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Human Health

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Introduction

- Vaccines, diagnostics, and therapeutics
  - Different core issues for each
  - But all of them face fundamental reimbursement issues that are, at heart, driven by a market failure of one sort or another
- Collectively, these tools are the fire department of medicine
  - Diagnostics: Smoke detectors (Is there a fire?) and Fire Chief (What kind of fire? How best should we fight this particular fire?)
  - Vaccines: Fire prevention services (Who is at risk? What kind of risk?)
  - Antibiotics: Fire trucks and fire fighters (Optimal annual rate of building fire is zero, but services must be ready at all times! Must prepare before smelling smoke!)

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Pop Quiz!

- Have you ever used the fire department?

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Pop Quiz!

- Have you ever used the fire department?

- In fact, you have … even if your house (hopefully!) has never caught fire!

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Introduction cont.

- We have market failures here as the very existence of these tools has benefits that are not captured by paying for them per use
  - Enablement value: appropriate use of these tools makes it safe to have procedures such as hip replacement
  - Diversity value: having and using a range of antibiotics and preventatives reduces selection pressure on other drugs
  - Option value: even if not used by any given individual, the existence of an effective diagnostic and antibiotic has an insurance-like value to the individual
- In short, we often pay for these tools as if we were paying the fireman on a per-fire basis. This is not good practice!

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Introduction cont.

- What can be done?
  - Each individual segment will present specific ideas
  - The ideas include both push (funding) and pull (reimbursement) strategies
- At a broader level, we have national and international conversations underway that speak to these issues
  - DRIVE-AB in Europe
  - Duke-Margolis process in the United States
  - Pew Trust, WHO, and others are contributing pipeline and market analyses
- The effort in the United States can be a powerful source of energy for all of these efforts

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Incentives for Vaccines

WG Co-chair: Kent Kester

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Overview

- Direct vs. indirect AMR vaccines
- Behavioral, economic, and legislative challenges that reduce willingness of companies to fund R&D
- Vaccines could address low-volume/high-severity or high-volume/low-severity conditions
- Vaccines should be included in legislation (GAIN, DISARM, READI Acts)

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Economic

Issue 1: Federal and nonfederal stakeholders lack a common understanding about the current and potential economic value and societal impact of vaccines directed at AMR pathogens. (1)

- **WG Recommendation:** Analyses on the cost and societal impacts associated with new vaccine development and administration in the AMR arena

Issue 2: There is limited funding for infectious disease vaccines, in particular for those targeting AMR pathogens. (2)

- **WG Recommendation:** An expanded range of incentives to encourage development of vaccines that could reduce AMR either directly or indirectly

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R&D

Issue 1: There are insufficient epidemiological data on antibiotic use due to infections caused by pathogens currently or potentially preventable through vaccination. (3)

- **WG Recommendation:** Expanded surveillance to measure antibiotic use due to infections that could be prevented or reduced by vaccination to assess the impact or potential impact of prevention through immunization, either by existing or to-be-developed vaccines

Issue 2: The clinical-stage pipeline for vaccines against AMR pathogens is weak. (4)

- **WG Recommendation:** Focused financial and regulatory incentives to encourage the development of vaccines directed at AMR pathogens across the R&D continuum

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Regulatory

Issue 1: The potential market for a new vaccine (as opposed to other AMR products) is uncertain, because vaccine uptake is heavily influenced by recommendations of the Advisory Committee on Immunization Practices (ACIP). (5)

- **WG Recommendation:** Early communication between the manufacturer, CDC, and ACIP to present and discuss a target product profile

Issue 2: The lack of clarity about regulatory pathways for vaccines focused on AMR pathogens reduces the willingness of sponsors to produce vaccines. (6)

- **WG Recommendation:** Early interaction between sponsors and FDA and workshops, hosted by FDA's Center for Biologics Evaluation and Research (CBER), explaining pathways and best practices

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Behavioral

Issue 1: Implementation strategies for optimal vaccine acceptance and utilization are inadequate. (7)

- **WG Recommendations:**
  1. Programs and interventions based on behavioral insights that aim to increase vaccine uptake in a variety of populations
  2. Continued, broadened economic incentives to influence behavior and increase uptake, such as reimbursement to ensure “first-dollar coverage”—that is, insurance coverage of vaccines without copayments or coinsurance costs

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Behavioral cont.

