IFPMA Consolidated answer to WHO AMR Consultation

Consultation on a draft Global action plan to address antimicrobial resistance

The questionnaire is divided into four sections. The questions are broadly framed and intended to give you the opportunity to enter into some depth and explain your organization's viewpoint. While only questions marked with * are mandatory, we would appreciate answers to as many as possible. Where a choice of answer needs to be selected please highlight your answer.

Before answering the questions, please refer to our list of supporting documents.


About you

1. Name of individual respondent: (deleted)

2. Email address: (deleted)

3. Are you authorised to represent your organization or interest group? Yes

4. Organization Name: International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

IFPMA represents the research-based pharmaceutical companies and associations across the globe. The research-based pharmaceutical industry’s 1.3 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.

5. Address of the organization: 15 Chemin Louis Dunant, 1211 Geneva 20, Switzerland

6. Organization website (if available): www.ifpma.org

7. Country: Switzerland

8. Type of Organization: Non Governmental Organization – Private Sector

9. Main sector of interest: Human Health

10. Would you like to be added to our mailing list to receive updates on the development of the global action plan? Yes

General questions

1. From the perspective of your organization, what are the most important areas of concern in AMR?

2. Is your organization currently involved in work related to AMR? Yes

If Yes, How?

The following companies are all members of IFPMA.
AstraZeneca (AZ) has an active development pipeline. At present, AZ have 5 small molecule antibacterial therapeutics in development (one on market, one in Phase 3, one in Phase 2, and two in Phase 1). AZ also supports a Phase 2 small molecule for treatment of tuberculosis via collaboration with the United States government (National Institute of Allergy and Infectious Diseases). Finally, AZ has a large molecule agent for prophylaxis moving into Phase 2. AZ has been active in the creation of the IMI ND4BB program and in driving regulatory change in the US and EU.

GSK has a dedicated R&D team focussed on antibacterials for serious and life-threatening infections. GSK has an early stage pipeline and is progressing new antibiotics for the treatment of Gram-positive, multidrug-resistant Gram-negative and bio-terror infections. GSK proactively works in open collaborations and partnerships, including with US Government (Biomedical Advanced Research and Development Agency (BARDA) and Defence Threat Reduction Agency (DTRA)) and the European Innovative Medicines Initiative, having played a key role in the creation of New Drugs for Bad Bugs and where GSK co-lead the COMBACTE, TRANSLOCATION and ENABLE programmes. GSK is active in proposing the need for new approaches for the commercialisation of antibiotics and have been a strong proponent for the last few years of models in which revenue to innovator is delinked from antibiotic usage.

MSD has several antimicrobial agents and vaccines to prevent antimicrobial infection on the market and several antimicrobial molecules and vaccine candidates in Phase 2 and Phase 3 development, including an investigational class A and C beta-lactamase inhibitor, an investigational combination of therapeutic antibodies targeting two C. difficile pathogenic toxins, (A and B), an investigational pneumococcal conjugate vaccine, and an investigational pediatric hexavalent combination vaccine for the prevention of six infectious diseases: diphtheria, tetanus, whooping cough (Bordetella pertussis), polio (polio types 1, 2, and 3), invasive disease caused by Haemophilus influenzae type b, and hepatitis B.

MSD has also been actively engaged in addressing issues of antimicrobial resistance. Most notably, since 2002, MSD has supported the Study for Monitoring Antimicrobial Resistance Trends (SMART). This ongoing surveillance study involves investigators at more than 200 sites around the world. It provides information about changes in the spectrum of microbial pathogens and trends in the antimicrobial resistance patterns in nosocomial and community-acquired intra-abdominal and urinary tract infections which is entered into a data base and provides information about resistance trends at the site, country and regional level that is essential to guide effective empiric therapy.

Pfizer markets several antibiotics, including Zyvox, the first-in-class oxazolidinone antibiotic for serious Gram positive infections such as MRSA, and Tygacil, an antibiotic for the treatment of serious Gram-positive and Gram-negative infections. Both products are primarily used in the hospital setting. Pfizer also developed and markets Eraxis and Vfend, which are used for the treatment of serious fungal infections.

Pfizer is engaged in efforts in medical education and global resistance monitoring.

- For instance, the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) is a global multi-center surveillance study designed to assess the in vitro activity of tigecycline and comparators against a range of important pathogens, from both the community and the hospital. Global stakeholders are allowed to search the database based on
country/geographic region, pathogen, resistance, type of infection, type of sample, etc. to gain information necessary to make appropriate treatment decisions.

