NATIONAL ACADEMY OF SCIENCE

COMMITTEE ON THE LONG-TERM MEDICAL AND ECONOMIC EFFECTS OF ANTIMICROBIAL RESISTANCE

The road towards the research and development of alternatives to antibiotics in the United States

Virtual Conference, January 7, 2020

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Antimicrobial Resistance

Warning from the father of antibiotics

Alexander Fleming
Penicillin
Nobel Lecture, December 11, 1945

"But I would like to sound one note of warning. Penicillin is to all intents and purposes non-poisonous so there is no need to worry about giving an overdose and poisoning the patient. There may be an danger, though, in under dosage. It is not difficult to make microbes resistant to penicillin in the laboratory exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body….."

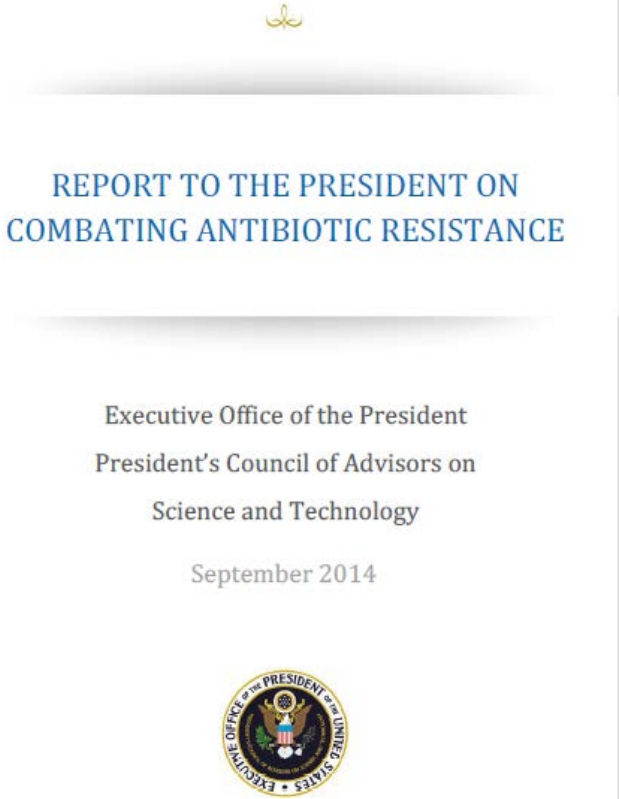
What are alternatives to antibiotics?

Alternatives to antibiotics are broadly defined as any substance that can be substituted for drugs that are increasingly becoming ineffective against pathogenic bacteria, viruses or parasites.

Gay C.G., Seal B.S., Lillehoj H.S., Donovan D.M. (2014) Alternatives to Antibiotics: Recent Scientific Advancements. OIE Conference Booklet, Ed. 2014: Responsible and Prudent Use of Antimicrobial Agents for Animals; 74-75

www.ars.usda.gov/alternativestoantibiotics

President's Council of Advisors on Science and Technology 2014



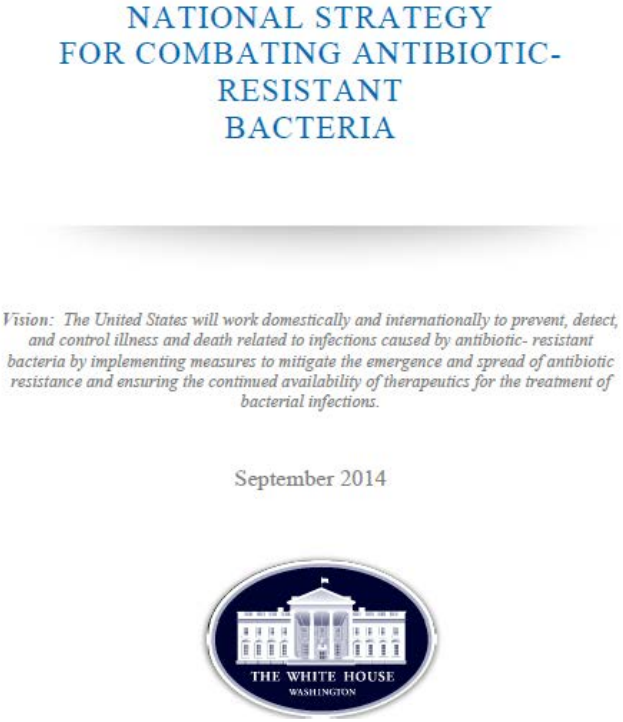
Recommendation 3. Fundamental Research

(1) Expand fundamental research relevant to developing new antibiotics and alternatives for treating bacterial infections.