Issue 2: Providers lack knowledge about the role of vaccines in preventing AMR. (8)

- **WG Recommendation**: Focused governmental vaccine-centric educational policies and approaches, with involvement of health care educational institutions (e.g., medical schools, academic health centers)

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Incentives for Diagnostics

WG Co-chair: Angela Caliendo

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Overview

- Types of diagnostic tests:
  - Antimicrobial Susceptibility Tests (AST)
  - Rapid tests that distinguish between bacterial and viral infections
  - Tests that can rapid identify bacteria and provide susceptibility
- Problems related to development of diagnostics:
  - Cost, reimbursement, regulatory process, lack of clinical implementation
- Problems related to limited use:
  - Availability, limited knowledge, interpretation of results

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Economic

Issue 1: There is a delay in availability of ASTs for newly approved antibiotics. (9)

- **WG Recommendations:**
  1. Dedicated use of a portion of funds provided for incentivizing antibiotic development to development and commercialization of an AST device (e.g., Etest or disc) when the new drug is approved
  2. Funding for the development of new antibiotics should always include the development of a concomitant AST device

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Economic cont.

Issue 2: Because there is no method to determine the value of a diagnostic test, reimbursement is not aligned with the value of the diagnostic test. (10)

- **WG Recommendation**: A “reimbursement-plus” system , established within the next few years , for tests of key public health importance (e.g., CRE colonization testing). Public health agencies such as CDC and CMS should assist with these decisions.

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Economic cont.

Issue 3: There is a lack of clinical and economic outcome studies showing that diagnostic tests prevent the emergence of antibiotic-resistant bacteria and are cost effective. (11)

- **WG Recommendation**: Increased funding for diagnostics outcomes studies (AHRQ, CDC, PCORI, NIH, DOD) including those assessing patient outcomes, reduced length of stay, improved antibiotic use, reduced rates for a certain population of patients, and reduced cost of care

Issue 4: The high cost of development of diagnostics is a disincentive for diagnostic companies. (12)

- **WG Recommendation:** Tax credit for a portion of the qualified clinical testing expense, potentially modeled after the Orphan Drug Tax Credit

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R&D

Issue 1: Rapid point-of-care tests are needed to distinguish between bacterial and viral infections in the outpatient setting. (13)

Issue 2: There is a need for better biomarker tests to aid clinicians in making decisions regarding when to initiate and discontinue antibiotics in the inpatient setting. (14)

Issue 3: Tests are needed that rapidly identify or quantify pathogens directly from the clinical specimen and provide rapid susceptibility results. (15)

- **WG Recommendations:**
  1. Sustained investment in funding mechanisms (e.g., grants) for developing new, cost-effective diagnostic tests and updating existing diagnostic tests (Small Business Innovation Research (SBIR), Small Business Technology Transfer (STTR), and others)
  2. Expanded funding to Clinical Trials networks like the Antibacterial Resistance Leadership Group (ARLG), and ensure that these networks work through a common IRB

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R&D cont.

Issue 4: Collaboration between diagnostic companies and other stakeholders is limited and inconsistent. (16)

- **WG Recommendation:** Federal government agencies (HHS, FDA, CDC, NIH, DOD, USDA) should come together and create a list of the most critically needed diagnostics for combating AMR. The pathogen list could be used to prioritize funding and tax credits.

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Regulatory

Issue 1: The regulatory approval clearance process for modifying and improving existing diagnostic tests is complex and expensive. (17)

- **WG Recommendation:** Revision of FDA regulatory process for improvements or updates of existing tests that consider real-world evidence and postmarketing study results

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Regulatory cont.