- Pfizer has also developed and sponsors a global evidence-based program focused on the optimization of antibiotic use as part of its commitment to the infectious disease community. The APEX™ (Antimicrobial Practices and Executions for eXcellence) program educates clinicians, hospital pharmacists and microbiologists on principles of antimicrobial stewardship.

Pfizer vaccine R&D program includes an ongoing focus on the prevention of pneumococcal disease, including in adults. Pfizer is also advancing vaccines for additional deadly adolescent and adult infections including Meningococcal B, *Staphylococcus aureus* and *Clostridium difficile*.

Roche is conducting research in the field of antibiotics to address the need for effective therapies for multi-resistant bacteria. Roche is exploring new antibiotic targets, new mechanisms for bacterial killing, and new ways to deliver therapeutics to the site of infection. The goal is to be more efficient at eliminating bacteria, improve patient outcomes, and provide therapies with fewer side effects. In partnership with Polyphor, Roche is evaluating RG7929 in phase II clinical trial for patients suffering from multi-drug resistant bacterial infections caused by *Pseudomonas aeruginosa* (PA). Roche is also engaged in research-stage partnerships and collaborations for the discovery and development of novel antibiotic drug compounds with firms including RQx Pharmaceuticals, Discuva Limited, and Spero Therapeutics. Roche has a long history of antibiotics development, including WHO essential medicines such as Rocephin and Bactrim.

Questions about the draft global action plan outline document

Before the WHA resolution was adopted, two WHO AMR Strategic Technical Advisory Group (STAG) meetings were held in anticipation, which included members plus a large number of representatives from other organizations. These meetings identified key issues, concerns and led to the development of a draft outline.

As this consultation progresses and stakeholder meetings are held, the secretariat will harvest and incorporate the input into the draft global action plan.

1. How would you rate your understanding of WHO’s intention in the development of a global action plan to address AMR?
   
   Very good **XX** Good ___ Fair ___ Poor ___

   Additional comments:

   IFPMA representatives participated in the 14-15 April 2014 AMR STAG meeting and in the 13 May 2014 WHO Antibiotic Business model consultations. IFPMA also made a statement during the 2014 World Health Assembly to express its support to the development of an AMR Global Action Plan¹.

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¹ [http://ifpma.org/fileadmin/content/Events/Statements/IFPMA_Statement_AMR.pdf](http://ifpma.org/fileadmin/content/Events/Statements/IFPMA_Statement_AMR.pdf)
2. From the perspective of your organization, are the major issues relating to AMR outlined in the draft global action plan? Y__ N _XX_.

If No, what additional issues need to be addressed?

Access to antibiotics is not well-highlighted. Paradoxically, underuse is an issue in some areas where infrastructure limits access to a secure supply chain or where affordability drives irrational purchase and use (e.g., purchase of one pill at a time).

The need for development of novel and sustainable incentive structures to promote the ongoing engagement of the private sector pharmaceutical industry in the research and development of new anti-microbial agents in the context of robust antimicrobial stewardship to address AMR is not sufficiently highlighted.

Questions on the ‘Building blocks’ described in the draft outline.

You will notice, the global action plan has been constructed around “building blocks” in recognition that different countries will have different starting points. In this situation, countries can choose building blocks to concentrate upon. Each building block specified has been identified as a key area where specific attention, planning and work are needed to achieve progress in addressing AMR. Through questions in this section, we would like to hear your opinions on these building blocks in more detail.
I. Building block-1: Increasing awareness and understanding about AMR and of the actions and changes needed: There will be a continuing need to reach audiences that range from heads of governments to policy developers, prescribers and associated professions, and from businesses to public, patients and civil society, across all sectors. The main objective will be to change behaviour and social norms (e.g. the recognition of antibiotics as a “public good”), and to secure continuing engagement and commitment. Actions need to include education and training for the relevant professional groups.

a) What do you consider to be the main issues under this priority?

The main issue differs by sector. See next answer.

b) What are the main actions that needs to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?

1) Raising awareness in the general public
   a) Awareness of importance of using antibiotics only when necessary e.g. not expecting an antibiotic when it is a viral infection
   b) Needs to be a simple message, tailored to age groups, cultures, diverse beliefs
   c) World Antibiotic Awareness Week is a good example of a productive start
   d) Also need to develop a message similar to the Fair Trade / Green / Eco messages in which consumers are educated on the reason to support the (sometimes higher priced) “antibiotic-free” food chain options (see further notes in Building Block 2)
   e) Pharmacists should play a greater role in ensuring the patient understands that antibiotics must be taken as prescribed
   f) Efforts are also needed to support patient and community advocacy efforts that highlight the impact of antimicrobial resistance and the need for the development of new antimicrobial medicines and effective antimicrobial stewardship.

