
Resilience

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***Standing together:
A co-ordinated response to drug resistance and other novel threats to public health***

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Determining the individual roles and responsibilities of the key parties in averting and tackling antimicrobial resistance is a matter of increasing urgency.

In its Global Risk Report 2013¹, the World Economic Forum (WEF) concluded that antibiotic resistance poses a major risk to human health. PwC's analysis of this case study, highlights the particular danger of complacency over antibiotic resistance—or more broadly, antimicrobial resistance (AMR)²—with many people assuming that advances in medical science will allow humanity to stay one step ahead of new and evolving infectious diseases or what may be broadly termed novel pathogens.

Many recent events have called this presumption into question.

In 2012, an outbreak of *K. pneumoniae*, an antibiotic-resistant superbug, killed 18 people at the U.S. National Institutes of Health's Clinical Center in Maryland. In the same year, physicians at Hinduja National Hospital in India reported that 12 patients had contracted a form of tuberculosis (TB) that had not responded to any known TB treatment; three of the cases

proved fatal.³ Subsequent tests confirmed that eight of these patients had contracted total drug resistant (TDR) TB, meaning they were resistant to all known first and second-line TB medications.⁴

The combination of AMR pathogens and other infectious diseases can produce an even greater threat. A 2011 study revealed that many of the 2009-2010 H1N1 influenza pediatric deaths occurred among children who had also acquired antibiotic-resistant bacterial infections. Researchers examined 838 pediatric intensive care cases across the United States and found that simultaneous infection with methicillin-resistant staphylococcus aureus (MRSA) bacteria produced an eightfold increase in the risk of death.⁵ While the risk of death is a frightening reality for patients afflicted with an AMR infection, there is greater concern that the prevalence and persistence of superbugs will cause an exponential rise in health care costs and the incidence of major personal disability.

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1 World Economic Forum Global Risk Report 2013: The Dangers of Hubris on Human Health < link: <http://reports.weforum.org/global-risks-2013/view/risk-case-1/the-dangers-of-hubris-on-human-health/> >

2 The broader threat to human health involves not just bacteria, but also viruses, parasites, and other existing and novel pathogens. Collectively referred to as microbials, the framework and resilience practices described within this paper can be applied more broadly to address anti-microbial vs. antibiotic resistance

3 Tuberculosis: The Second Coming, *The Economist*, January 2002. < link: <http://www.economist.com/blogs/babbage/2012/01/tuberculosis> >

4 National Tuberculosis Institute validates Hinduja Hospital's report that 8 infected people are fully drug resistant, *The Times of India*, May 2012. < link: http://articles.timesofindia.indiatimes.com/2012-05-02/mumbai/31537667_1_state-tb-tdr-tb-tb-patients >

5 "MRSA a major factor in kids' H1N1 flu deaths, study finds," *The Washington Post*, November 7, 2011. < link: http://www.washingtonpost.com/blogs/the-checkup/post/mrsa-a-major-factor-in-kids-h1n1-flu-deaths-study-finds/2010/12/20/gIQAUWBluM_blog.html >

In addition to having severe individual and global public health consequences, such disease outbreaks can have tremendous economic implications for both companies and countries. Outbreaks of novel pathogens may result in a sudden spike in workplace absenteeism, reduced travel and tourism, a downturn in trade, overburdened hospitals, increased insurance premiums, and increased rates of death and disability. However, unlike other catastrophic risks like earthquakes, hurricanes and nuclear or chemical threats, infectious diseases are living organisms capable of evolving and adapting for survival. In 2003 an outbreak of some unknown pathogen stormed across Asia before spreading to Europe, Australia, Africa and North and South America. By the time the outbreak was over, the contagion identified as a novel coronavirus and named SARS, had caused the deaths of 774 people and infected over 8,000 other individuals, worldwide—all within the span of nine months⁶.

Given the impact of disease on both health and the economy, the concerns over AMR infections are shared by individuals, corporations, national governments and international organizations. However, despite the common understanding that AMR is worsened by overuse, stakeholders are incentivized to act in their own interest rather than that of the common good. Patients will seek treatment if ill, clinicians will prescribe, pharmacies fill, and drug companies sell, without consideration for the potential longer-term impact.

