

Recommendations for Incentivizing the Development of Therapeutics, Diagnostics, and Vaccines to Combat Antibiotic-Resistance

PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Overview of Working Group Activity

Chair: Martin Blaser

Vice Chair: Lonnie King

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Overarching Task

PACCARB's current task is addressing the best way to incentivize the development of therapeutics/anti-infectives (including alternatives to antibiotics), rapid diagnostics, and vaccines for both humans and animals.

Approach

Created 3 Working Groups:

- Incentives for Vaccines Working Group
- Incentives for Diagnostics Working Group
- Incentives for Therapeutics/Anti-Infectives Working Group

Approach

Working Groups developed an analysis framework based on issues and recommendations divided into four broad themes:

- **Economic-** Issues that influence the ROI to companies or food animal producers regarding product development or use
- **R&D-** Issues related to discovery research and the development process
- **Regulatory-** Issues related to the federal regulatory processes that influence the development or modification of a product ranging from basic research through studies that meet approval criteria
- **Behavioral-** Issues related to the behavior of consumers, providers, and companies relative to product use or development

Acknowledgements

Thank you to all Working Group members:

- Vaccines
 - Helen Boucher, Aileen Marty, Robert Weinstein, Jay Butler, Elizabeth Wagstrom, Joseph Larson, Cyril Gay, Peter Marks, Jane Knisely, Barbara Mulach, Anthony Fiore, Brian McCluskey, Kim Thompson, Tim Cooke, David Fleming, Ann Ginsberg, Saad Omer, Nate Smith
- Diagnostics
 - Michael Apley, Sara Cosgrove, Sherrie Dornberger, Matthew Erdman, Steven Gitterman, Jane Knisely, Alec Ritchie, Neena Anandaraman, Jean Patel, Paige Waterman
- Therapeutics/Anti-Infectives
 - Alicia Cole, Ramanan Laxminarayan, Richard Carnevale, Elizabeth Jungman, Joseph Larson, Robert Guidos, Francios Franceschi, Jane Knisely, Cyril Gay, Paige Waterman, Zuoyu Xu, John Jernigan

Procedure

1. Drs. Kent Kester and Thomas Shryock will be presenting the working groups' top 10 recommendations.
2. Co-chairs will present recommendations from each working group.
3. Council will deliberate on report and recommendations.
4. Council vote.

Notes Regarding Report

- Limited to antibiotic resistant bacteria
- Report summarizes issues and corresponding recommendations discussed at length
- Prevention only discussed in terms of vaccines and alternatives to antibiotics
- One Health approach
- 46 critical issues identified with 64 recommendations
 - Top 10 recommendations highlighted in executive summary

Human Health	Incentives to Develop	Animal Health
<p> Provide additional funding for the development of new product pipelines for vaccines that prevent viral or bacterial syndromes that drive antibiotic use</p> <p> Optimize the interactions among sponsors, regulatory agencies (such as FDA), and use policy committees (e.g., the ACIP)</p> <p> Incentivize the uptake of vaccines by influencing behavior, such as reimbursement to ensure “first-dollar coverage”</p>	<p> Vaccines</p>	<p>Develop and fund a National Policy and Innovation Institute under USDA whose main functions will include the following:</p> <p> Support basic research on immunology across species for the development of vaccines</p>
<p> Include the development of a concomitant AST as part of any new antibiotic funding (or funding for new antibiotics)</p> <p> Provide financial support for diagnostic manufacturers to bring new tests to market</p> <p> Continue funding for clinical trials networks with common rules or shared IRBs</p>	<p> Diagnostics</p>	<p> Promote educational programs for veterinarians on the use and interpretation of diagnostic tests</p>
<p> Develop new economic models (pull incentives) for therapies to support the currently available push incentives</p>	<p> Therapeutics / Anti-Infectives</p>	<p> Provide resources to conduct, evaluate, and create a database of efficacy studies of alternative products</p>

Human Health – Vaccines

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Animal Health – Overarching Recommendations

- National Policy on Innovation for Food Animal Disease Interventions
- Innovation Institute within USDA
 - Entrepreneurial coordinating and resource center for start-ups, universities, researchers, and small companies
 - Intended to complement and streamline ongoing activities within USDA, FDA CVM, and other agencies, plus establish connectivity with various animal health organizations, funders, companies, etc.

