuals remain contagious in society, putting anyone at risk. Recent work in South Africa suggests most of their XDR-TB may result from recent airborne transmission (42). Indeed, more research is needed to understand the role of primary transmission and the neglect of airborne infection prevention and control (IPC) in the MDR-TB pandemic (43, 44). In certain large countries, drug-resistant TB is increasing, gradually replacing drug-susceptible TB which is declining (41). Yet, the Global Fund spends far less on TB than on HIV or malaria; funding for TB from all sources is woefully inadequate (41).

Unlike other infectious diseases, however, the global response to drug-resistant TB was propelled by two major shocks coinciding with a massive resurgence of TB worldwide, leading WHO to declare a global emergency (45) (Figure 1).

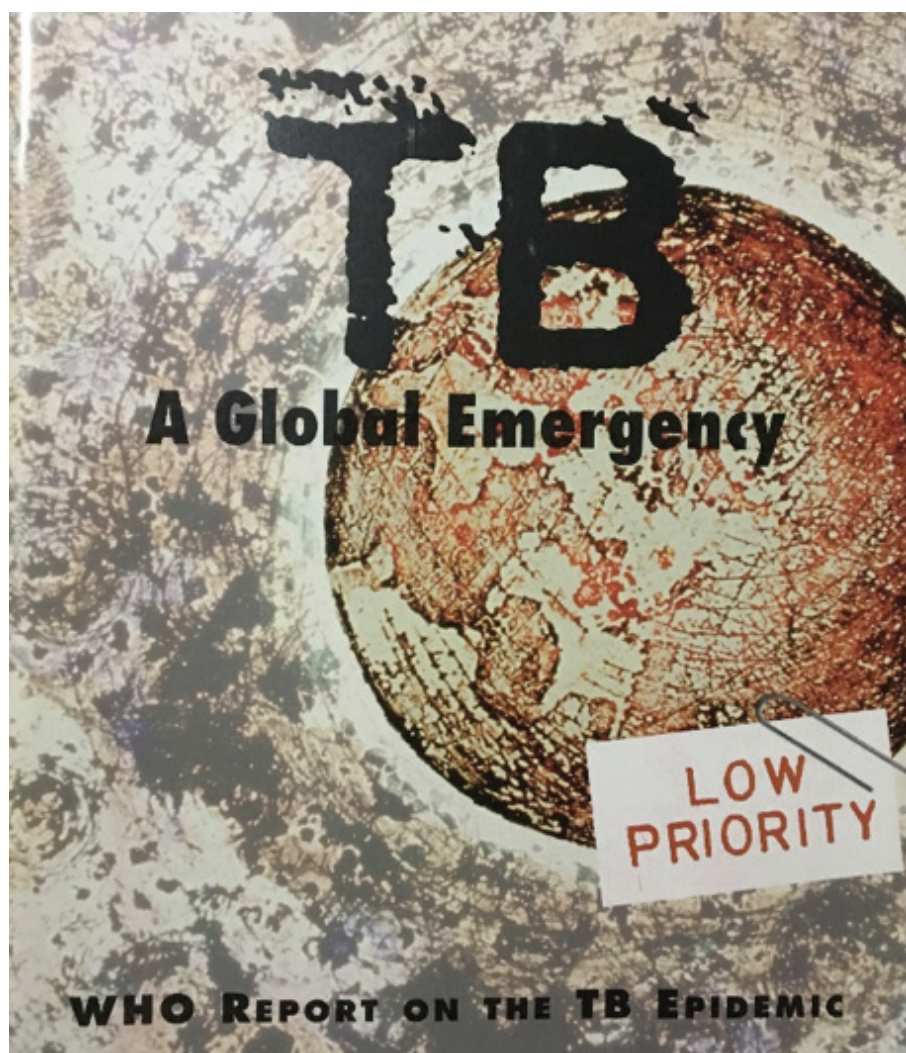


Fig. 1. In 1994, the World Health Organization declared tuberculosis to be a global health emergency after decades of neglect from public health authorities worldwide. (Reproduced with permission.)

First, in the early 1990s, more than a dozen outbreaks of MDR-TB first in the USA, then Argentina, Italy and other countries caused worldwide alarm—90% of patients died within weeks of diagnosis, airborne transmission put everyone at risk, and healthcare workers were being infected. TB was the front cover of Newsweek Magazine (16 March 1992) (46). Outbreaks were subsequently reported in many countries, revealing that a stealth pandemic of potentially massive dimensions had gone undetected.

Second, in 2006, Shah *et al.* first reported the global emergence of a new entity, extensively drug-resistant (XDR) TB that was functionally untreatable (28, 47). While the “X” capitalized on popular culture, it also conveyed the gravity of resistance so severe that there was no satisfactory

treatment (47). Widespread public attention and alarm exploded several months later when Gandhi *et al.* reported from South Africa the first outbreak of XDR-TB, with 52 of 53 individuals dying in a median of two weeks (48).

In 2013, drug-resistant tuberculosis was on the cover of Time magazine (Figure 2). This level of publicity led to action at the highest levels – from national governments, multilateral agencies, funding organizations, industry; and from medical, public health, and affected communities, including WHO, the US Centers for Diseases Control and Prevention, South Africa, the government of India, and many others (47, 49–52).

Indeed, in 2009 the World Health Assembly for the first time called explicitly for appropriate diagnosis and



Fig. 2. In 2013, *Time Magazine* put drug-resistant tuberculosis on its front cover raising public awareness of this widespread threat to public health and to tuberculosis control programs. (Reproduced with permission.)

treatment not only for TB in general, but for **drug-resistant** TB explicitly. Early efforts cultivating MDR-TB treatment programs in LMICs worldwide ripened into nationwide programs and their experiences led to robust WHO guidelines focusing on drug-resistant TB (53–57). Governments, donor agencies, biomedical technology, and pharmaceutical companies started investing in research and development directly related to MDR-TB, from basic science to large epidemiological studies and randomized controlled clinical trials (58–65). Four years later, WHO first endorsed Xpert MTB/RIF™, a revolutionary rapid molecular test that transformed diagnosis for both drug-resistant TB and TB in general worldwide (66). Then, by 2014, WHO approved two new drugs, bedaquiline and delamanid, for the treatment of MDR-TB (67, 68). In 2019, a novel three-drug regimen, including the new drug pretomanid, was approved by the US Food and Drug Administration for XDR-TB and selected MDR-TB patients (69, 70). The outlook for drug-resistant TB is less grim than it has been since the 1990s (71).