Initiatives undertaken to address AMR have mostly been voluntary and have been impeded by a lack of coordination and integration. We need to take

concerted action now before it's too late. Antimicrobials are a limited resource that we risk depleting, and once gone, we will be hard pressed to recover. The dangers are heightened by the fact that the current antimicrobial pipeline is weak. As such, the challenge of becoming resilient in the face of an increase in AMR has taken on increased urgency, presenting a critical frontier in the on-going battle to preserve the length and quality of human life.

A plan for action—Building on the WEF response

In PwC's response to the WEF case study, we take an expanded view to focus on the underlying threat of novel pathogens. First, we move beyond the challenge of antibiotic resistance, which applies only to bacterial infections, and include all communicable pathogens such as viruses and fungi, against which antimicrobials are used. Overuse of antimicrobials increases the natural rate of genetic mutation in pathogens. This man-made, accelerated evolution of disease is culpable for the higher incidence and prevalence of novel pathogens. While the emergence of communicable disease is a major concern, it is our weakened ability to fend off such diseases that makes this a global public health imperative. Using our past events as a prologue for today, the world must act quickly and strategically to bolster our existing arsenal of antimicrobials and diagnostics, which are or will rapidly become completely ineffective.

Yet AMR is just one of three main catalysts for the accelerated emergence and evolution of novel pathogens we're seeing today. The second factor, increased contact between human and

animal populations, as well as travel, has created an environment where pathogens are readily passed between species—creating a global mixing bowl of pathogens. The third catalyst is, ironically, our advances in biomedical. Tools such as genetic engineering provide the ability to custom-build microbes, including novel man-made pathogens.

To address the unprecedented acceleration in the emergence and evolution of novel pathogens, a public and private sector organizations must alter how they perceive and approach the problem; moving towards proactive integration of individual efforts that all support a higher-level, comprehensive framework. Recognising the global nature of the threat and the multitude of contributing factors, the World Economic Forum and the World Health Organization have called for a solution that involves greater international and multi-stakeholder collaboration. Recommendations include creating public-private partnerships, and embarking on international efforts to lower barriers in drug development, to name a few. We suggest going a step further and confronting the challenge as a manageable system of interconnected activities and incentives.

In our response to the WEF case study, we recommend adding structure around this collaboration, outlining a basic framework for a robust, comprehensive, and integrated response built around the pillars of detect, develop and deliver. This framework addresses the capabilities needed to become resilient against these novel pathogens—to continuously and rapidly identify, characterise, develop and make available treatments against them. It also looks at how to

6 The Economic and Social Impact of Emerging Infectious Disease: Mitigation through Detection, Research, and Response (accessed via http://www.healthcare.philips.com/main/shared/assets/documents/bioshield/ecoandsocialimpactofemerginginfectiousdisease_111208.pdf)

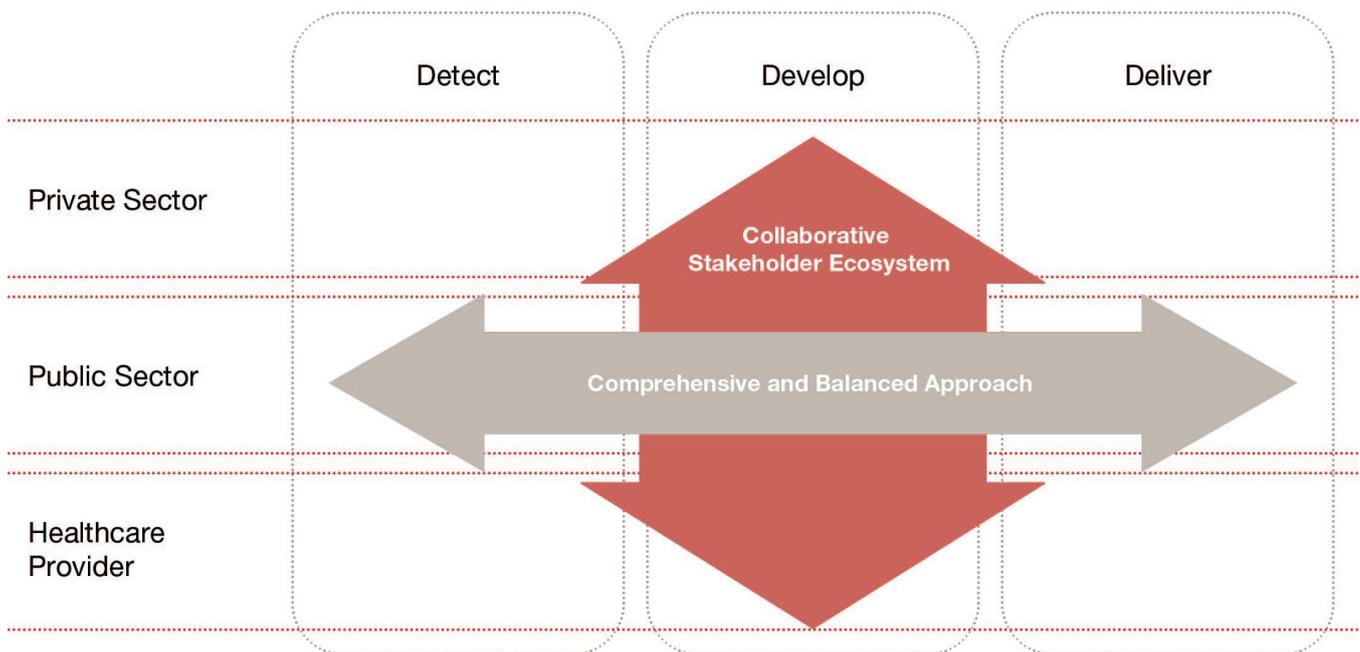
re-align incentives to reduce activities that accelerate the emergence of novel pathogens.