(2) Develop alternatives to antibiotics in agriculture.

http://www.whitehouse.gov/blog/2014/09/18/pcast-releases-new-report-combating-antibiotic-resistance

President's National Strategy for Combating Antibiotic Resistant Bacteria 2014



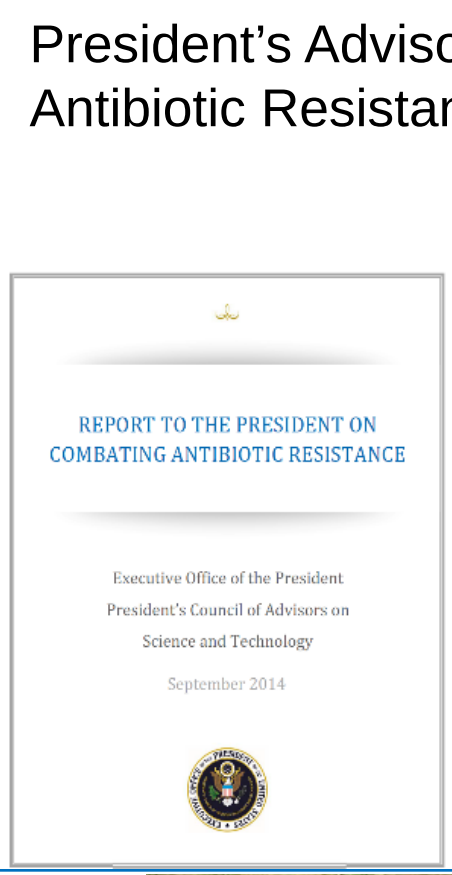
Goal 5: Research and Development: Incentivize development of therapeutics and diagnostics for humans and animals.

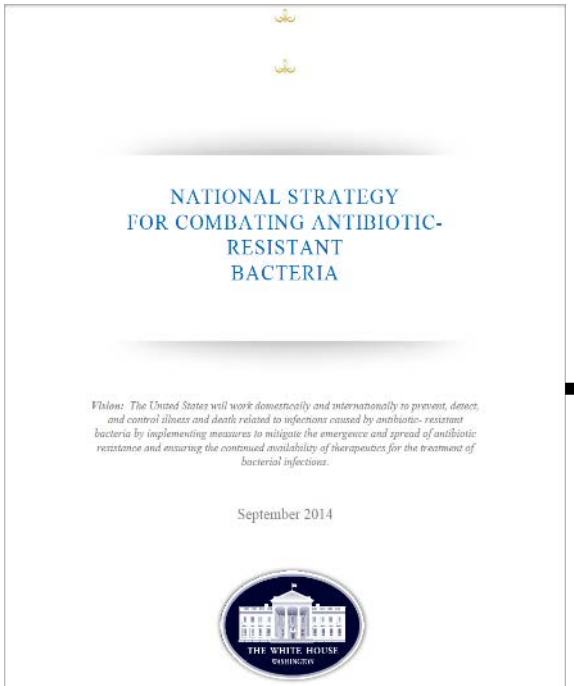
5.5 *Establish and promote international collaboration and public-private partnerships to incentivize development of new therapeutics to counter antibiotic resistance including new, next-generation, and other alternatives to antibiotics; vaccines; and affordable, rapidly deployable, point-of-need diagnostics.*

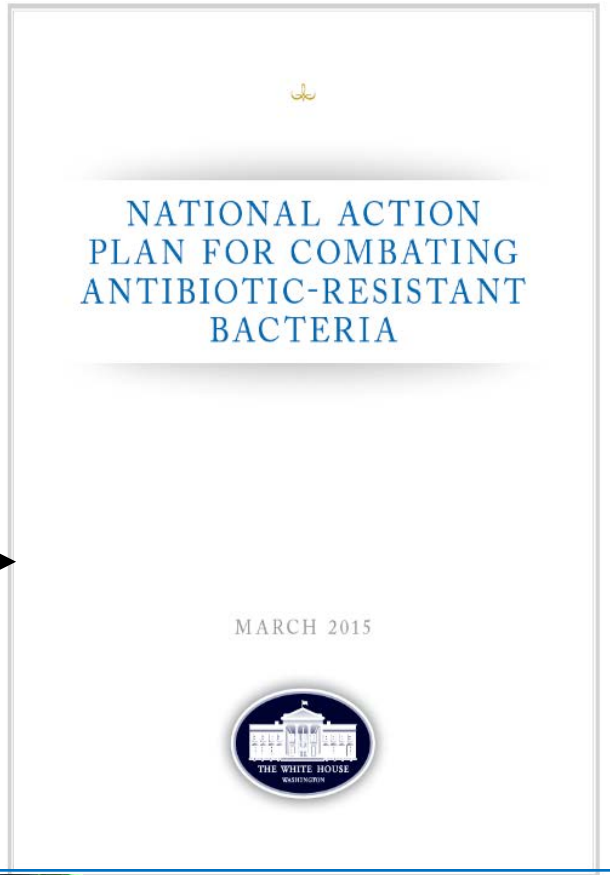
http://www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria

U.S. Interagency Coordination

- Interagency Task Force for Combating antibiotic Resistant Bacteria
- Executive Order 13676 established the President's Advisory Council on Combatting Antibiotic Resistant Bacteria (PACCARB)

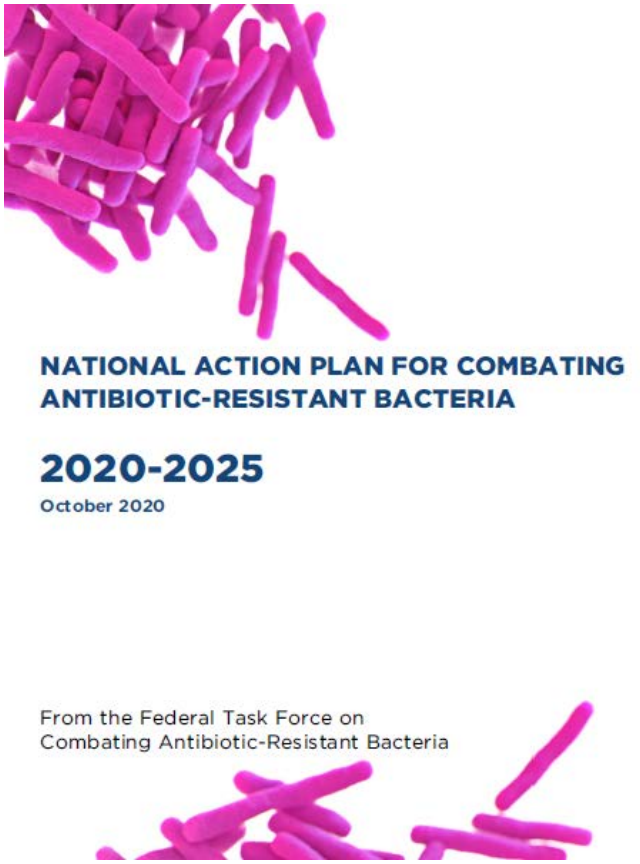






National Action Plan 2020-2025

Goal 1: Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections
Goal 2: Strengthen National One Health Surveillance Efforts to Combat Resistance
Goal 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria
Goal 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines
Goal 5: Improve International Collaboration and Capacities for Antibiotic-Resistance Prevention, Surveillance, Control and Antibiotic Research and Development



https://aspe.hhs.gov/system/files/pdf/264126/CARB-National-Action-Plan-2020-2025.pdf

International Symposium

Alternatives to Antibiotics (ATA)

Challenges and Solutions in Animal Production

The World Organisation for Animal Health (OIE)
12 Rue de Prony, 75017
Paris, France
25-28 September, 2012

www.ars.usda.gov/alternativestoantibiotics

Symposium Conclusions

1) Insufficient research to support their effective use in animal agriculture
2) Alternatives to antibiotics must be developed according to national and international standards and meet requirements for efficacy, safety, and quality
3) Regulatory pathways to enable the registration of alternatives to antibiotics are in place

Examples of alternatives to antibiotics

Drugs, biologics, and feed additives

- **Vaccines**
- **Microbial-derived**
- **Phytochemicals**
- **Immune-related**
- **Innovative drugs**

www.ars.usda.gov/alternativestoantibiotics

Recommended Publications

https://www.biomedcentral.com/collections/alternatives-to-antibiotics (2018)

Vaccines as alternatives to antibiotics for food producing animals. Part 1: challenges and needs
Authors: Karin Hoelzer, Lisa Bielke, Damer P. Blake, Eric Cox, Simon M. Cutting, Bert Devriendt, Elisabeth Erlacher-Vindel, Evy Goossens, Kemal Karaca, Stephane Lemiere, Martin Metzner, Margot Raicek, Miquel Collell Suriñach, Nora M. Wong, Cyril Gay and Filip Van Immerseel

Vaccines as alternatives to antibiotics for food producing animals. Part 2: New approaches and potential solutions
Authors: Karin Hoelzer, Lisa Bielke, Damer P. Blake, Eric Cox, Simon M. Cutting, Bert Devriendt, Elisabeth Erlacher-Vindel, Evy Goossens, Kemal Karaca, Stephane Lemiere, Martin Metzner, Margot Raicek, Miquel Collell Suriñach, Nora M. Wong, Cyril Gay and Filip Van Immerseel