Laboratory systems and drug-resistance surveillance

The MDR-TB outbreaks of the 1990s were obviously only the visible tip of a massive iceberg of MDR-TB in the population of unknown dimensions. Airborne, mainly nosocomial, transmission was the proximate cause. These outbreaks spotlighted widespread deficiencies in diagnostics and laboratory systems, surveillance systems, and resource allocation. Because of the tragic and costly consequences, resources were allocated leading to concerted action followed by remarkable results. Because of airborne transmission of pathogens besides *M. tuberculosis* as well as common laboratory contaminants, the lessons learned apply to microbiology laboratories and surveillance systems broadly.

Mounting a response, however, required first quantifying the magnitude, distribution, and trends; otherwise, responses would be blind. Wisely, as the first step, WHO, the International Union Against Tuberculosis and Lung Disease (the Union), and the directors of leading mycobacteriology reference laboratories set up a global surveillance system for drug-resistant TB, providing crucial quantitative information on magnitude, distribution, trends, risk factors, and outcomes that are now used ubiquitously to benchmark national MDR-TB programs (72–74). Over time, the Supranational TB Reference Laboratory (SRL) Network and Global Project on Anti-TB Drug Resistance Surveillance (<https://www.who.int/tb/areas-of-work/laboratory/srl-network/en/>) helped develop national reference laboratories and, in turn, national laboratory networks and surveillance systems globally (75, 76). Having quantitative information or science-based best estimates for every country has been foundational in every aspect of global and national responses to drug-resistant TB.

The lesson that applies to all pathogens is that laboratories and surveillance are crucial. Countries can build on the recent WHO, UK, EU, and US reports (2, 8, 31, 32, 77), taking an important step toward halting the alarming spread of pan-resistant pathogens by establishing laboratory systems, drug-resistance testing, and reporting/surveillance systems, as well as expanding these services as rapidly as practicable. Advances in rapid molecular diagnostic technologies at or near the point of patient care are transforming diagnostics and surveillance systems, making them far more accessible and practical. Routine testing and surveillance of drug resistance among priority pathogens and dissemination/use of these data are crucial components of systems designed to contain and control drug-resistant pathogens.

The 2015 advent of the Global Antimicrobial Resistance Surveillance System was a major step in this direction. The Center for Disease Dynamics, Economics, and Policy disseminates these data with its web-based, interactive data visualization tool ResistanceMap (<https://resistancemap.cddep.org/>). This system and other surveillance systems focused on drug-resistant infections would do well to disaggregate infections among HCWs both to protect these essential workers and to monitor them as a sentinel population.

Healthcare-associated infections, healthcare workers, and infection prevention and control

Following the spate of institutional MDR-TB outbreaks in the early 1990s, many high-income countries mandated IPC measures through worker protection laws and regulatory bodies. In contrast, measures to prevent institutional transmission of *M. tuberculosis* and other pathogenic microbes in LMICs have not yet been widely implemented or have been implemented poorly. HCWs have a much higher risk of TB, ranging from three times to 20 times higher than same-age peers in other jobs, not to mention other airborne infections (78, 79, 80).

Apart from TB, other pathogens are airborne; measles and varicella zoster virus are the two main examples, but SARS-CoV2 may also be transmitted by the airborne route. From the environment, *Legionella*, fungal spores can be aerosolized, as well as *Aspergillus*, *Histoplasma*, and *Coccidioides*, infecting people through the respiratory route (81, 82). Small droplet transmission differs, but IPC precautions overlap. Proper transmission-based precautions would prevent the spread of all these infections; hence, incorporating airborne and small droplet precautions into universal precautions as well as into surveillance systems and WHO program indicators would help protect HCWs and prevent transmission to their contacts both inside and outside the workplace for all these pathogens.

Apart from airborne infections, HCWs are at tremendous risk of becoming infected during outbreaks of

infectious diseases, often accounting for a large proportion of cases. During the 2002–2004 SARS epidemic, for example, 28–51% of cases in two of the highly affected countries were among HCWs (83, 84). HCWs are exposed not only to airborne pathogens but also to pathogens transmitted by respiratory droplets, blood/body fluids and direct/indirect contact/fomites. What would happen if increasing numbers of HCWs, fearing for their own safety, refused to work? HCWs should be protected, compensated for hazardous duty (e.g. as in the Russian Federation), and protected financially if they develop occupational diseases. Occupational diseases and deaths should be identified and reported diligently (85).

Drug-resistant organisms have repeatedly been first described in acute care facilities, and their impact is often worst in healthcare settings. MDR-TB is a prime example. In addition to the seven priority pathogens identified by WHO or the six pathogens reviewed by O'Neill et al., AMR emerges and spreads for virtually all pathogens treated with antimicrobial agents (2, 8, 32, 86, 87). Preventing and controlling infections is tied quantitatively to lowering the use of antibiotics, including in animal husbandry, and therefore emergent drug resistance.

Nevertheless, O'Neill et al. state that 'IPC [infection prevention and control] is too often seen as a cost pressure, rather than a means to deliver better value and better outcomes for patients; managers and senior clinicians often give it insufficient focus as a result' (78). As a result, IPC programs are chronically under-resourced. Unfortunately, IPC practices are not routine despite their potential benefit and impact, especially in settings with limited resources. Surveillance among HCWs and in healthcare facilities is rudimentary in most LMICs.

How can this agenda move forward? Standardized surveillance worldwide has been central in the response to MDR-TB. Surveillance is crucial to preventing HAIs (87). In LMICs, surveillance among HCWs for TB, especially drug-resistant TB, and for other HAIs, especially AMR infections, is lagging far behind other surveillance efforts despite their importance as a sentinel population. Including HCWs in surveillance systems would provide accurate estimates of magnitude, trends, risk factors, and outcomes, which are the foundations of an appropriate response.