In this article, we will expand upon this framework by further exploring the role of each stakeholder group in combating the issue.

Combating resistance— A framework for practical implementation

The call for an international and multi-stakeholder solution in the fight against resistance is much more challenging in practice than in theory.

A structured approach toward addressing this challenge can facilitate both planning and execution. We propose that any effective solution include the following elements:



- **A comprehensive, balanced approach:** A successful response requires action across the healthcare continuum, from pathogen detection through delivery of care. A comprehensive approach includes understanding the desired outcomes and basic activities required in a response, and directing resources appropriately to enable effective execution of those activities.
- **A collaborative stakeholder ecosystem:** Since many organisations have a role to play in responding to AMR, any framework for response must include an assessment of the stakeholder ecosystem. To build resilience, it is critical to understand the roles, motivations, and interdependencies of each stakeholder and any factors that might result in inaction or insufficient action.

1. *What needs to be done?*

A balanced approach that spans the continuum of care: Detect, Develop and Deliver:

- **Detect:** Developing a health surveillance capability that enables rapid detection and characterisation of novel pathogens. Detection also includes the sharing of information across the ecosystem of stakeholders to prompt a timely response.
- **Develop:** Augmenting the arsenal of antimicrobials available to combat novel pathogens.

- **Deliver:** Improving the accessibility of diagnostics and antimicrobials worldwide with responsible use policies and practices.

An imbalance in any of these elements, represented by insufficient resources or outcomes, will result in an incomplete and ineffective solution. For example, governments may build state-of-the-art health surveillance capabilities, but without treatment or an effective mechanism for delivery, the root causes contributing to resistance will not be addressed, and the problem will persist and worsen. Rather, in a comprehensive response, all three elements must be present and working as intended.

2. *Who should be involved?*

Responsibility for combating the problem isn't isolated to governments or health systems, but rather must involve a comprehensive and coordinated 'ecosystem' approach. This implies combined and synchronised efforts from all stakeholders involved in the Detect-Develop-Deliver spectrum, which broadly includes the private sector, public sector and healthcare providers (HCPs). While PwC's response to the WEF case study generally introduces the reader to each stakeholder group, this article will detail the roles and responsibilities of each group, as well as explore the role that each stakeholder should play in risk mitigation.

- **Private sector:** Primarily comprised of product developers. In the case of AMR, these organisations develop drugs, platform technologies, new molecular diagnostic tests and more. Non-pharmaceutical companies also have an important role to play. Large employers with global footprints have access to huge sets of valuable data, which can be referenced for the purposes of surveillance, advocacy and information sharing. While commercial opportunities for these organisations are limited, non-pharmaceutical companies may be compelled into action as leaders in maintaining healthy and productive workforces.
- **Public sector:** Includes advocacy groups (e.g., Alliance for the Prudent Use of Antibiotics), professional organisations (e.g., Infectious Diseases Society of America) regulatory authorities (e.g., European Medicines Agency), academia, NGOs (e.g., Project Hope) and international organisations (e.g., WHO) and policy-makers/funders (e.g., national and local governments).
- **Health care providers:** Includes the healthcare payer and provider community, including patients.