2) Raising awareness in prescribers and pharmacists
   a) Must ensure that medical curricula teach the basic of Infectious Diseases
   b) Ensure that continuing medical education requirements contain a regular update on AMR
   c) WHO could create readily accessed guidelines (e.g., mobile apps)
   d) Encourage the adoption of technology to facilitate stewardship (e.g. mobile technologies, etc) (see further notes in Building Block 3)
   e) WHO could seek to bring medical associations together behind this
   f) It will be important to anticipate issues in settings where prescribers generate income via prescribing & dispensing — there will be an economic disincentive in these settings that must be considered.

3) Raising awareness with policy makers and politicians
   a) Need to ensure good understanding of the problem, including issues of antimicrobial stewardship and the implications on the incentive structure for antimicrobial R&D
   b) Need to ensure understanding of medical and economic consequences of inaction
      i) Work in this area will require commitments of people and funding
      ii) There are many areas other than AMR that call out for attention!
      iii) However, failure to address AMR could produce major societal disruption
3) The recent report by Sertkaya et al. is a powerful analysis of the right kind of data
   i) “Analytical framework for examining the value of antibacterial products”
   ii) http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm
   iii) The report shows that new antibiotics have a societal value in the $10s of billions of dollars whereas the price paid by society for these drugs is insufficient from the standpoint of an innovator.

4) Raising awareness on the part of Pharmaceutical Industry
   a) Private sector involvement and investment in R&D is critical to successful creation of new agents
   b) Industry is aware of the issues but is hesitant to return without a path to at least reasonable profitability
   c) We must raise awareness that concrete steps need to be taken to create a viable commercial path in order to raise sustainable investment in R&D for antimicrobial agents
      i) In doing this, WHO must avoid stances that are largely dependent on corporate responsibility or goodwill as these are not sustainable over the longer term.
      ii) Failure to engage fully with industry will only perpetuate the current gap

   c) What steps have already been taken to address this priority? (please provide references where possible)

   1) World Antibiotic Awareness Week
   2) WHO’s use in 2011 of World Health Day to focus on AMR
   3) US CDC’s Antibiotic Awareness campaigns
   4) ECDC EuroBarometer reports and similar
   5) Well-supported National Strategy/Action Plans eg UK
   6) IDSA activities to prioritize AMR and create sustainable investment pathways
   7) Ongoing Transatlantic Task Force on Antimicrobial Resistance (TATFAR) activities (follow link for 2014 TATFAR report)
   8) Ongoing activities of ReAct (http://www.reactgroup.org/) to promote AMR awareness, product innovation, and stewardship.
   9) Public-Private Partnerships with government based agencies (e.g., the EC’s ND4BB project within IMI, work by BARDA and NIAID in the US).
   10) Individual country initiatives

   d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)

   1) Public
      a) % population aware of or understanding AMR (opinion polls)
      b) % schools having organised an activity on prudent use of antibiotics

   2) Prescribers & Pharmacists
      a) % prescribers & pharmacists having received education on prudent use of antibiotics and AMR (use of continuing medical education for example)
      b) % hospitals having stewardship programs (perhaps measured / required as part of accreditation)
      c) % of hospitals having Infection Prevention (Infection Control) programs

   3) Policymakers & Politicians
a) % Member States taking part in the World Antibiotic Awareness Week
b) % Member States having organised a public awareness campaign on prudent use of antibiotics (WHO might provide a framework for such programs)
c) % Member States with a national strategy on AMR
d) % Member States with a national action plan on AMR

4) Big picture outcome measures
   a) % Member States that show a favourable trend in antimicrobial use
   b) Reduction in resistance rates in surveillance programs
   c) Number of multinational pharmaceutical firms with antibiotics in development or commercialization phases
      i) An antibiotic commercialization is only viable if it is in the global distribution chains, a crude measure of success would be to focus on the number of multinational firms progressing one or more antibiotics
   d) Number of new agents in development
II. Building block-2: Identifying the most important approaches for preventing development of infections and the steps needed to move beyond guidance to more effective implementation of such approaches: The Advisory Group identified these priorities for inclusion in the global action plan: infection prevention and control in healthcare, including hand hygiene, standard precautions, and safe injection; vaccination of healthcare workers and patients; prevention of sexually transmitted infections; focus on infection prevention in livestock husbandry and aquaculture; promote use of effective vaccines to reduce infections that result in antimicrobial treatment (both appropriate and inappropriate use).

a) What do you consider to be the main issues under this priority?