Training and political commitment are crucial to efforts to ensure HCW safety. The International Council of Nurses, the US Agency for International Development (USAID), US CDC, WHO, Harvard/Partners in Health, and other non-governmental organizations such as the Union, PATH, Services for Health in Asian African Regions (SHARE), International Center for AIDS Care and Treatment Programs (ICAP), Project Hope, Stop TB Partnership, and the Royal Dutch Anti-TB Foundation (KNCV) have been engaged in promising initiatives in

countries of the former Soviet Bloc (including Latvia, the Russian Federation, and Tajikistan), Latin America (Peru), sub-Saharan Africa (South Africa and Malawi), India, and China (88–95). Over the past two decades, the authors have had the opportunity and privilege to help develop and work with highly successful Centers of Excellence in Riga, Latvia; Vladimir, Russian Federation; and Dushanbe, Tajikistan. Launched with USAID support, these centers have become self-sustaining training and consulting organizations for professionals throughout the world, resulting in substantial improvements in the participants' home institutions and countries. Such training institutes could play an important role in the IPC response to AMR and HAI.

Laboratories and laboratory networks in LMICs benefited greatly from collaboration with the SRL network and participation in the global anti-TB drug resistance surveys. Similarly, to address the threat of occupational risk among HCWs and of AMR more broadly, LMICs could benefit from the experience gained with IPC and antibiotic stewardship programs in countries that have already implemented cost-effective measures. Many IPC experts from both high-income countries and LMICs would welcome the opportunity to work with colleagues in LMICs to strengthen IPC programs.

To protect HCWs, health systems and facilities at all levels should consider making IPC a foundational priority. Airborne IPC, including TB specifically, should be integrated into general IPC at every level to prevent the transmission in facilities of airborne pathogens in general, especially drug-resistant pathogens. This type of expertise generalizes to other airborne infections. During the SARS epidemic of 2002–2004, the US CDC deployed experts from the Division of TB Elimination because of their expertise in airborne infections. Coordinated efforts across all levels of healthcare providers and systems have demonstrated clear impact in reducing levels of HAIs and drug resistance as evidenced by sharp reductions in methicillin-resistant *Staphylococcus aureus*, healthcare-associated TB, *Clostridioides difficile*, catheter-associated bloodstream infections, and surgical site infections in countries where governments, regulators, and health system leaders established IPC as system-wide priorities (32, 78).

Programmatic initiatives often bundle together IPC policies and practices, making it difficult to determine the cost-effectiveness of any specific practice or technology. Even modest funding for targeted studies, such as the US CDC's Study on the Efficacy of Nosocomial Infection Control, could demonstrate the efficacy and cost-effectiveness of interventions to improve IPC (96, 97). Preventing one case of TB in the United States saves an average treatment cost of US\$17,000 for drug-susceptible TB or US\$175,000 for MDR-TB; globally, the

corresponding median figures are US\$973 and US\$6,430, respectively (7, 98). Therefore, strong economic arguments favor vigorous programs (33). Although the total economic cost of AMR is difficult to calculate, in 2009, the European Centre for Disease Prevention and Control and the European Medicines Agency estimated that the overall cost for the EU in terms of extra healthcare costs and productivity losses totaled at least €1.5 billion (approximately US\$1.63 billion) each year (6). For the United States, estimates are as high as US\$20 billion in excess direct healthcare costs, with additional costs to society for lost productivity as high as US\$35 billion a year (86).

O'Neill et al. identified a fundamental lack of effective, informed leadership in IPC programs and activities:

'Ultimately, to embed better practices within any organisation requires effective internal leadership and professional ownership. Greater value must be placed on prevention, treatment, and control of infectious diseases. Too often, the person responsible for IPC [infection prevention and control] in an organisation is relatively junior, and formal standards for accreditation are limited. Consequently, individuals responsible for overseeing and improving IPC may lack the influence necessary to guide budget and procurement decisions, or to change engrained practices and shift priorities across multiple clinical disciplines. Top-down priority and target setting can be no substitute for strong, empowered leadership at the front line'. (78)

In many countries, IPC professionals are often nurses who may not have specialized training in IPC. In a recent analysis of reports of external expert TB program reviews, IPC was not explicitly included in three of seven low-income African and Asian countries. Implementation was variable, from lacking to laudable (99). Programs focused prevention and screening efforts on children, prisoners, refugees (in certain countries), and HIV clinics, but not on healthcare facilities in general.

Screening HCWs to assess their risk relative to the population is important for monitoring nosocomial infections, especially AMR infections, as well as the effectiveness of IPC programs as has been done for decades in the Russian Federation and throughout countries from the former Soviet Union. WHO collects data on TB notification among HCWs, although notification is incomplete (7). Specifically, WHO states, 'The risk of TB among healthcare workers relative to the risk in the general adult population is one of the indicators recommended by WHO for measuring the impact of interventions for TB infection prevention and control in healthcare facilities' (7). Resources, infrastructure (e.g.

crowding and poor ventilation) and training were universal themes. Countries could consider including their ministries of health and HCWs in labor laws and regulations focused on occupational health because, too often, these groups are omitted, leaving HCWs to slip through the gaps. For example, surveillance among HCWs was highly variable in an analysis of TB programs in seven low-income African and Asian countries (99). Reports from China and South Africa provide further examples of TB surveillance among HCWs (100, 101).

Fragmentation and coordination

The slow pace of implementing proper IPC practices and policies is partially due to fragmentation among IPC professionals into a kaleidoscope of distinct domains, each with its own science, its own publications and professional societies, and its own pathogens. Yet drug resistance has evolved to nearly all pathogens over decades, stepwise one pathogen to one drug (or class of drugs) at a time. We are responding to a universal phenomenon with pathogen-specific, piecemeal solutions. Seeing the broader picture, it makes sense to integrate solutions to achieve synergy.

At the same time, the public health responses to these infections are compartmentalized at the highest levels. For example, WHO's first global priority list of antibiotic-resistant pathogens published in 2017 did not include viruses, parasites, fungi, or even TB, the leading cause of death due to drug-resistant bacteria, leading to controversy and acrimony (2, 102–104). Leading proponents of public health globally may help overcome this fragmentation by insisting on collaboration. Fragmentation causes different groups to work at cross-purposes.

