Antimicrobials: access and sustainable effectiveness

A *Lancet* series of 5 articles

Molly Miller-Petrie

Antimicrobial Stewardship Workshop

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Global Antibiotic Resistance Partnership

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Supporting National Action

- Lancet commentary signed by Ministers of Health from Kenya, Mozambique, South Africa and India.

- In Kenya in 2015, the Ministry of Health formed a multi-sectoral National Antimicrobial Resistance advisory committee with representatives from human and animal health, and created a position for an antimicrobial resistance focal point. The Ministry is now designing a national-level plan, with support from the advisory committee. The Ministry also actively supports formal awareness-raising activities throughout the country.

- The Global Antibiotic Resistance Partnership (GARP) continues to support these efforts as it expands in Phase III to two regional hubs: one in southern and eastern Africa and one in south and southeast Asia.

Access to effective antimicrobials: a worldwide challenge

Ramanan Laxminarayan and colleagues

Key messages

Access

- *Antibiotic consumption in humans is increasing globally, driven by rising incomes, health insurance and a large remaining burden of infectious disease*
- *Lack of access and delays in access to antibiotics kill more people than antibiotic resistance.*
  - We estimate that universal provision of antibiotics could avert 0.445 million (min: 0.332 million; max: 0.541 million) community-acquired pneumonia deaths in children aged 0-5 years, a 75.4% (min: 60.7%; max: 85.0%) reduction across the 101 countries in our analysis.

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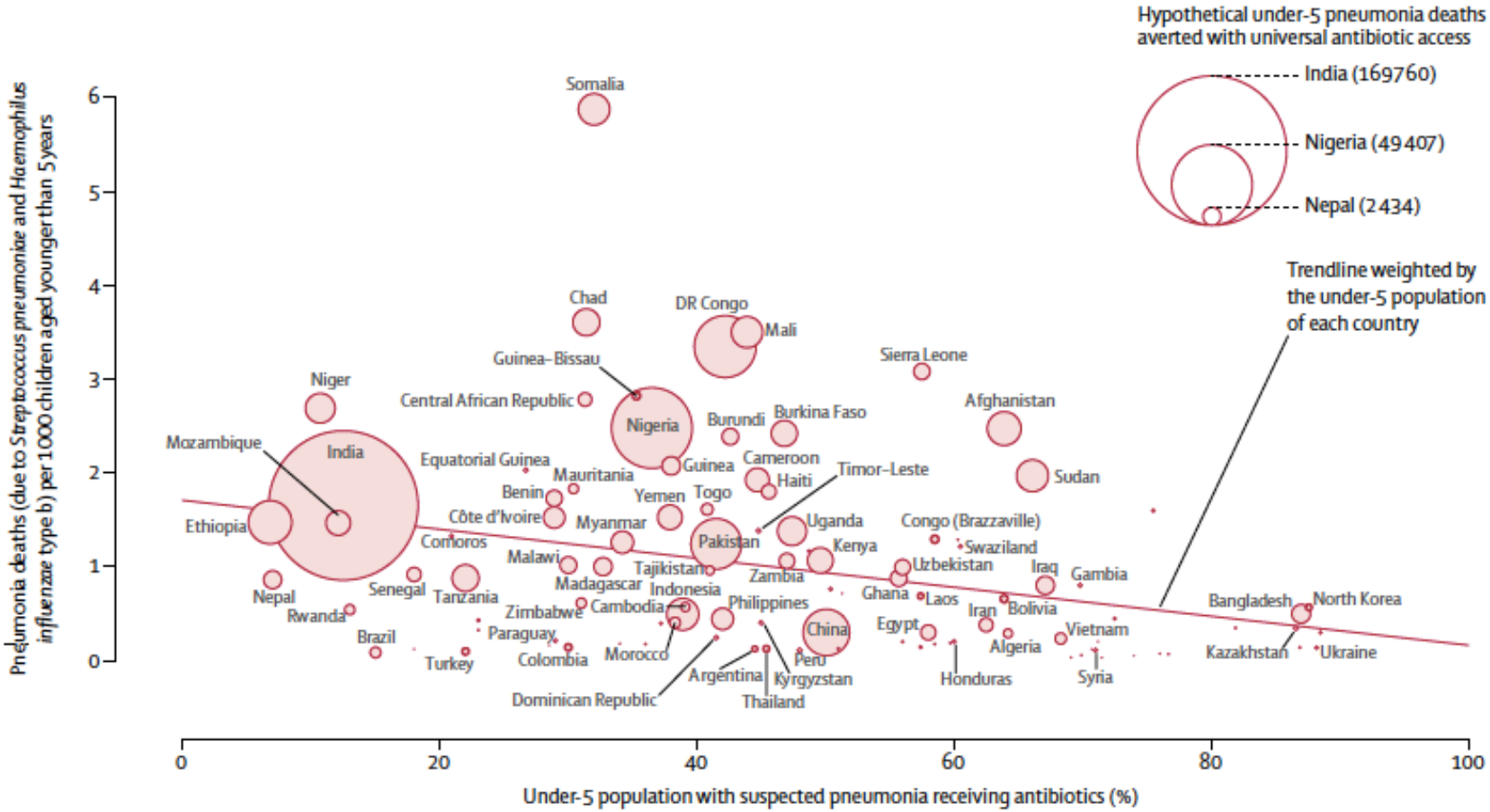
Estimated pneumonia deaths avertable in children <5 with antibiotic access