Where does your organisation fit?

Each stakeholder group identified in our analysis plays a role in each of the Detect, Develop and Deliver pillars, though some are especially prominent (Detect–public sector, Develop–private sector, Deliver–HCPs). Primary

stakeholders are often supported by secondary actors that may play an equally important, albeit indirect role.

Acknowledging and understanding the role that each actor should play within each pillar of response is critical to building resilience. Practices aimed at improving resilience should consider

the unique challenges that prevent each stakeholder from performing the role required to combat resistance, and should focus on establishing incentives for stakeholders to perform activities outlined in **Figure 1** below and described further in this article.

Figure 1: Outlining roles and responsibilities

	Detect	Develop	Deliver	
Product Developers	<ul style="list-style-type: none"> Work with public sector to identify current and future AMR threats, identify challenges, and define policies AMR threats and policies and challenges Understand trends to improve market forecasting 	<ul style="list-style-type: none"> Design business models designed to support pre- or non-competitive research and development ('diplomacy') Develop broad spectrum TPPs, platform technology, and new molecular Dx tests 	<ul style="list-style-type: none"> Deliver commercially viable product to target populations (globally) through manufacturing, pricing, distribution, and/or marketing strategy 	Private sector
Advocacy Groups	<ul style="list-style-type: none"> Identify patterns of disease and direct the focus of stakeholders toward priority issues and challenges 	<ul style="list-style-type: none"> Facilitate spread of best practices and S&T across industries & sectors Facilitate public/private sector dialogue and recommend research and development policy 	<ul style="list-style-type: none"> Increase awareness and attention to the issue Communicate guidelines and policies to healthcare (HC) provider communities 	
Regulatory Authority	<ul style="list-style-type: none"> Utilize post marketing surveillance data to monitor product usage (human/ animal), patient readmission rates, and potentially detect or predict AMR/patterns of disease 	<ul style="list-style-type: none"> Adopt new regulatory approaches to facilitate research and development (priority review vouchers; conditional approvals incentives)³ Develop Clinical Trial Guidance and support Critical Path Initiatives⁴ 	<ul style="list-style-type: none"> Adopt/implement quality management systems to stop counterfeits Implement global regulatory framework to improve supply chain processes and security (reduce theft, counterfeit, etc) 	Public sector
Academia	<ul style="list-style-type: none"> Monitor global health trends and identify novel and (re) emerging pathogen threats Support and leverage clinical laboratory networks and facilities 	<ul style="list-style-type: none"> Deliver early stage research and development (lead compounds) to bolster the antimicrobial product development pipeline Leverage government/private sector infrastructure, capabilities and resources for research 	<ul style="list-style-type: none"> Recommend best practices for prevention and control of AMR and deliver/distribute knowledge openly to the global community 	
Policy-Makers & Funders	<ul style="list-style-type: none"> Establish disease surveillance systems and networks Recommend policies that facilitate the exchange of information/data (globally) such as TATFAR 	<ul style="list-style-type: none"> Establish antibiotic research and development incentive programs (GAIN) Develop and implement value-based reimbursement policies⁵ Support Public Private Partnerships 	<ul style="list-style-type: none"> Recommend prevention and control policies (rational use, increase vaccine and immunizations) Seek co-funding or co-development opportunities for novel antimicrobial treatments and diagnostics 	
HC Provider Community	<ul style="list-style-type: none"> Establish locally based sentinel surveillance systems (active surveillance program in Wyoming for DRSP)² 	<ul style="list-style-type: none"> Contribute to clinical specimen repositories, provide data through network (sentinel) labs 	<ul style="list-style-type: none"> Establish medical staff-approved antimicrobial stewardship programs (AMSP) in all healthcare environments¹ 	Healthcare providers
	Information & Data	Technology & Tools	Operations, Processes and Services	

Source: PwC

1. DETECT

Private sector: While the private sector is generally a secondary actor in detection, it is a consumer of information gathered by other stakeholder groups. The private sector can use this information to improve market forecasting and, in turn, profitability. Increased and early visibility of the spread of a novel pathogen will reduce lead times associated with research and development (R&D), regulatory approval, distribution and dispensing, policies for diagnostics and concomitant treatment—or lead times associated with R&D, regulatory approval, distribution and dispensing, policies for new diagnostics and concomitant treatment. In the absence of full access to data related to emerging trends and potential demand, private sector actors may not have meaningful incentives to invest in product development.