1) Human Health
   a) The essential elements here are well known:
      i) Adequate sanitation (water/sewage) infrastructure
      ii) Appropriate food handling
      iii) Hand washing and other infection control measures in Health Care settings
      iv) Use of vaccination where it is available
         (1) We must advocate for both better public health policies to emphasize increased compliance with vaccine schedules.
   b) The challenge is principally around education and implementation

2) Agriculture
   a) Appropriate use of antimicrobials in agriculture in-line with the guidance and recommendations of the FDA, WHO, and OIE should be ensured.
   b) Use of vaccination should be promoted where it is available.

b) What are the main actions that needs to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?

1) WHO and OIE could contribute by creating standard approaches:

2) E.g., WHO could define components of a stewardship program
   a) WHO to define a ladder of measuring quality of use
      i) E.g., % of prescriptions based on a diagnostic test
      ii) % of prescriptions based on a guideline
   b) Countries to set expectations for stewardship programs
   c) Facilities: to implement stewardship programs
      i) Measure: % of countries with guidelines
      ii) Measure: % of facilities with stewardship programs

3) WHO could create community-level quality indicators
   a) E.g., % over-the-counter use
   b) % by prescription, by qualified provider, or by guideline
      i) Due to access concerns, It may not be feasible to limit dispensing of antibiotics to use with a prescription and thus approaches based on guidelines or a qualified provider are needed
   c) WHO could use sentinel surveys as a starting point for tracking these ideas
4) WHO and OIE should create common standardized guidelines for the appropriate use of antimicrobials in agriculture and create country-level indicators.
   a) Countries should adopt the guidelines for use of antimicrobials in agriculture
   b) % compliance with guidelines for use of antimicrobials in agricultural settings

c) What significant work has already been done to address this? (please provide references where possible)

1. The 2014 TATFAR report makes recommendations for future collaboration (between the EU and the US) in three key areas:
   a) Key Area I. Appropriate therapeutic use in human and veterinary medicine
   b) Key Area II. Prevention of drug-resistant infections
   c) Key Area III. Strategies for improving the pipeline of new antimicrobial drugs

The specific recommendations under each of these key areas should be considered for adoption more broadly by WHO and nations around the world.

2. The CDC National and State Healthcare-Associated Infections Progress Report is a report that gives a closer look at the healthcare-associated infections (HAIs) in the US that are most commonly reported to CDC using the National Healthcare Safety Network (NHSN). This is an annual report that describes national and state progress in preventing central line-associated bloodstream infections, catheter-associated urinary tract infections, surgical site infections after colon surgery and surgical site infections after abdominal hysterectomy.

d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)

1) % of global population with ready access to clean water and sewage systems
2) % of health care systems with an Infection Prevention program
3) % of population that have received (age-appropriate) vaccination with all relevant vaccines
4) Evidence of improved use in man based on process-level measures
   a) Outpatient settings
      i) 100% of dispensing is via prescription, guideline, or similar process
      ii) High % of dispensing events are supported by accurate diagnostic
      iii) Low rate of use for upper respiratory infections, eg % reduction of non-recommended/guideline –compliant-use.
   b) Inpatient settings
      i) 100% of facilities have stewardship programs or (at a minimum) antibiotic usage guidelines
      ii) (almost) 100% of antibiotic prescribing events are supported by a diagnostic test of some type
      iii) 100% of facilities have an automatic stop and review for continued need at a fixed number of days (3 days is often suggested) after antibiotic prescribing
5) % of member states with national policies on use of antibiotics agriculture
   a) % compliance with agricultural use policy
6) Reduction in incidence of sentinel illnesses that could be controlled by better practice (e.g., sexually transmitted diseases, vaccinatable childhood illnesses, etc).
III. Building block-3: Optimizing the use of existing antimicrobials for human and animal health and in agriculture: Use of medicines (prescription, dispensing, administration) should be guided by evidence, diagnosis, and rational protocols, and enhanced through post-marketing clinical (research) studies in relevant settings and contexts. There is also a need for innovation in antibiotic regulation (e.g. to consider antibiotics as a different class of medicines requiring a different approach from development to use), to focus on quality (SSFFC) strengthening medicines regulations in all sectors, including the capacity to monitor compliance and enforce regulations.

a) What do you consider to be the main issues under this priority?