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Access to effective antimicrobials: a worldwide challenge

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Key messages

Resistance

- *Resistance to antibiotics threatens gains made in child survival.*
  - Globally, an estimated 0.214 million neonatal sepsis deaths (min: 0.139 million; max: 0.318 million) are attributable to resistant pathogens each year.

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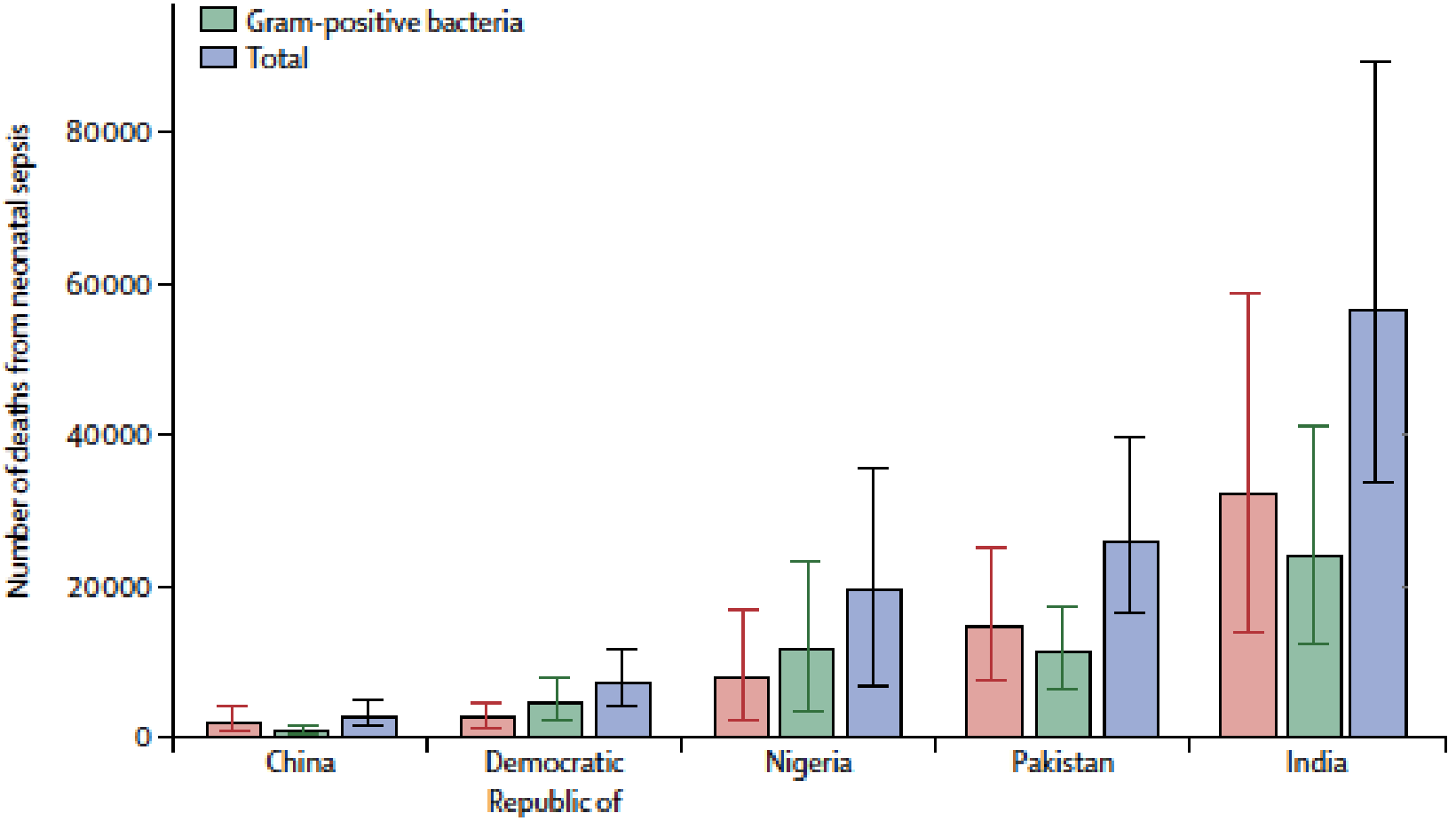
Estimated neonatal sepsis deaths attributable to resistance to first-line antibiotics in 5 high-burden countries