For TB, IPC interventions in certain countries have been implemented mainly in the context of HIV, such as through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) or WHO's 3-I's initiative, not in general healthcare facilities or community settings. These efforts could now move beyond focusing solely on HIV-associated facilities, just as TB IPC with funding from PEPFAR is moving beyond focusing efforts exclusively in HIV settings. The Global Fund against AIDS, TB, and Malaria (GFATM) may serve as a platform for fostering IPC and AMR initiatives across diseases by requesting applications to include an IPC risk assessment/review, a strategic plan for addressing IPC gaps, and funding to implement the strategy. Fostering cooperation across TB, HIV, hepatitis B and C, as well as other infectious disease programs could be prioritized. The WHO/Stop TB Partnership's Green Light Committee, which works closely with the Global Fund, established an effective precedent by requiring applicants to include IPC in their

applications for support in setting up MDR-TB programs (105).

Cooperating and coordinating across disciplines and diseases require leadership. To adapt our stewardship of all antimicrobial agents, we should handle them as precious resources, not as food additives for livestock or home remedies. The O'Neill report, the US Combating Antibiotic Resistant Bacterial Strategy and Plan, and WHO reports on antimicrobial resistance may be extended to cover all pathogens prioritized based on epidemiology, not on department, identifying and acting on common structural themes and comprehensive solutions (106–108). The UN's Inter-Agency Coordinating Group on Antimicrobial Resistance and the multilateral Global Health Security Agenda, launched in 2014 in the wake of transnational outbreaks and the threat of AMR, may serve as a model; these organizations are based on a strategy of comprehensive and structural solutions, including biosafety and IPC, HCW, and AMR as core elements.

Communication, social change, and social/behavioral sciences

The response to MDR-TB was driven not so much by resurgent TB, because TB had always been present, but by the sudden risk and fear of lethal, highly drug-resistant TB. What pushed the response was the degree of public attention and alarm causing policy makers to act.

Even though the threat of AMR is manifold greater, both the threat and the messaging around the threat are too repetitive and incremental to lead to concerted social action on a broad scale. Humankind is neurologically hardwired to respond to sharp contrasts, sudden changes, and acute threats (109). When faced with insidious, incremental, or indirect threats, that same wiring leads to inaction, especially in complex social and political contexts. We do not respond with nearly the same vigor to a preventable, curable infection, such as TB, that kills over *4,000 people every day, year after year*, than when smaller numbers die in an acute, unexpected event such as an airplane crash, an act of terrorism, or an explosive epidemic. The broader fields of AMR and of IPC could harness communications and action strategies that effectively influence behavior and policy, transforming sudden events into opportunities for leadership by responding decisively with coordinated and determined communication followed by action.

At the same time, we cannot wait for disasters and emergencies. In addition to focusing on the sciences of microbiology, pharmacology, and epidemiology, we may also engage the sciences of communication, social change, and human behavior. Such work might help identify low-cost, practical, but effective means of improving IPC and reducing AMR in countries at all income levels (110, 111).

We suggest engaging social scientists, marketing experts, advertising agencies, thespians of all types and film makers, artists and musicians, social media experts, political and industry leaders to become both more active and more creative about the social changes that are needed to prevent the nightmare scenario of 10 million deaths per year and trillions of dollars in economic losses due to burgeoning antimicrobial resistance.

Our former affiliation with the US Centers for Disease Control and Prevention (JPC and PAJ) prevents us from making specific recommendations because CDC has specific channels through which it makes formal US government guidelines and recommendations. That said, to recap the salient points, from the perspective of our leadership positions at regional, national or global programs, these have been our priorities in professional practice related to MDR-TB that may apply to AMR more broadly:

- Prioritizing comprehensive IPC, data-driven by HCW surveillance, supported by laboratory testing for AMR, targeting transmission-based precautions, and including airborne IPC measures.
- Because effective surveillance is the foundation of public health, supporting surveillance systems to be accurate, timely, and informative is a fundamental priority, including sentinel populations and antimicrobial resistance by pathogen, by drug, and by location.
- Investing time and resources in robust, biosafe public health microbiology laboratories and networks has always been and remains an important priority, both infrastructure and human capacity to identify pathogens specifically, promptly, and test them for drug resistance, emphasizing rapid and affordable point-of-care tests made widely available
- Ensuring effective, professional and public communications, promoting social mobilization, and engaging leaders and champions who are highly visible in popular culture.
- Developing training centers and demonstration sites from the beginning of our international work.
- Engaging multilateral organizations, national and regional governments, major funding organizations, nongovernmental organizations, and civil society.

Conclusions

Most people are not aware of the precipice in new antimicrobial drugs because development, regulatory approval, and commercialization of final products lag behind discovery by 10–20 years, creating the false impression of new drugs. Chemical variations on a prototype compound are further developed sometimes over decades, contributing to this illusion. The 'TB world' went over this cliff of drug resistance 25 years ago. Public alarm pushed governments, multilateral organizations, industry,

and nongovernmental organizations to focus on MDR-TB and its progeny, and many countries took regulatory action requiring diligent attention to IPC. Today, AMR is an imminent calamity facing humankind on an even greater scale, but it has just begun to receive broader attention and targeted resources. AMR has not yet reached the level of public alarm necessary for an effective response. Attention to IPC has been inadequate. Addressing IPC, especially in the context of AMR, collectively and urgently requires action and coordination across domains. Quantitation is foundational, that is, resourced, coordinated laboratory networks and surveillance systems that include data on the risk to HCWs, especially due to AMR infections. HCWs are the front-line of defense and the most important sentinel population in terms of emerging and epidemic infectious diseases. Comprehensive IPC, including airborne pathogens, surveillance among healthcare workforce, and antibiotic stewardship are crucial for public health policy and programs. Addressing these issues will require capacity building, infrastructure, training, and resources. The structures for coordinated responses to infectious disease threats that are being put into place and are leading global and national responses would do well to focus on AMR and on IPC. High-income countries can help build capacity and an evidence base for LMIC. Coordination, leadership, and communication would do well to incorporate a broad range of stakeholders, especially social and behavioral sciences, to change our current trajectory and avoid widespread, untreatable infectious diseases.

Disclaimer

The findings and conclusions presented in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention or the US government, or the funding agencies.