Issue 2: The current regulatory process for new diagnostics is time-consuming and costly, posing a disincentive for developers. (18)

- **WG Recommendations:**
  1. Additional or enhanced clinical trials networks that function with a common IRB to reduce the regulatory burden of test approval
  2. Modified requirements for Clinical Laboratory Improvement Amendments (CLIA) waivers
  3. Complementary structuring of the FDA-CDC Antimicrobial Resistance Isolate Bank and the ARLG virtual repository to increase diagnostics companies' access to isolates

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Regulatory cont.

Issue 3: There are no requirements for hospitals to update their microbiology laboratories with newer technologies. (19)

- **WG Recommendation:** CLIA requirements to update microbiology laboratories' technology as part of the accreditation process

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Behavioral

Issue 1: Clinicians do not always use diagnostic tests, believe the results, and act on them. (20)

- **WG Recommendations:**
  1. Evidence-based research
  2. Inclusion of experts in clinical use of diagnostics on clinical guidelines committees that address prevention, diagnosis, and treatment of infectious diseases
  3. Clinician education on the use and interpretation of diagnostic tests
  4. Development of tools and mechanisms that improve clinicians' abilities to make decisions in the ambulatory setting

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Incentives for Therapeutics

WG Co-chair: John Rex

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Overview

- As noted earlier, you have to build fire services before the fire
  - And this is what makes it safe to live or work in any given building

- Free market for antibiotics will likely fail for several reasons:
  - I take antibiotics, am cured, and no longer spread. Other citizens benefit and owe me … but I do not receive that value ("Positive externality")
  - I take antibiotics, that drives up resistance and hurts other citizens. In theory, I should pay them some fee … but that doesn't happen ("Negative externality")
  - Use of any antibiotic gradually reduces its effectiveness for others ("Non-excludability")
  - Caps on reimbursement led to pricing inefficiencies ("Distorted reimbursement")

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Economic

Issue 1: The return on investment (ROI) for developing new antibiotics is lower than for most other drugs. (21)

- **WG Recommendations:**
  1. A combination of general and targeted incentives to introduce a more predictable and sufficient ROI for antibiotic manufacturers, including push incentives and pull incentives
  2. Expansion of targeted push incentives across all phases of discovery and development
  3. Adoption of some form of a de-linkage model as a pull incentive
  4. For pull incentives, development by CMS and the Treasury Department of value metrics for antibiotics and diagnostics as well as options for plausible business models for antibiotics, including de-linkage

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R&D

Issue 1: Finding molecules that kill bacteria without also harming the patient is scientifically challenging. (22)

- **WG Recommendation:** Strengthened funding for existing mechanisms that support innovation and R&D

Issue 2: Showing the utility of a new antibiotic against resistant bacteria paradoxically requires that resistant infections occur with sufficient frequency to enable clinical study. (23)

- **WG Recommendations:**
  1. Continued development of FDA guidance documents, with a particular emphasis on guidance for developing very narrow-spectrum agents
  2. By BARDA and NIAID, creation of clinical trials networks (and hence clinical trials capacity) supporting both broad- and narrow-spectrum agents

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Regulatory

Issue 1: It is difficult for manufacturers to develop clear and specific data for any new drug on clinical efficacy in infections caused by highly resistant bacteria. (24)

Issue 2: It is difficult to enroll the number of patients needed to show efficacy of a narrow-spectrum antibiotic because of the low rate of infections caused by specific pathogens. (25)

- **WG Recommendations:**
  1. Establishment of clear expectations by FDA through regular stakeholder engagement as guidance is developed
  2. Via multi-agency collaboration (FDA, CDC, CMS, Treasury), development of approaches to assessing all aspects (medical, financial, societal) of antibiotic value using limited amounts of data

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Behavioral

Issue 1: Stewardship activities appropriately limit the use of current and new antibiotics; therefore, novel antibiotics have a low financial ROI from the perspective of the developer. (26)

- **WG Recommendation:** Continued efforts by CMS and Treasury to ensure that solutions to the problem of incentives incorporate and support stewardship

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Conclusion

Thank you to all WG members:

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