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Animal Health – Innovation Institute

- **Vaccines:** Support basic research of immune systems across species for the development of vaccines
- **Diagnostics:** Promote educational programs for veterinarians on the use and interpretation of diagnostic tests
- **Therapeutics/Anti-Infectives:** Provide resources to conduct, evaluate, and create a database of efficacy studies of alternative products

Human Health

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Incentives for Vaccines

WG Co-chair: Kent Kester

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Economic Recommendations

Corresponding to Issue Statements: 1, 2

1. Analyses on the cost and societal impacts associated with new vaccine development and administration in the AMR arena developed via a multi-agency process that involves at least CDC, CMS, and Treasury, in partnership with industry and public health stakeholders.
2. An expanded range of incentives to encourage development of vaccines that could reduce AMR by preventing the syndromes caused by bacteria and viruses that lead to antibiotic use.



R&D Recommendations

Corresponding to Issue Statements: 1, 2

1. Expanded surveillance by the CDC and CMS 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.
2. Focused financial incentives to encourage the development of vaccines directed at pathogens that have high rates of AMR across the R&D continuum (from early to advanced development).



Regulatory Recommendations

Corresponding to Issue Statements: 1, 2

1. Early interaction between sponsors and FDA and workshops, hosted by FDA's Center for Biologics Evaluation and Research (CBER), explaining pathways and best practices.
2. Early communication between the manufacturer, FDA, and CDC to present and discuss a target product profile with particular reference to impact on AMR pathogens.



Behavioral Recommendations

Corresponding to Issue Statements: 1, 2

1. Programs and interventions based on behavioral insights that aim to increase vaccine uptake.
1. 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 for all ages, not just children.
2. Focused governmental vaccine-centric educational policies and approaches, including vaccination as a means of achieving antibiotic stewardship, with involvement of health care facilities and health-related educational institutions (e.g., medical schools, academic health centers).



Incentives for Diagnostics

WG Co-chair: Angela Caliendo

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Economic Recommendations

Corresponding to Issue Statements: 1, 2, 3, 4

1. Funding for the development of new antibiotics should always include the development of a concomitant AST device.
2. A “reimbursement-plus” system for tests of key public health importance (e.g., CRE colonization testing). Public health agencies such as Centers for Medicare and Medicaid Services (CMS) should assist with these decisions.
3. Increase funding of diagnostics outcomes studies (e.g., from the Agency for Healthcare Research Quality [AHRQ], CDC, the Patient-Centered Outcomes Research Institute [PCORI], NIH, and DOD), including those assessing patient outcomes, length of stay, changes in antibiotic use, rates of antibiotic use for certain patient populations, and costs of care.
4. Tax credit for a portion of the qualified clinical testing expense, potentially modeled after the Orphan Drug Tax Credit



R&D Recommendations

Corresponding to Issue Statements: 1, 2, 3, 4

- 1-3 Sustained investment in funding mechanisms (e.g., grants) for developing new, cost-effective diagnostic tests and updating existing diagnostic tests through Small Business Innovation Research and Small Business Technology Transfer grants, among others.
- 1-3 Expanded funding for clinical trials networks (e.g., NIH-supported ARLG) and ensure that these networks work through a common IRB.
4. Federal government agencies (e.g., HHS, FDA, CDC, NIH, DOD, USDA) should come together to create a list of the most critically needed diagnostics for combating AMR.