Public sector: Public sector actors play a primary role in the detection phase. Roles and responsibilities typically include implementing disease surveillance systems, facilitating the exchange of information, monitoring product usage and identifying, monitoring and communicating trends. National borders and differences in regulatory systems, however, present a challenge to international collaboration and information sharing, and may negatively impact the timely dissemination of data across the stakeholder ecosystem, including to the HCP community.

Health care providers: HCPs are also secondary actors in detection, although their role in this pillar is critical. Since infected patients will typically seek treatment through a number of

channels, any single HCP will not have access to, or visibility of, the full range of data that can ease the identification of emerging trends. However, by recording information and reporting to relevant authorities in a timely manner, HCPs can speed up the process through which the spread of a pathogen is identified. Ineffective communication between the public sector and HCPs may result in delays associated with accurately diagnosing a disease—leading to the use of antimicrobials where not appropriate, or exacerbating the problem of resistance.

2. DEVELOP

Private Sector: The private sector is a primary actor in the development of new medicines, platform technologies and kits that enable effective diagnosis and treatment of diseases. However, since limited commercial incentives exist for developing new antimicrobials, private sector actors are generally more focused on developing treatments for which there is a longer duration of care (e.g., non-communicable diseases). Such circumstances result in a limited pipeline for new and innovative products.

Public sector: Public sector actors play a secondary role in antimicrobial development. Roles and responsibilities include performing early-stage R&D, providing funding for advanced-stage R&D, sharing best practices and encouraging dialogue between public and private sectors. Regulators may introduce incentives to facilitate R&D through initiatives such as priority review vouchers and conditional approvals. Barriers to public sector participation include justifying time and resources spent on addressing AMR at the expense of other priority challenges.

Health care providers: HCPs collect, catalogue and store biological material for the purpose of laboratory research. HCPs may help perform clinical trials and can share lab results pertinent to research and development. HCPs may also contribute to the specification of product requirements (Target Product Profiles) for therapeutic interventions. Challenges faced by HCPs primarily include the timely sharing of information with product developers, and the availability of accurate diagnostics to ensure appropriate treatment.

3. DELIVER

Private Sector: The private sector is a secondary actor in the deliver pillar. Once products have been developed and tested, and have cleared all necessary regulatory hurdles, the private sector has a vested interest in marketing products to increase potential sales. Product developers are also responsible for manufacturing and delivering products to the market and for developing competitive pricing strategies. These organisations play a critical role in assuring the affordability and availability of key drugs in global markets, and in educating consumers on appropriate use. Private sector actors also have a commercial incentive to protect against counterfeit/sub-par quality drugs—another factor contributing to increased resistance. Barriers to full private sector participation in delivery include insufficient manufacturing and delivery capacity to meet global demand, limited commercial attractiveness in some markets, and poor delivery infrastructure to some locations.

Public sector: Public sector actors play a secondary role in the deliver pillar, encouraging the adoption of consistent standards and policies to be adopted by national and local governments related to proper dispensing, rational use and aligning health system incentives. Public sector organisations often take a lead role in educating patients on appropriate use of products, and can facilitate Public Private Partnerships (PPPs) focused on improving access to and availability of products. Regulators issue guidance on quality management standards to combat counterfeit products. Public sector challenges related to deliver include coordinating and standardising policies across governments and other public health organisations that are required for a consistent and systematic response.

Healthcare providers: HCPs play a primary role in the deliver pillar, as they are the closest to the patient. HCPs are responsible for diagnosing diseases and prescribing the appropriate courses of action. Formularies play a direct role in educating patients that seek treatment at hospitals, clinics, and/or pharmacies. They are responsible for implementing guidance and policy dictated by the public sector. Misaligned doctor and health system incentives and the limited availability of accurate diagnostics may result in inaccurate diagnoses and can result in inappropriate treatment.

Turning understanding into action

This series of articles is intended to inform and motivate. As a collaborative ecosystem of stakeholders we are all involved in the fight against AMR irrespective of whether or not we work in the organisations spotlighted in this article. We are patients and families of patients. We are active in our communities, and are international travellers. We are business leaders looking out for our workforces and our revenues, and online global citizens with the means to influence. Understanding the role that we each play in the ecosystem is an important first step. Following from this understanding, we must develop a coordinated and integrated action plan that addresses the challenges and barriers that might cause us to deviate from these roles.

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