1) Prescribing/dispensing:
   a) All such should either be by a health care provider (HCP) or by protocol in settings where HCP is not feasible
      i) This is true both for human and veterinary use
      ii) In the process, irrational pack sizes should be eliminated – dispensing should always be adequate for an entire treatment course
      iii) Where laws exist mandating prescription-only dispensing, they should be enforced rigorously
   b) Evidence-based recommendations for prescribing exist in many territories, but not all
      i) Such recommendations may not be readily accessible
      ii) Barriers could include simple document access but also access in a local language
      iii) Facilitating point-of-care access to such guidance would be a major advance (e.g., mobile apps)
   c) Diagnostic tools have not been developed or are not uniformly available to guide prescribing
      i) The key diagnostic tests that would have a dramatic impact on prescribing have not been developed due to scientific, regulatory and reimbursement hurdles.
         (1) These key tests include simple, accurate, inexpensive tests that can be performed at point of care to guide appropriate prescribing of common infections.
      ii) Diagnostic capacity needs to be globally available
      iii) This includes both laboratory-based testing, but most importantly point-of-care (rapid) diagnostics
      iv) This will require infrastructure building and development of affordable, rapid/point of care diagnostics. Strategies to support the development of needed diagnostics include investment in research, incentives for development, ensuring appropriate reimbursement of diagnostic testing vs. empiric prescribing, and coordination of stakeholders to increase chance of success.
   d) Enhance systemic incentives to encourage appropriate use of antibiotic and discourage inappropriate antibiotic use across the supply chain, including for healthcare providers, veterinarians, pharmacists, hospitals, wholesalers, and manufacturers.

2) Regulation and Enforcement: A globally harmonized regulatory approach is needed on multiple levels
   a) Approval of novel agents
   b) Sale of bulk agents for agricultural use
   c) Quality of agents sold at all levels (inferior or counterfeit agents drive resistance)
   d) Enforcement efforts to reduce prevalence of counterfeit/substandard drugs
(Comments on changing the economics of antibiotics are given separately below)

3) Development of public-private partnerships/models for development of and commercialization of rapid and point-of-care diagnostic tests.

b) What are the main actions that needs to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?

See comments above

In addition, where feasible, WHO should encourage the use of technology to support stewardship strategies tailored at the local level. It would not be enough to have a protocol or guideline or clinical pathway. These pathways need to be digitized/automated. Mobile technology (cloud-based) clinical decision support (to automate pathways, report lab results more rapidly, support surveillance efforts and development of local antibiograms) is something that even resource-poor countries could invest in.

Getting clinical decision support technology into the hands (and integrated into the workflow) of prescribers is critical. Activities in Colombia present a great example. A non-profit organization in Cali, Colombia, CIDEIM (http://www.cideim.org.co/site/) helps local hospitals develop treatment pathways by using WHONET to develop local antibiograms that inform empirical treatment decisions. CICEIM is developing an app that will integrate this information. These hospitals do not have electronic health records, so mobile technology is particularly valuable.

c) What steps have already been taken to address this priority? (please provide references where possible)

1) India’s move to eliminate purchase without a prescription
2) Danish example of antibiotic elimination as an agricultural growth promoter
3) Recent collaborative approach in the US to agreement with all 26 US-based animal drug manufacturers to adhere to FDA Guidance #213 and withdraw antibiotics from animal use completely or to revise the labels so the drugs can only be used with a veterinarian’s order.
4) Efforts to develop rapid point-of-care diagnostics, including the recent announcement of a GBP 10m Longitude prize in the UK for development of diagnostic tests and UNITAID model to promote product development and market development for GeneXpert for TB and point-of-care tests for HIV viral load and early infant diagnosis.
5) In 2007, the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) released guidelines for developing an institutional program to enhance antibiotic stewardship. The American Society of Health-System Pharmacists (ASHP) provided input and endorsed the guidelines. According to IDSA and SHEA, effective antibiotic stewardship programs (ASPs) are evidence-based and can improve patient care and be financially sustainable. A detailed account and assessment of health care institutions employing some form of ASP is unknown.
6) Antibiotic Stewardship, Prevention of Infection & Control (ASPIC) programme was initiated by the Indian Council of Medical Research (ICMR) during 2011 – 2012 in response to the above need. The program brings together experts and key stakeholders from several disciplines including clinical pharmacology, microbiology and others to collaborate on initiating and
improving antibiotic stewardship and concurrently curbing hospital infections through feasible infection control practices. This programme involves the participation of 20 centers per year throughout the country which come together for a training workshop.