Conflict of interest and funding

All authors have declared that they have no conflicts of interest. Funding was provided by the End Tuberculosis Transmission Initiative (ETTi) of the Stop TB Partnership, Geneva, Switzerland.

Ethical statement

This manuscript was cleared by the ethics review procedures of the US Centers for Disease Control and Prevention.

Authors' contributions

All authors contributed to conceiving and outlining this article. JPC wrote the first draft and each successive draft, incorporating critical input and revisions from each of the other authors. All authors approved the final draft of this article.

References

1. Ventola CL. The antibiotic resistance crisis, part 1: causes and threats. *P T* 2015; 40(4): 277–83.
2. World Health Organization. Global action plan on antimicrobial resistance. Geneva: WHO; 2015. WHA68/2015/REC/1, Annex 3.
3. World Health Organization. Antimicrobial resistance: global report on surveillance. Geneva: WHO; 2014.
4. World Health Organization. Report on the burden of endemic health care-associated infection worldwide a systematic review of the literature. Geneva: WHO; 2014.
5. Interagency Coordination Group on Antimicrobial Resistance (IACG). No time to wait: securing the future from drug-resistant infections. Report To The Secretary-General Of The United Nations. April 2019. Available from: <https://www.who.int/antimicrobial-resistance/interagency-coordination-group/en/> [cited 2 May 2019].
6. European Centre for Disease Prevention and Control, European Medicines Agency. ECDC/EMA JOINT TECHNICAL REPORT The bacterial challenge: time to react. Stockholm: European Centre for Disease Prevention and Control, September; 2009. EMEA doc. ref. EMEA/576176/2009, ISBN 978-92-9193-193-4. doi: 10.2900/2518
7. World Health Organization. Global tuberculosis report 2020. Geneva: World Health Organization; 2020. License: CCBY-NC-SA 3.0 IGO.
8. O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. The review on antimicrobial resistance. December 2014.
9. Ventola CL. The antibiotic resistance crisis, part 2: management strategies and new agents. *P T* 2015; 40(5): 344–52.
10. World Health Organization. Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017. WHO/EMP/IAU/2017.12. Licence: CC BY-NC-SA 3.0 IGO.
11. Food and Agriculture Organization / World Organization for Animal Health / World Health Organization. Global framework for development & stewardship to combat antimicrobial resistance: draft roadmap. Geneva: United Nations; 2017. WHO/EMP/IAU/2017.08 (revised 19 October 2017).
12. Sciarretta K, Rottingen JA, Opalska A, Van Hengel AJ, Larsen J. Economic incentives for antibacterial drug development: literature review and considerations from the transatlantic task force on antimicrobial resistance. *Clin Infect Dis* 2016; 63(11): 1470–4. doi: 10.1093/cid/ciw593
13. The antibiotics industry is broken – but there's a fix: attempts to develop new antibiotics are failing because the projects aren't profitable. Maryn McKenna, WIRED.com – 4/27/2019, 7:30 AM.
14. Aminov RI. A brief history of the antibiotic era: lessons learned and challenges for the future. *Front Microbiol* 2010; 1(134): 1–7. doi: 10.3389/fmicb.2010.00134
15. Theuretzbacher U, Gottwalt S, Beyer P, Butler M, Czaplowski L, Lienhardt C, et al. Analysis of the clinical antibacterial and antituberculosis pipeline. *Lancet Infect Dis* 2019(Feb); 19: e40–50. doi: 10.1016/S1473-3099(18)30513-9
16. Pearson ML, Jereb JA, Frieden TR, Crawford JT, Davis BJ, Dooley SW, et al. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis*: a risk to patients and health care workers. *Ann Intern Med* 1992; 117: 191–6. doi: 10.7326/0003-4819-117-3-191
17. Rogers PD, Krysan DJ. Ch. 61: Antifungal agents. In: Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's