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Access to effective antimicrobials: a worldwide challenge

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Key messages

Vaccines

- *Scaling up vaccines against pneumococcus and Haemophilus influenzae type b (Hib) could avert the need for antibiotics globally and reduce selection pressure.*
    - We estimate that universal coverage with a pneumococcal conjugate vaccine could avert up to 11.4 million days of antibiotics for pneumonia caused by *Streptococcus pneumoniae* in children under 5 per year, a 47% reduction in days on antibiotics in the 75 countries included in our analysis.

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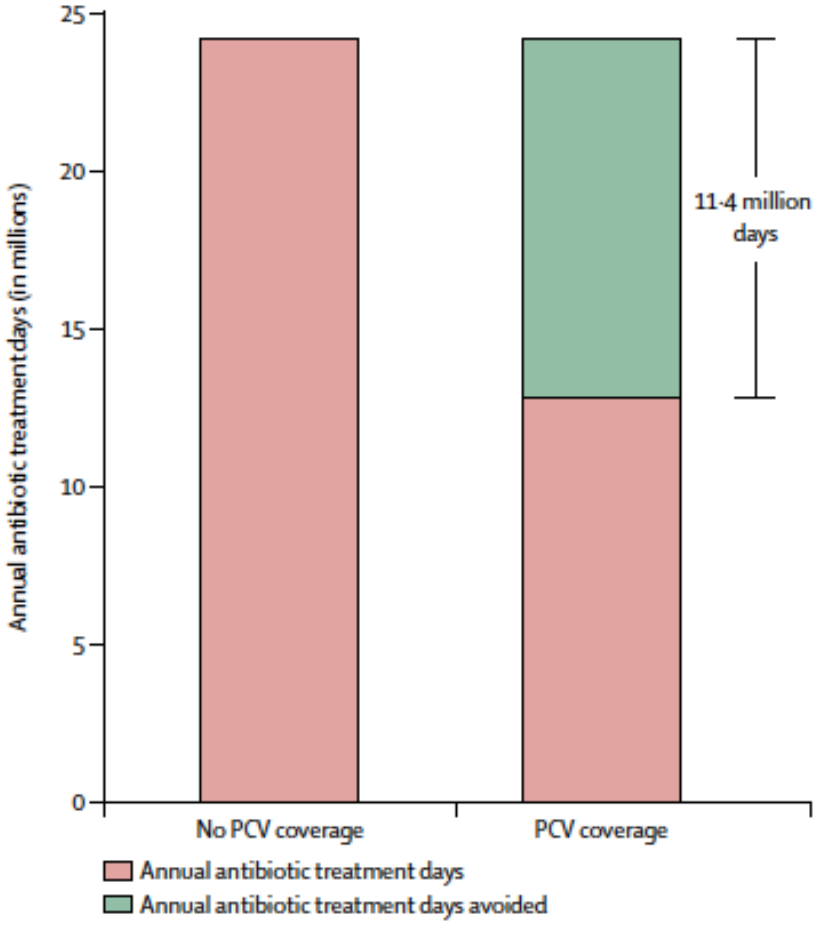
Days on antibiotics for suspected pneumonia avertable by pneumococcal conjugate vaccine



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Key messages

Animal health

- *Antibiotics are an essential element of animal health but the increasing use of antibiotics in sub-therapeutic concentrations for growth promotion and disease prevention (as a substitute for hygiene) is placing significant selection pressure for resistance to evolve.*
    - Global antimicrobial consumption in animals is projected to rise by 67% from 63,151 (±1,560) tons in 2010 to 105,596 (±3,605) tons in 2030, and nearly double in the BRICS countries over that period, placing significant selection pressure on susceptible bacteria. A one-health approach to improving animal health that recognizes the interlinked nature of animal and human health is essential.