7) In the US, The American Hospital Association (AHA) has compiled a new toolkit on antimicrobial stewardship in partnership with Association for Professionals in Infection Control and Epidemiology (APIC) and five other national organizations. The toolkit is composed of three sections: Hospital and health system resources; Clinician resources; and Patient resources.

8) UK FIVE Year Antimicrobial Resistance Strategy and Action Plan 2013-2018. This new integrated UK Five Year AMR strategy and action plan seeks to accelerate progress by building on the 2000 UK Strategy and Action Plan as well as developments at EU and international level, including the 2011 EU Strategic Action Plan, and 2012 EU Council Conclusions. It will champion the responsible use of antibiotics, strengthen research and surveillance capability, and facilitate behaviour change and work to reposition antibiotics at a societal level.

d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)

1) % of dispensing without a prescription
2) % of members states with guidance available in local language(s)
3) Availability and use of diagnostic tests to guide prescribing
4) Improvement in (point measures of) rates of counterfeit drugs

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2 It is available at: http://www.ahaphysicianforum.org/resources/appropriate-use/antimicrobial/index.shtml
IV. Building block-4: Identifying and closing critical gaps in knowledge needed to address AMR: The Advisory Group emphasised the importance of knowledge (information and data) in guiding all actions. The global action plan needs to address development and assessment of the evidence base for action, quality of data, and ability to monitor and evaluate progress. Surveillance, including the development and maintenance of laboratory capacity, should be given a high profile in the action plan.

a) What do you consider to be the main issues under this priority?

1) We lack the tools to track resistance rates at a global level
   a) We lack the required physical infrastructure (lack of laboratories in many regions, cultures not done at all in some settings)
   b) We lack a ready way to share the data even within regions (e.g., the United States has only limited ability to track infection rates nationally)
   c) We lack ways to track isolate spread — a global database for identifying clonal pathogens does not exist

b) What are the main actions that need to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?

WHO and countries need to build surveillance capacity and reporting tools.

Development of a broad surveillance program across multiple body sites and all countries, potentially through a public private partnership involving multiple stakeholders

c) What steps have already been taken to address this priority? (please provide references where possible)

1) Regional efforts do exist: US CDC, European CDC
2) At least one global clonal pathogen database exists but it is not widely known
3) As one example of the kind work needed, a prevalence survey in 10 geographically diverse states was recently completed to determine the prevalence of health care–associated infections in acute care hospitals and generate updated estimates of the national burden of such infections. These surveys were conducted in 183 hospitals and included 11,282 patients. Of that number, 452 had 1 or more health care–associated infections (4.0%), the most common types included pneumonia (21.8%), surgical-site infections (21.8%), and gastrointestinal infections (17.1%). Clostridium difficile was the most commonly reported pathogen (causing 12.1% of health care–associated infections). Further details may be found in the original publication in N Engl J Med 20143.

d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)

1) WHO global goals and reporting.
2) % of healthcare facilities with local surveillance programs
3) % of member states with member state-level surveillance programs

V. Building block-5: Developing an innovative and sustainable approach to develop and distribute critical products and technologies needed to address AMR. New market models need to ensure access to and stewardship of both new medicines and existing medicines, and for other technologies and interventions. Plan need to address how such models and other innovations can be implemented.

a) What do you consider to be the main issues under this priority?

1) Developing sustainable commercial models that adequately incentivize private investment in antibiotics is critical. We need models that

a) Encourage the private investment required to create an ongoing, diverse, vibrant pipeline for new antibiotics
b) Encourage/reward the kind of risk-taking required for pursuit of truly novel therapies with model(s) that work for both large and small companies
c) Are commercially viable over the life time of the antibiotic (Assumption being within the patent period)
d) Reflect the societal value of having new antibiotics available in advance of resistance rates needing them.
e) That (principally) reward bringing a new product successfully through the registration process and incentivise continued development after initial registration
f) That (where possible and appropriate) separate reward from volume usage or provide adequate return with limited usage
g) That provide some incremental reward for near-term usability and where the reward for different molecules may vary
h) That have potential for global use and that aren’t dependent on changes to laws (IP or otherwise)

2) The new models must work within the bounds of recognised processes for developing medicines

a) Within that concept, the unique challenge of antibiotics may require and support options that would not be applicable to other disease areas (e.g., grants, R&D tax credits (including refundable tax credits), prizes, advance market commitments, wild-card patent term extension)

b) Several business model options are likely needed

i) Premium pricing may work in some settings but does not address all needs (e.g., it might increase the unpredictability of budgets and company incomes)

ii) Delinking revenue from usage is a new approach with the potential to reduce uncertainty for company, reduce need to drive sales, and align with public health goals

(1) In this context, delinkage refers to the idea of rewarding innovation via payments that are not a function of drug usage volume.