Regulatory Recommendations

Corresponding to Issue Statements: 1, 2

1. Advancing FDA regulatory efforts for improvements or updates of existing tests that utilize postmarketing study results and real-world evidence to promote development of improved tests.
2. Additional or enhanced clinical trials networks that function with a common IRB to reduce the regulatory burden of test approval.
2. Modification of requirements to simplify process for obtaining Clinical Laboratory Improvement Amendments (CLIA) waivers.



Regulatory Recommendations (cont.)

Corresponding to Issue Statements: 2, 3

2. Utilization of postmarketing study results and real-world evidence to facilitate the approval process of new diagnostics.

2. Complementary structuring of the FDA-CDC Antimicrobial Resistance Isolate Bank and the ARLG virtual repository to increase diagnostics companies' access to isolates.

3. CLIA requirements to update microbiology laboratories' technology as part of the accreditation process.



Behavioral Recommendations

Corresponding to Issue Statement: 1

- Evidence-based research, supported by public and private resources, to facilitate a better understanding of the behavior that affects decisions about using rapid diagnostics, with a goal of identifying drivers that prevent adoption.
- Inclusion of experts in clinical use of diagnostics who can provide information regarding appropriate use of relevant rapid tests on clinical guidelines committees that address prevention, diagnosis, and treatment of infectious diseases.
- Clinician education on the use and interpretation of diagnostic tests.
- Development of tools and mechanisms that improve clinicians' abilities to make decisions in the ambulatory setting (e.g., linking antibiotic prescriptions, accompanied by laboratory results, to pharmacy dispensing of antibiotics and antivirals through an electronic medical record).



Incentives for Therapeutics

WG Co-chair: John Rex

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Economic Recommendations

Corresponding to Issue Statement: 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.
- Expansion of targeted push incentives across all phases of discovery and development.
- Adoption of some form of a delinkage model as a pull incentive.
- For pull incentives, development by CMS and the Treasury Department of value metrics for antibiotics and diagnostics, the required size of delinked MER reward, and options for plausible business models for antibiotics, including delinkage, in consultation with FDA and CDC, and through collaboration with public health experts and the international community.



R&D Recommendations

Corresponding to Issue Statements: 1, 2

1. Strengthened funding for existing mechanisms that support innovation and R&D.
2. Continued development and refinement of FDA guidance documents, with a particular and urgent emphasis on expanding the guidance on narrow-spectrum agents that address unmet medical need.
2. Clinical trials networks based on common master protocols and facilitated by BARDA and NIH, to accelerate Phase II and Phase III programs for agents that have adequate spectrum to permit study in the common infections for which standard trial designs exist.



Regulatory Recommendations

Corresponding to Issue Statements: 1, 2

- 1-2 Establishment of clear expectations by FDA through regular stakeholder engagement as guidance is developed.

- 1-2 Development by CMS, Treasury, and other USG agencies of approaches to assess antibiotic value using limited amounts of data.



Behavioral Recommendation

Corresponding to Issue Statement: 1

- Continued efforts by CMS and Treasury to ensure that solutions to the problem of incentives incorporate and support stewardship.

Animal Health

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Incentives for Vaccines

WG Co-chair: Randall Singer

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Economic Recommendation

Corresponding to Issue Statement: 1

- Incentives for use of vaccines that reduce bacterial and viral disease prevalence in farm animals to reduce the need for antibiotics.



R&D Recommendations

Corresponding to Issue Statement: 1

- Funding dedicated to supporting basic research of immune systems across species to optimize vaccine and adjuvant development, with shared funds across agencies, as this issue addresses AMR in both human and animals.
- Sufficient funding for the proposed Innovation Institute within USDA to develop new technology accelerator programs.



R&D Recommendations (cont.)

Corresponding to Issue Statements: 2, 3

2. Funding provided by the Innovation Institute dedicated to supporting improved vaccine delivery in animal production, with shared funds across agencies, as this issue addresses AMR in both human and animals.
3. Studies to estimate amount of antibiotic use that can be eliminated with vaccines, including viral disease vaccines.