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Taking action in Africa

- Increase access to antibiotics
- Improve time to treatment and quality of treatment
- Increase water and sanitation coverage
- Increase vaccination coverage particularly for Hib, pneumonia, influenza and rotavirus
- Reduce antibiotic use in agriculture

Understanding the mechanisms and drivers of antimicrobial resistance

Alison H. Holmes and colleagues

Key messages

- The emergence of AMR is a natural evolutionary response to antimicrobial exposure. At a societal level, complex and interlinking drivers are increasing prevalence of AMR microbes, predominantly arising from use in humans and agriculture and the pollution of the environment.

- Acquisition of AMR mechanisms does not necessarily compromise microbial fitness. Worldwide clonal spread and long-term persistence of resistant bacteria are also seen in the absence of direct antibiotic selection pressure.

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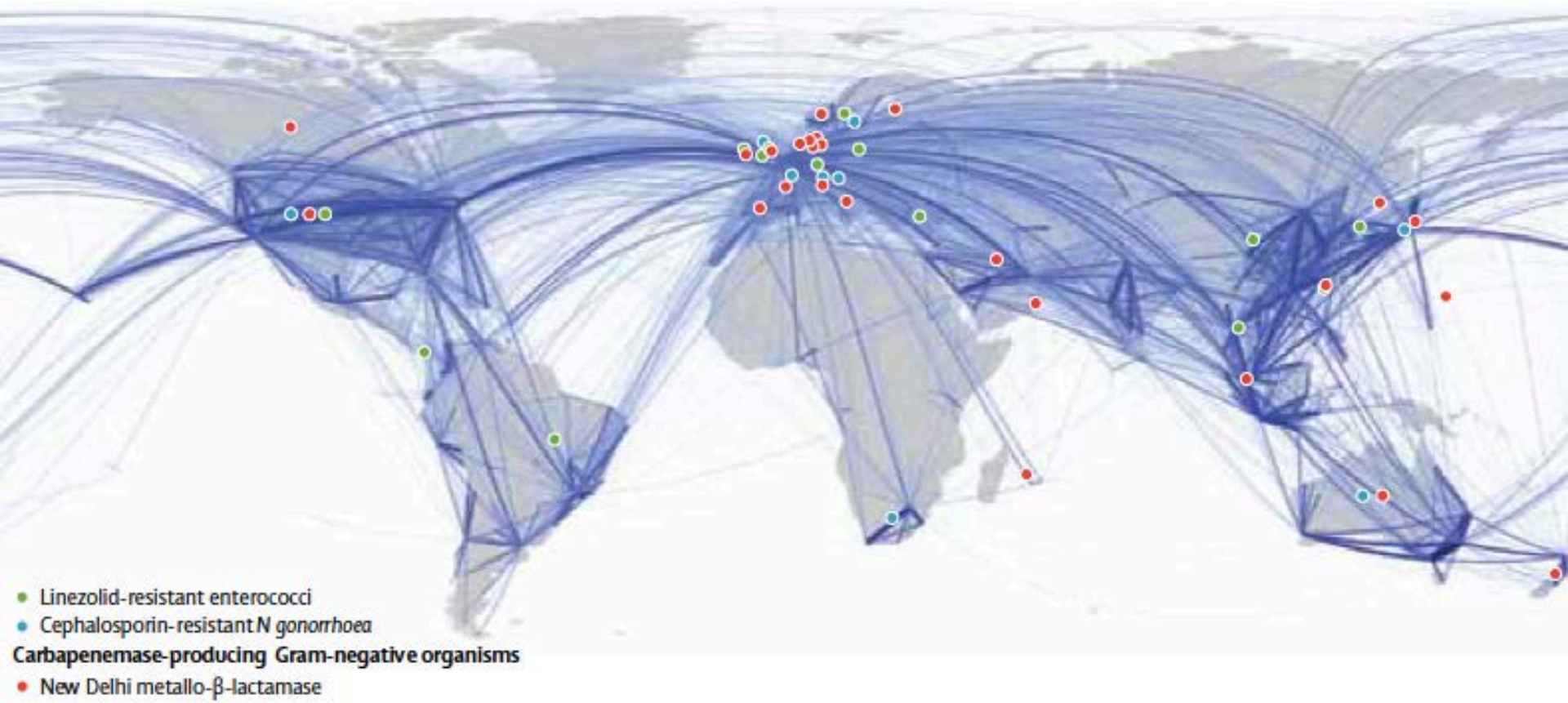
Worldwide travel routes and emergence of antimicrobial resistance



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Understanding the mechanisms and drivers of antimicrobial resistance

Alison H. Holmes and colleagues

Key messages

- Reversibility of AMR following withdrawal of antimicrobial selective pressure is consequently not clear cut; minimising emergence of resistance to new and future agents is therefore essential.