- the pharmacologic basis of therapeutics – 13 ed. New York: McGraw-Hill; 2018, pp. 1087–104.
18. Richtel M, Jacobs A. Fungus immune to drugs quietly sweeps the globe. *The New York Times*, Vol. CLXVII, No. 58,290. Sunday, April 7, 2019, p. 1.
 19. Vinetz JM. Ch. 53: Chemotherapy of malaria. In: Brunton LL, Hilal-Dandan R, Knollman BC, eds. *Goodman & Gilman's the pharmacologic basis of therapeutics – 13 ed.* New York: McGraw-Hill; 2018, pp. 969–86.
 20. Fairhurst RM, Wellems TE. Malaria (Plasmodium species). ch. 276. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases–8th ed.* Elsevier: Philadelphia, 2015, pp. 3070–3090.”
 21. Beyrer C, Pozniak A. HIV drug resistance – an emerging threat to epidemic control. *N Engl J Med* 2017 Oct 26; 377(17): 1605–7. doi: 10.1056/NEJMp1710608
 22. King DH. History, pharmacokinetics, and pharmacology of acyclovir. *J Am Acad Dermatol* 1988; 18(1)(part 2): 176–9. doi: 10.1016/S0190-9622(88)70022-5
 23. World Health Organization. Update on oseltamivir resistance to influenza H1N1 (2009) viruses. December 15, 2010. Archived (PDF) from the original on January 30, 2011. [cited 30 December 2010].
 24. Centers for Disease Control and Prevention. Antiviral drug resistance among influenza viruses guidance on the use of influenza antiviral agents (Current for the 2013–14 Influenza Season). CDC. Archived from the original on 13 February 2014. [cited 21 April 2014].
 25. Talbot GH, Bradley J, Edwards JE Jr, Gilbert D, Scheld M, Bartlett JG. Bad bugs need drugs: an update on the development pipeline from the antimicrobial availability task force of the Infectious Diseases Society of America. *Clin Infect Dis* 2006; 42: 657–68. doi: 10.1086/499819
 26. Bartlett JG, Gilbert DN, Spellberg B. Seven ways to preserve the miracle of antibiotics. *Clin Infect Dis* 2013; 56(10): 1445–50. doi: 10.1093/cid/cit070
 27. Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al. for the IDSA. The epidemic of antibiotic resistant infections: a call to action for the medical community from the IDSA. *Clin Infect Dis* 2008; 46: 155–64. doi: 10.1086/524891
 28. Shah NS, Wright A, Bai GH, Barrera L, Boulahbal F, Martin-Casabona N, et al. Worldwide emergence of extensively drug-resistant tuberculosis. *Emerg Infect Dis* 2007; 13(3): 380–7. doi: 10.3201/eid1303.061400
 29. Spellberg B, Gilbert DN. The future of antibiotics and resistance: a tribute to a career of leadership by John Bartlett. *Clin Infect Dis* 2014; 59(S2): S71–5. doi: 10.1093/cid/ciu392
 30. 2009 E.U.-U.S. Summit Declaration, p. 3, 3 Nov 2009.
 31. O'Neill, et al. Tackling a global health crisis: initial steps. The Review on Antimicrobial Resistance. World Bank; 2015. Available from: <https://amr-review.org/sites/default/files/Report-52.15.pdf> [cited 30 June 2021].
 32. O'Neill, et al. Tackling drug-resistant infections globally: final report and recommendations: the review on antimicrobial resistance. World Bank; 2016. Available from: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf [cited 30 June 2021].
 33. Taylor J, Hafner M, Yershalmi E, Smith R, Bellasio J, Vardavas R, et al. Estimating the economic costs of antimicrobial resistance: model and results. Santa Monica, CA: RAND Corporation; 2014.
 34. Interagency Coordination Group on AMR (IACG). AMR framework for action supported by the IACG Working Document, August 2017.
 35. IACG. Meeting the challenge of antimicrobial resistance: from communication to collective action. IACG Discussion Paper July 2018.
 36. IACG. Reduce unintentional exposure and the need for antimicrobials, and optimize their use. IACG Discussion Paper July 2018.
 37. WHO. Available from: <https://www.who.int/news/item/27-09-2019-end-tb-at-the-74th-un-general-assembly> [cited 6 June 2021].
 38. Stop TB Partnership. Available from: http://www.stoptb.org/assets/documents/global/advocacy/unhlm/UNHLM_Targets&Commitments.pdf [cited 14 September 2019].
 39. Centers for Disease Control and Prevention. Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugs – worldwide, 2000–2004. *MMWR* 2006; 55(11): 301–5.
 40. Pooran A, Pieterse E, Davids M, Theron G, Dheda K. What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa? *PLoS One* 2013; 8(1): e54587. doi: 10.1371/journal.pone.0054587
 41. The Economist Intelligence Unit. Time to end drug-resistant tuberculosis: a call to action. The Economist. London: The Economist Intelligence Unit, Ltd; 2019, pp. 1–36.
 42. Shah NS, Auld SC, Brust JC, Mathema B, Ismail N, Moodley P, et al. Transmission of extensively drug-resistant tuberculosis in South Africa. *N Engl J Med* 2017 Jan 19; 376(3): 243–53. doi: 10.1056/NEJMoal1604544
 43. Wollenberg KR, Desjardins CA, Zalutskaya A, Slodovnikova V, Oler AJ, Quiñones M, et al. Whole genome sequencing of Mycobacterium tuberculosis provides insight into the evolution and genetic composition of drug-resistant tuberculosis in Belarus. *J Clin Microbiol* 2017 Feb; 55(2): 457–69. doi: 10.1128/JCM.02116-16
 44. Gelmanova IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. *Bull World Health Organ* 2007 Sep; 85(9): 703–11. doi: 10.2471/BLT.06.038331
 45. World Health Organization Global Tuberculosis Programme. TB: a global emergency, WHO report on the TB epidemic. Geneva: World Health Organization; 1994.
 46. Beck-Sagué C, Dooley SW, Hutton MD, Otten J, Breeden A, Crawford JT, et al. Hospital outbreak of multidrug-resistant Mycobacterium tuberculosis infections. Factors in transmission to staff and HIV-infected patients. *JAMA* 1992 Sep 9; 268(10): 1280–6. doi: 10.1001/jama.268.10.1280
 47. The Lancet Editors. XDR-TB – a global threat. *Lancet* 2006 (Sep16); 368(9540): 964. doi: 10.1016/S0140-6736(06)69391-4
 48. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006 Nov 4; 368(9547): 1575–80. doi: 10.1016/S0140-6736(06)69573-1
 49. World Health Organization, Stop TB Partnership. The global MDR-TB and XDR-TB response plan 2007–2008. Geneva: World Health Organization; 2007. WHO reference number: WHO/HTM/TB/2007.387.
 50. World Health Organization. Report of WHO global task force on XDR-TB emergency meeting in Geneva, Switzerland, 9–10 October 2006. Geneva: World Health Organization; 2007. WHO reference number: WHO/HTM/TB/2007.375. Available from:

- <https://www.who.int/tb/publications/tb-xdrtb-report2006/en/> [cited 30 June 2020].
51. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. Geneva: World Health Organization; 2008. ISBN: 978 92 4 154758 1. WHO reference number: WHO/HTM/TB/2008.402.
 52. Udawadia ZF, Amale RA, Ajbani KK, Rodrigues C. Totally drug-resistant tuberculosis in India. *Clin Infect Dis* 2012 Feb 15; 54(4): 579–81. doi: 10.1093/cid/cir889
 53. Gupta R, Cegielski P, Espinal MA, Henkens M, Kim JY, Lambregts-van Weezenbeek CSB, et al. Increasing transparency in partnerships for health: introducing the Green Light Committee. *Trop Med Internat Health* 2002; 7: 970–6. doi: 10.1046/j.1365-3156.2002.00960.x
 54. Nathanson E, Lambregts-van Weezenbeek C, Rich ML, Gupta R, Bayona J, Blondal K, et al. Multidrug-resistant tuberculosis management in resource-limited settings. *Emerg Infect Dis* 2006; 12: 1389–97. doi: 10.3201/eid1209.051618
 55. W.H.O. Countries provide successful model for massive tuberculosis treatment scale-up. Available from: <https://www.who.int/mediacentre/news/releases/2006/pr24/en/> [cited 30 June 2019].
 56. Green Light Committee Initiative of the Working Group on Multidrug-resistant Tuberculosis Annual report 2009. WHO reference number: WHO/HTM/TB/2010.14. Available from: <https://www.who.int/tb/publications/tb-glcannual-report/en/> [cited 30 June 2019].
 57. Rich ML, Cegielski P, Jaramillo E, Lambregts-van Weezenbeek C (Eds-in-Chief). Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2006. WHO/HTM/TB/2006.36.
 58. Kurbatova EV, Gammino VM, Bayona J, Becerra M, Danilovitz M, Falzon D, et al. Predictors of sputum culture conversion among patients treated for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2012; 16(10): 1–9. doi: 10.5588/ijtld.11.0811
 59. Dalton T, Cegielski JP, Akksilp S, Ascencios L, Campos-Caoili J, Cho SN, et al. Prevalence of and risk factors for second-line drug resistance among adults with multidrug-resistant tuberculosis in eight countries: a prospective cohort study. *Lancet* 2012; 380(9851): 1406–17. doi: 10.1016/S0140-6736(12)60734-X
 60. Yuen CM, Kurbatova EV, Tupasi TE, Caoili JC, van der Walt M, Kvasnovsky C, et al. Association between regimen composition and treatment response in patients with multidrug-resistant tuberculosis: a prospective cohort study. *PLoS Med* 2015; 12(12): e1001932. doi: 10.1371/journal.pmed.1001932
 61. Smith S, Ershova J, Vlasova N, Nikishova E, Tarasova I, Eliseev P, et al. Risk factors for acquired anti-tuberculosis drug resistance during multidrug-resistant tuberculosis treatment in Arkhangelsk Oblast, Russia. *Emerg Infect Dis* 2015 Jun; 21(6): 1002–11. doi: 10.3201/eid2106.141907
 62. Cegielski JP, Dalton T, Yagui M, Wattanaamornket W, Volchenkov GV, Via LE, et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. *Clin Infect Dis* 2014; 59 (8): 1049–63. doi: 10.1093/cid/ciu572
 63. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012 Jun 7; 366(23): 2151–60. doi: 10.1056/NEJMoa1112433
 64. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014 Aug 21; 371(8): 723–32. doi: 10.1056/NEJMoa1313865
 65. Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, et al. A trial of a shorter regimen for Rifampin-resistant tuberculosis. *N Engl J Med* 2019; 380: 1201–13. doi: 10.1056/NEJMoa1811867
 66. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system: Policy statement. 15 February 2011. ISBN: 978 92 4 150154 5. WHO reference number: WHO/HTM/TB/2011.4.
 67. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis Interim policy guidance. 16 February 2013. ISBN: 978 92 4 150548 2. WHO reference number: WHO/HTM/TB/2013.6.
 68. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis Interim policy guidance. 10 June 2014. WHO reference number: WHO/HTM/TB/2014.23.
 69. US Food and Drug Administration. FDA approves new drug for treatment-resistant forms of tuberculosis that affects the lungs [media release]. Aug 14 2019. Available from: <https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-resistant-forms-tuberculosis-affects-lungs> [cited 7 February 2021]
 70. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* 2020; 382: 893–902. doi: 10.1056/NEJMoa1901814
 71. Cegielski JP. Tuberculosis multidrogo resistente en la era final de la tuberculosis. *Rev Peru Med Exp Salud Publica* 2018; 35(1): 110–7. doi: 10.17843/rpmpes.2018.351.3618
 72. Pablos-Méndez A, Raviglione MC, Laszlo A, Binkin N, Rieder HL, Bustreo F, et al. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance surveillance. Global surveillance for antituberculosis-drug resistance, 1994–1997. *N Engl J Med* 1998 Jun 4; 338(23): 1641–9. doi: 10.1056/NEJM199806043382301
 73. Laszlo A, Rahman M, Espinal M, Raviglione M; WHO/IUATLD Network of Supranational Reference Laboratories. Quality assurance program for drug susceptibility testing of *Mycobacterium tuberculosis* in the WHO/IUATLD Supranational Reference Laboratory Network: five rounds of proficiency testing, 1994–1998. *Int J Tuberc Lung Dis* 2002 Sep; 6(9): 748–56.
 74. Zignol M, Dean AS, Falzon D, van Gemert W, Wright A, van Deun A, et al. Twenty years of global surveillance of antituberculosis-drug resistance. *N Engl J Med* 2016 Sep 15; 375(11): 1081–9. doi: 10.1056/NEJMSr1512438
 75. World Health Organization Global Tuberculosis Database. Available from: <https://www.who.int/tb/country/data/download/en/> [cited 1 July 2019].
 76. The World Health Organization /International Union Against Tuberculosis and Lung Disease Global Project on Anti-tuberculosis Drug Resistance Surveillance 1994 – 1997. Anti-tuberculosis drug resistance in the world. Geneva: WHO Global Tuberculosis Programme, Geneva; 1997, p. 14. WHO/TB/97.229.
 77. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Atlanta, GA: Department of Health and Human Services; 2013.
 78. O’Neill, et al. Infection prevention, control and surveillance: limiting the development and spread of drug resistance. The