Regulatory Recommendation

Corresponding to Issue Statement: 1

- Process evaluation by USDA's Center for Veterinary Biologics (CVB) to improve speed of approval of new strains in commercial vaccines.



Behavioral Recommendation

Corresponding to Issue Statement: 1

- Education and training in assessing the effectiveness of disease prevention programs that balance productivity and welfare through improvements in veterinary and animal science curricula, continuing education, and funding for training programs that assess herd and flock health programs.



Incentives for Diagnostics

WG Co-chair: Peter Davies

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Economic Recommendation

Corresponding to Issue Statements: 1, 2

1. Funding from the Innovation Institute for diagnostics outcomes studies, including animal health and welfare outcomes, AMR, and the impact on cost of production.
2. Ongoing financial support for veterinary diagnostic laboratories that perform diagnostic testing and AST for animal pathogens.



R&D Recommendations

Corresponding to Issue Statements: 1, 2, 3

1. Investment in research on diagnostics that rapidly identify pathogens in food animals or provide rapid susceptibility results directly from the clinical specimen in the field setting.
1. Investment in translational research to adapt diagnostics platforms developed for humans to animals.
2. Support for research to develop culture-independent methods for detecting microbial contamination of carcasses and meats as a tool for improved process controls.
3. Research grants for the generation and integration of additional data necessary for CLSI to establish test methods, quality-control range data, and interpretive categories (i.e., breakpoints) for priority animal pathogens for which there are currently none available or where human breakpoints are used.



Regulatory Recommendations

No regulatory issue was identified, therefore no recommendations were made.



Behavioral Recommendations

Corresponding to Issue Statement: 1

- Support for research into therapeutic decision-making behavior in veterinary medicine, including the use of AST and the potential for rapid diagnostics.
- Educational programs for veterinarians on the use and interpretation of diagnostic tests and stronger curricula and continuing education programs linked to antibiotic stewardship.



Incentives for Alternatives

WG Co-chair: Tom Shryock

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Economic Recommendations

Corresponding to Issue Statement: 1

- Initial funding for the Innovation Institute as per the National Policy.
- Enhanced support for small business innovation on alternatives through existing government programs (e.g., SBIR funding) and private-sector investment incentives.
- Enhanced technology transfer pathways within the Innovation Institute.



R&D Recommendations

Corresponding to Issue Statements: 1, 2

1. Support services provided by the Innovation Institute to connect innovators across sectors to the needed resources for R&D.
1. Specific solutions outlined in the National Policy to meet the needs and challenges of early developers.
2. Grants to researchers or food animal production companies to conduct field studies using alternative products to establish optimal conditions of use and compare effectiveness with established products in their own production environment, with the condition that study data be entered into a central database so that others can benefit from the work.



Regulatory Recommendations

Corresponding to Issue Statements: 1, 2

1. The proposed Innovation Institute to serve as the single point of contact for basic research scientists and small companies to facilitate and obtain feedback from the CVM and USDA.
2. Ongoing exploration of novel technologies (e.g., via education, scientific meeting attendance, expert consultations, workshops, cross-agency exchanges or with counterpart regulatory agencies in other countries, etc.) to inform FDA/CVM and USDA efforts to find new ways of satisfying evidentiary requirements via innovative regulatory approaches appropriate for the alternative candidates.



Behavioral Recommendations

Corresponding to Issue Statements: 1, 2

1. Awareness of the need and process for initiating patent protection of new technologies, included as part of the educational resources and outreach efforts of the proposed Innovation Institute.
1. Additional incentives for early phase innovators or organizations could also include patent application fee reimbursements or post-patent award or fee waivers to encourage submissions.
2. Analysis of information gathered in the proposed database repository from alternative product studies to assess health outcomes and possibly affected business aspects (e.g., ROI).