- Gaining insight into the mechanisms of AMR, long-term persistence, and successful clonal spread, is fundamental to the development of novel targets for both diagnostic tests and therapeutic agents with integration of these into sustainable AMR strategies.

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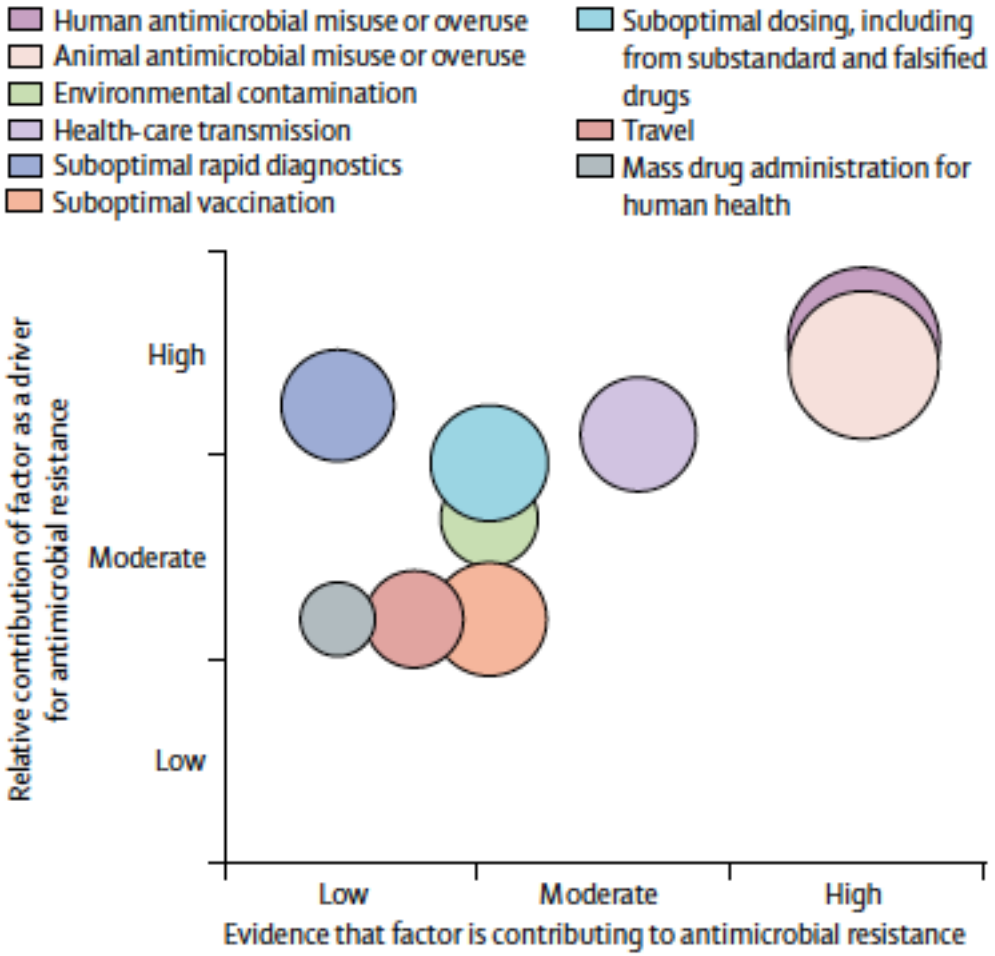
Role of modifiable drivers towards antimicrobial resistance: a conceptual framework



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Understanding the mechanisms and drivers of antimicrobial resistance

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Key messages

- Gaps in understanding and areas for innovation are clear, yet progress towards these goals is still urgently needed, with a careful awareness of any potential impact on access to effective antimicrobial treatment.

- There is no single solution and multiple, synergistic, overlapping and complementing approaches will be needed, with a strong overarching shared goal to ensure and sustain access to effective antimicrobial therapies.

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Taking action in Africa

- Increase understanding of the effectiveness of stewardship programs and the optimization of antibiotic use
- Ban antimicrobial use for growth promotion in animals
- Increase access to non-medicated animal feed
- Restrict antibiotic classes to animal or human use
- Utilize a one health approach
- Expand research on the quality of existing antimicrobials
- Increase availability of international resistance data

Maximising access to achieve appropriate human antimicrobial use in low- and middle-income countries

Marc Mendelson and colleagues

Key messages

- Access to assured quality antimicrobials is part of the human right to health yet universal access is often undermined in LMICs
- There is no single model that increases access while limiting excess, hence access programmes must be context-adjusted and apply across the healthcare spectrum.
- To achieve appropriate antimicrobial prescribing, LMICs must strengthen their health systems including health insurance, provision of laboratory support, and increased access to diagnostics and primary prevention measures.