(2) For example, an insurance-like approach could be considered in which a fixed annual payment is made by a national or regional body to ensure ready access via an active supply chain.

iii) For delinkage to work, various models need to be explored to provide an acceptable return on investment. With this topic as its focus, a project entitled DRIVE-AB is launching on 6 Oct 2014 in Geneva. This project is part of the ND4BB (New Drugs 4 Bad Bugs) family of projects within the EC-EFPIA collaborative IMI project.

c) Careful debate will be needed as we test such delinkage models
i) Proscriptive pre-defined Target Product Profiles may limit innovation
ii) Clear and transparent rules are needed but may be difficult to define and agree
iii) Beginning with regional pilots probably makes sense

3) We need to continue to adapt regulatory and payer requirements for approval of new antibiotics
i) Regulatory bodies and reimbursement authorities need to adopt new paradigms for judging the clinical effectiveness of antibiotics.
ii) It is important that regulatory authorities (FDA/EMA/PMDA/others) as well as payers and their respective self-governing and decision bodies (NICE/HAS/GBA/AIFA/CADTH) work together to have consistent guidance on study design requirements (pertaining to patient populations, endpoints, non-inferiority margins, acceptability of comparators, etc.) and that indication wording should provide consistent, enhanced labelling, highlighting the use of novel agents against specific resistant organisms in key sections of labelling such as Indications, Clinical Studies and Microbiology.
iii) Good discussions of this topic have been held and regulatory guidance documents have taken many steps along the needed pathway (e.g., the 2013 EMA Antibacterial guidance Addendum, EMA/CHMP/351889/2013, accessible online at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500153953.pdf

b) What are the main actions that needs to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?

1) Major projects focused on this area are starting now, principally in the EU (the IMI DRIVE-AB project)
2) WHO should participate in these projects rather than starting new projects.
3) Work should continue on the creation of expedited development options with limited use labels for new antibiotics.
   a) Guidance for these routes will need to be globally harmonized and agreed by FDA, EMA and others. We recognize that this action is outside the scope of WHO’s authority, but we also recognize that WHO’s actions can only be successful if all parts of the antibiotic R&D ecosystem are functioning. As a key stakeholder, WHO’s voice in calling for continued evolution of this area would be in valuable.

c) What steps have already been taken to address this priority? (please provide references where possible)

See above
1. A recent report, commissioned by the Swedish Government, was issued by the London School of Economics and Political Science (LSEPS). The report makes a broad recommendation for governments to create new incentives to promote the research and development of antibiotics in light of the growing concern over resistance to existing antibiotics.
2. Incentivizing new antibacterial drug development in the US has come in the form of several legislative proposals and laws. The Generating Antibiotics Incentives Now or “GAIN” Act, Public Law⁴ provides important new incentives for the development of treatments for serious or life-threatening infections caused by bacteria and fungi and for the maintenance of a steady supply of new antibiotics or other treatments to meet the continued threat of emerging infectious disease. The GAIN Act was designed to provide pharmaceutical and biotechnology companies with incentives to develop new innovative antibiotics for the treatment of life-threatening infectious diseases caused by drug resistant pathogens. This is a welcome first step in which a number of small pharmaceutical and biotechnology companies should benefit from the current format of the GAIN Act, and it will certainly enhance the attractiveness of licensing deals between these companies and larger pharmaceutical companies that may help to incentivize late stage development of new antibiotics. The Act also calls for the FDA to adhere to specific timetables on developing and issuing draft and final guidance for antibiotic trials. This provision essentially allows pharmaceutical and biotech companies to request written recommendations from the Secretary of the Department of Health and Human Services (HHS) on the guidance for antibiotic trials if such guidance is lacking. It also requires the FDA to issue guidance on pathogen-focused antibacterial drug development, clarifying the necessary clinical trials and endpoints for approval. There several new proposals being considered in the US Congress that expand and improve on the original provisions of the GAIN Act.

d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)

Implementation of one or more pilot projects would be an obvious metric.