- review on antimicrobial resistance. World Bank; March 2016. Drug-resistant infections a threat to our economic future.
79. Nasreen S, Shokoohi M, Malvankar-Mehta MS. Prevalence of latent tuberculosis among health care workers in high burden countries: a systematic review and meta-analysis. *PLoS One* 2016; 11(10): e0164034. doi: 10.1371/journal.pone.0164034
 80. Iseman MD. A clinician's guide to tuberculosis. Philadelphia, PA: Lippincott Williams & Wilkins; 2000, pp. 115–28.
 81. Tellier R, Li Y, Cowling BJ, Tang JW. Recognition of aerosol transmission of infectious agents: a commentary. *BMC Infect Dis* 2019; 19: 101, 1–9. doi.org/10.1186/s12879-019-3707-y
 82. Nelson KE, Williams CM, eds. Infectious disease epidemiology: theory and practice – 3rd ed. Burlington, MA: Jones & Bartlett; 2014, pp. 465–610.
 83. Masur H, Emanuel E, Lane HC. Severe acute respiratory syndrome: providing care in the face of uncertainty. *JAMA* 2003; 289: 2861–3. doi: 10.1001/jama.289.21.JED30036
 84. Centers for Disease Control and Prevention. Update: outbreak of severe acute respiratory syndrome – worldwide, 2003. *MMWR* 2003; 52(12): 241–8.
 85. International Labour Organization. Meeting of experts on updating the list of occupational diseases: report. Geneva, International Labour Organization; 13–20 December 2005, MEULOD/2005/10. Available from: <http://www.ilo.org/public/english/standards/relm/gb/docs/gb295/pdf/meulod.pdf> [cited 25 February 2020].
 86. Transatlantic Taskforce on Antimicrobial Resistance (TATFAR). TATFAR progress report May, 2014.
 87. World Health Organization. WHO guidelines on tuberculosis infection prevention and control, 2019 update. Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO.
 88. Scott C, Mangan J, Tilova Z, Jensen PA, Ahmedov S, Ismoilova J, et al. Evaluation of the Tuberculosis Infection Control Training Center, Tajikistan, 2014–2015. *Int J Tuberc Lung Dis* 2017 May 1; 21(5): 579–85. doi: 10.5588/ijtld.16.0518
 89. Cirule A. Oral presentation. Available from: https://www.who.int/tb/events/archive/icmeeting_oct07/05_cirule.pdf [cited 1 July 2019].
 90. Volchenkov G. Oral presentation: the global crisis of drug-resistant TB and leadership of BRICS countries: challenges and opportunities. Available from: <http://nationalacademies.org/hmd/~media/Files/Activity%20Files/Research/DrugForum/2013-JAN-16/Presentations/January%2017%20%20Session%20II%20%20Volchenkov%20Grigory.pdf> [cited 1 July 2019].
 91. Dokubo EK, Odume B, Lipke V, Mulanga C, Onu E, Olutola A, et al. *MMWR* – building and strengthening infection control strategies to prevent tuberculosis – Nigeria, 2015. *Weekly* 2016; 65(10): 263–6. doi: 10.15585/mmwr.mm6510a3
 92. Ayalew A, Gashu Z, Anteneh T, Hiruy N, Habte D, Jerene D, et al. Improvement in tuberculosis infection control practice via technical support in two regions of Ethiopia. *BMC Infect Dis* 2018; 18: 557. doi: 10.1186/s12879-018-3459-0
 93. Mphahlele MT, Tudor C, Van der Walt M, Farley J. An infection control audit in 10 primary health-care facilities in the Western Cape Province of South Africa. *Int J Infect Control* 2012; 8(3). doi: 10.3396/ijic.v8i3.025.12
 94. Engelbrecht MC, Kigozi G, van Rensburg APJ, van Rensburg DHJ. Tuberculosis infection control practices in a high-burden metro in South Africa: a perpetual bane for efficient primary health care service delivery. 2018 May 30.
 95. Farley JE, Tudor C, Mphahlele M, Franz K, Perrin NA, Dorman S, et al. A national infection control evaluation of drug-resistant tuberculosis hospitals in South Africa. *Int J Tuberc Lung Dis* 2012 Jan; 16(1): 82–9. doi: 10.5588/ijtld.10.0791
 96. Hospital Infections Program, National Center for Infectious Diseases, CDC. Public health focus: surveillance, prevention, and control of nosocomial infections. *MMWR Weekly* 1992; 41(42): 783–7.
 97. Dixon RE. Control of health-care-associated infections, 1961–2011. *MMWR* 2011; 60: 58–63.
 98. Castro KG, Marks SM, Chen MP, Hill AN, Becerra JE, Miramontes R, et al. Estimating tuberculosis cases and their economic costs averted in the United States over the past two decades. *Int J Tuberc Lung Dis* 2016 July; 20(7): 926–33. doi: 10.5588/ijtld.15.1001
 99. End TB Transmission Initiative. TB infection control in national TB program reviews. Geneva: Stop TB Partnership; 2018.
 100. Chai SJ, Mattingly DC, Varma JK. Protecting health care workers from tuberculosis in China: a review of policy and practice in China and the United States. *Health Policy Plan* 2012. doi: 10.1093/heapol/czs029
 101. Tudor C, Van der Walt M, Hill MN, Farley JE. Occupational health policies and practices related to tuberculosis in health care workers in KwaZulu-Natal, South Africa. *Public Health Action* 2013; 3(2): 141–5. doi: 10.5588/pha.12.0098
 102. Castro JL. The World Health Organization made a big mistake on TB. It must fix it. *Stat News*, March 13, 2017. Available from: <https://www.statnews.com/2017/03/13/tuberculosis-who-antibiotic-resistance/> [cited 21 May 2019].
 103. Ditiu L, Spigelman M, Castro JL. A baffling omission from the ‘priority pathogen’ list. *Financial Times*, March 5, 2017.
 104. Stop TB Partnership. Open Letter to the WHO to put #TbontheList. TB Community Demands WHO to include #TbontheList! Available from: http://www.stoptb.org/news/stories/2017/ns17_014.asp [cited 7 February 2021]
 105. Green Light Committee. Instructions for applying to the Green Light Committee for access to second line anti-TB drugs, 2nd ed. Geneva: World Health Organization; 2006. WHO/HTM/TB/2006.369.
 106. U.S. Congress, Office of Technology Assessment. Impacts of antibiotic-resistant bacteria, OTA-H-629. Washington, DC: U.S. Government Printing Office; September 1995.
 107. Rosenkrantz BG. Coverage of antibiotic resistance in the popular literature, 1950 to 1994. Historical review: responses to antibiotic resistance. Contract Report to the Office of Technology Assessment; 1995.
 108. The White House. National Action Plan for combating antibiotic-resistant bacteria. March 2015.
 109. Hubel DH, Wiesel TN. Brain mechanisms of vision. *Sci Am* 1979 Sep; 241(3): 150–62. doi: 10.1038/scientificamerican0979-150
 110. Vlaev I, King D, Dolan P, Darzi A. Theory and practice of ‘nudging’: changing health behaviors. *Public Admin Rev* 1979 July/August; 76(4): 550–561. doi: 10.1111/puar.12564
 111. Dyson J, Lawton R, Jackson C, Cheater F. Development of a theory-based instrument to identify barriers and levers to best hand hygiene practice among health care practitioners. *Implement Sci* 2013; 8: 111. doi: 10.1186/1748-5908-8-111

***J. Peter Cegielski**

Independent Consultant
 1361 Council Bluff Drive NE
 Atlanta, GA 30345
 USA
 Email: pcegielski11@comcast.net