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Panel 2: **Persuasive and restrictive interventions from economically developed settings that could be adapted for possible use in low-income and middle-income countries**

Community practitioners

- Multifaceted interventions are most effective at achievement of overall reduction in antibiotic use, and interactive educational approaches outperform didactic education.[66]
- Blended learning programmes with a combination of online, seminar-based, and context-bound learning with practice using simulated patients might be beneficial in settings where relevant facilities (eg, reliable internet connection with sufficient bandwidth) are available. This approach safely reduced all-cause antibiotic prescribing at a general medical practice level over a year.[71]
- Group education meetings that included general practitioners and their collaborating pharmacists resulted in decreased antibiotic prescribing.[72]
- Training of clinicians in enhanced consultation skills and point-of-care tests of C-reactive protein have an additive effect on safe appropriate antibiotic use, and both are cost effective, an important factor in resource-poor settings.[73,74]

Hospital practitioners

- The UK Start Smart Then Focus campaign,[75] which aims to achieve optimum antimicrobial stewardship by ensuring rapid prescription of the right antibiotic at the right dose at the right time followed by active review at 48 h, Thailand's Antibiotics Smart Use programme,[76] and Vietnam's VINARES programme[77] could be adopted in low-income and middle-income countries that have adequate surveillance and stewardship programmes.

Maximising access to achieve appropriate human antimicrobial use in low- and middle-income countries

Marc Mendelson and colleagues

Key messages

- De-linkage to uncouple innovation and sales must be adopted so that public health needs drive innovation for antimicrobials and diagnostics.
- As a global challenge, universal access demands a long-term commitment, with sustained financing from all affected countries, moving away from current donor driven models in resource-poor states.
- The key enablers, of financing, research & development, equitable management of knowledge and intellectual property, 'managed marketing', and procurement & distribution of antimicrobials must be strengthened to support the World Health Assembly Global Action Plan to combat antimicrobial resistance.

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Taking action in Africa

- Aim for universal and appropriate access to antibiotics
- Improve integrated community case management (iCCM) for children and prevent disease
- Strengthen health systems and surveillance
- Increase utilization of diagnostics, protocols and education for improved prescribing
- Improve hospital prescribing and infection prevention and control

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Exploring the evidence base for national and regional policy interventions to combat resistance

Osman A. Dar and colleagues

Key messages

- The impact of AMR policies appears to be variable; lack of progress is partly due to an insufficient evidence base to inform policy makers about the effectiveness, generalisability and cost-effectiveness of AMR initiatives.
- Policies encouraging responsible use of antimicrobials in primary care/outpatient settings have been demonstrated to be effective but are not easily generalisable. Stewardship programmes in secondary care can be effective in encouraging responsible use of antibiotics and should be scaled up in both HICs and LMICs where feasible
- Public awareness campaigns when sustained have shown some impact but should be implemented with caution in LMICs, where cost and impact needs better evaluation.

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Exploring the evidence base for national and regional policy interventions to combat resistance

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Key messages

- Reducing the demand and need for antimicrobials can be achieved through effective Infection Prevention and Control interventions (IPCI) . Evidence on appropriate strategies for IPCIs in LMICs is lacking.
- The evidence base to determine the most cost-effective systems for surveillance of antibiotic use and resistance remains weak worldwide and in the animal and environmental sectors IPCI and surveillance suffer from chronic underfunding.
- A global surveillance system should be created to help secure accountability for AMR control and improve between-country comparisons. For LMICs, additional focus is needed to improve monitoring of antimicrobial drug quality and marketing to curb the proliferation of counterfeits and substandard drugs.

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Exploring the evidence base for national and regional policy interventions to combat resistance

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Key messages

- There is a need for standardised policy evaluations that include measures of cost-effectiveness, acceptability to populations and stakeholders; and assessment of the political, regulatory and technical environments in which they are implemented.

- A ‘One Health’ approach to AMR will help bridge gaps in levels of commitment being shown each sector and enable policy development that is inclusive, sensitive and sufficiently flexible to accommodate the varying needs of different countries and regions.