# of companies (large and small) with active antibiotic R&D investment

# of products in industrial pipeline (meeting prioritised public health needs)

Guidance documents issued by national health authorities (regulatory and payer bodies) on alternative incentive and economic models that take into consideration the issues outlined in (a)

⁴ No. 112-144, §§801-806, 126 Stat. 1077, 1077—82 (2012),
VI. Building block-6: Assessing the long term economic, developmental and social costs and implications of AMR as a basis for sustainable investment and action. Economic impact assessment includes the need to understand the cost of doing nothing, vs. cost and benefit of action. The global action plan should include the need to quantify national and global investment needs (allowing for what is already being done/invested, and consider timescales). National AMR programmes will be more sustainable if integral to health systems and to universal health coverage; capacity development, including training, will be essential, especially in low-resource settings. Include options for minimizing the adverse impacts and gaining synergy with existing initiatives.

a) What do you consider to be the main issues under this priority?

1) Reports such as the above-cited Sertkaya report are critical to understanding of the value of having (vs. not having) a diverse, sustainable pipeline of effective antibiotics
2) Pan-national economic reviews by neutral third party groups (e.g., World Bank) are especially powerful and also more likely to reflect multi-stakeholder viewpoints.
3) Adapting these data to address local (member state-level) issues is also needed.

b) What are the main actions that needs to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?

1) Do the research
   a) Some work has already been done
   b) Additional work in other geographies is required
   c) Work on the cost(s) of inaction is especially needed
      i) Sertkaya 2014 is the first such credible report
      ii) It only analyzes certain types of costs
      iii) Estimates from different perspectives are needed
      iv) WHO could work to develop a standard template for measuring these costs
   d) The above-mentioned DRIVE-AB project in the EU will also be a new source of insight into the challenges of this area.

2) Communicate the results
   a) Data on what it costs to ACT
   b) Data on what it might cost to NOT ACT
   c) Education on the importance of seeing antibiotic availability as a form of societal insurance

c) What steps have already been taken to address this priority? (please provide references where possible)

These reports exist:

1) Sertkaya et al. 2014: Analytical framework for examining the value of antibacterial products”
   a) http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm
   b) This report demonstrates the enormous gap between the private value of antibiotic to an innovator and its public value to society.

a) Consistent with the work of Sertkaya, this paper demonstrates that the cost/QALY of a novel antibiotic can be remarkably low.

3) Sharma & Towse 2011 OHE: New drugs to tackle antimicrobial resistance: Analysis of EU policy options
   b) This is an earlier paper that also shows the low private value of an antibiotic to an innovator

4) Smith & Coast 2013
   a) www.lshtm.ac.uk/php/economics/assets/dh_amr_report.pdf
   b) This a general review of the societal cost of lack of antibiotics. It concludes that all prior estimates give an underestimate of this cost (and hence, underestimate the value of antibiotics).

   d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)

   The best metric here is probably not the number of reports but rather the metrics for action by policy makers and politicians given under Building Block #1

Concluding questions

3. What contribution would your organization be able to make in implementing the global action plan? (TBC after discussion on the draft Action Plan)

   The IFPMA and its members companies and associations stand ready to provide expertise and to help design solutions to effectively combat anti-microbial resistance. Industry is ready to work collaboratively with other stakeholders and to discuss potential new commercial models. The IFPMA will concentrate its efforts on three areas: Data collection (Block 4) (pipeline inventory), Innovative financial models (Block 5) (Models that will lead to a sustainable pool of novel antibiotics) and assessment of the long term impact of AMR (Block 6).

4. Additional input that you feel would be facilitating development of the GAP.

   1) We believe that we as a community should be pragmatic, especially with respect to antibiotic business models. Sustained private investment will be required and this can only be achieved if a reasonable return on investment is possible.
   2) We believe that it would be better to implement a strong series of smaller steps than a failed grand gesture
   3) Where a relevant ongoing project now exists, we believe WHO should participate in that project rather than start a new initiative.
   4) Finally, we note that this recent report provides a useful view on the way to construct a global action plan. This report could be reviewed for elements to pull into the WHO GAP:
      a) Chatham House 2013: Antimicrobial Resistance: Incentivizing change towards a global solution
      b) http://www.chathamhouse.org/publications/papers/view/196795?dm_i=1TYE,24DOM,EC0E,BJ,7NP2H,1