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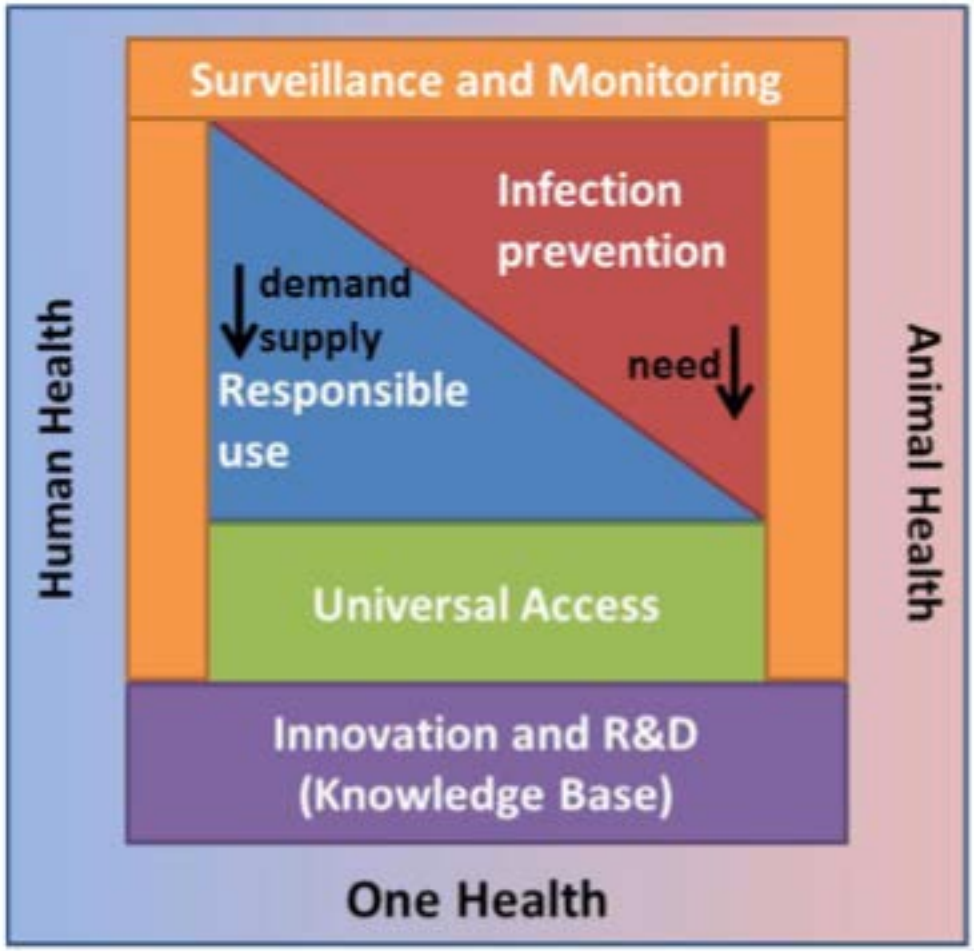
Policy framework for sustainable access to effective antimicrobials



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Taking action in Africa

- Raise awareness about antibiotic resistance in human and animal health
- Conduct pilot studies at the national level to assess the impact of interventions to decrease resistance

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International cooperation to improve access to and sustain effectiveness of antimicrobials

Christine Årdal and colleagues

Key Messages

- Global collaboration is necessary to improve access to antimicrobials and sustain their effectiveness. This is well known and accepted. Yet current collaborative efforts remain far too modest and poorly funded.
- The policy areas of universal access, responsible use and innovation require interlinked global collaboration. Increasing innovation and global access without responsible use provisions may increase the emergence of resistance. Stronger efforts towards responsible use may lead to smaller and less lucrative markets, thus dampening innovation and possibly impeding access. To avoid improper incentives to waste antimicrobials, the price of antimicrobials should be delinked from the volumes sold.

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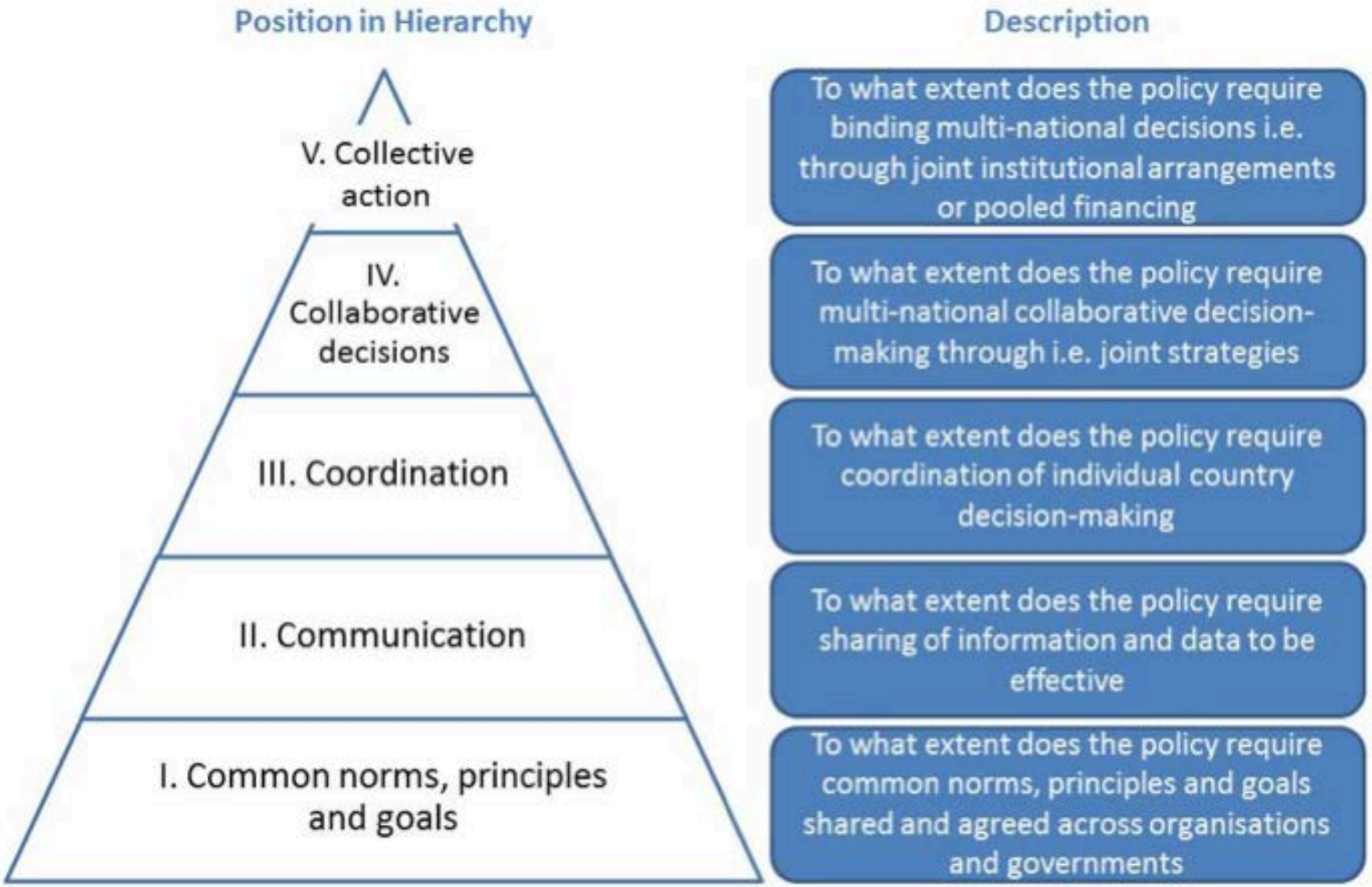
5C Framework: Assessment of minimum collaboration needed for a successful policy



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International cooperation to improve access to and sustain effectiveness of antimicrobials

Christine Årdal and colleagues

Key Messages

- The World Health Organization cannot successfully tackle this problem on its own. Due to the multi-sectoral nature of the problem, requiring action across the health, agriculture, and veterinary sectors, and the need to build new business models for antimicrobial innovation and use, multi-sectoral coordination under a ‘One Health’ paradigm is necessary to bring about action and real change.

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International cooperation to improve access to and sustain effectiveness of antimicrobials

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Key Messages

- Global actions to address this challenge need to be a combination of quick wins and long-term efforts. For example, a few large markets could agree to restrict certain classes of antimicrobials to human use only while a more formal global mechanism is being negotiated and adopted. This combination of short- and long-term strategies needs to be taken for each policy area, namely surveillance, universal access, infection prevention, responsible use, and innovation.
- Better global coordination and financing mechanisms are required. Two leading institutional options are a new UN-level coordinating body and an international treaty with strong implementation mechanisms.

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Lessons learned

- Low- and middle-income countries are likely to bear the brunt of the problem of resistance - where antibiotics are often not available to those who need them, and those that are may not be affordable.

- LMICs face the same challenges in implementing resistance policies as high-income countries, as well as additional challenges: weaker health-care systems, difficulty in enforcing regulations, an inadequate supply of trained health-care providers, poor public health infrastructure, a higher burden of infectious disease, and limited resources.

- Successful policy generation through the GARP network, including in Kenya, and other partners shows that national level action on antibiotic resistance is possible, and as this series illustrates, urgently needed.

For research, updates and tools on drug resistance and other global health topics, visit:

www.cddep.org

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