Microbial-derived products as potential new antimicrobials
Authors: Bruce S. Seal, Djamel Drider, Brian B. Oakley, Harald Brüssow, David Bikard, Joseph O. Rich, Stefan Miller, Estelle Devillard, Jason Kwan, Gérard Bertin, Stuart Reeves, Steven M. Swift, Margot Raicek and Cyril G. Gay

Phytochemicals as antibiotic alternatives to promote growth and enhance host health
Authors: Hyun Lillehoj, Yanhong Liu, Sergio Calsamiglia, Mariano E. Fernandez-Miyakawa, Fang Chi, Ron L. Cravens, Sungtaek Oh and Cyril G. Gay

The potential for immunoglobulins and host defense peptides (HDPs) to reduce the use of antibiotics in animal production
Authors: Albert van Dijk, Chris J. Hedegaard, Henk P. Haagsman and Peter M. H. Heegaard

Innovative drugs, chemicals, and enzymes within the animal production chain
Authors: Yousef I. Hassan, Ludovic Lahaye, Max M. Gong, Jian Peng, Joshua Gong, Song Liu, Cyril G. Gay and Chengbo Yang

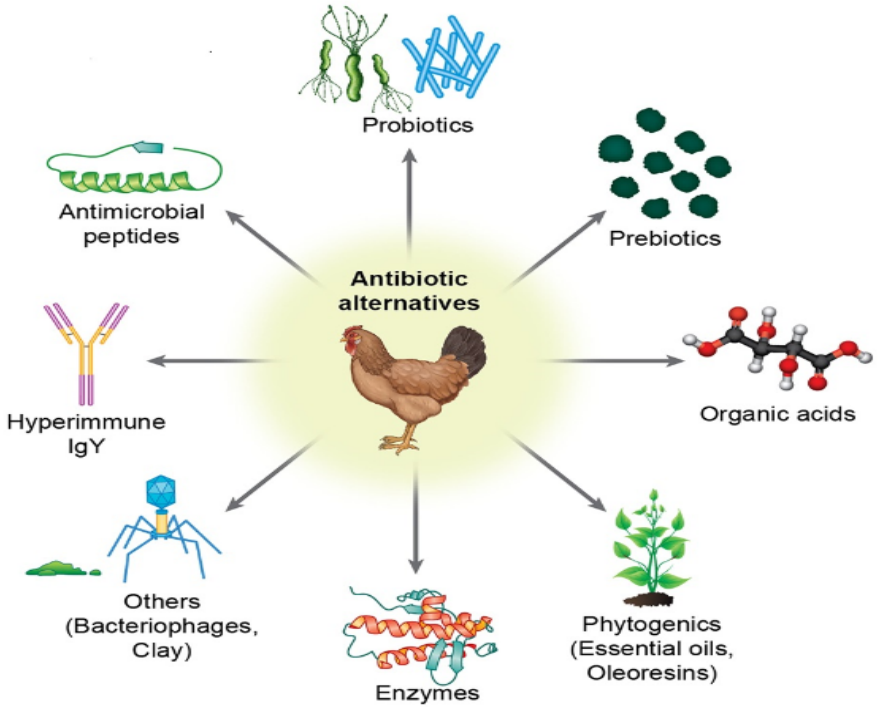
https://www.sciencedirect.com/science/article/pii/S1045105618300587?via%3Dihub (2018)

Regulatory pathways to enable the licensing of alternatives to antibiotics
Authors: Faye Ioannou, Cindy Burnsteel, David K.J. Mackay, Cyril G. Gay

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6896835/pdf/fvets-06-00429.pdf (2019)

Strategic Priorities for Research on Antibiotic Alternatives in Animal Agriculture
Authors: Kurt T, Wong N, Fowler H, Gay C, Lillehoj H, Plummer P, Scott HM, Hoelzer K.

Antibiotic alternatives: How to maximize health, growth performance, and feed efficiency in the absence of antibiotics?



Gadde, U., Oh, S., Kim, W., Lillehoj, H. 2017. Alternatives to antibiotics. Animal Health Res Rev. 9:1-20

USDA
United States Department of Agriculture
Agricultural Research Service

USDA ARS Antimicrobial Resistance (AMR) and Alternatives to Antibiotics (ATA) Accomplishment Summary

2016-2018

https://www.ars.usda.gov/alternativestoantibiotics/PDF/reports/Combined%20AMR_ATA%20Accomplishment%20Summary.pdf

CONCLUSIONS

1. A paradigm shift is needed on how we approach the research and development of antibiotic alternatives
2. Defining mechanisms of action will be paramount to enable the effective use of alternatives to antibiotics in animal agriculture
3. A portfolio of alternatives to antibiotics may need to be considered to achieve optimum health and disease management for different animal production systems
4. There is a critical need to incentivize the research and development of alternatives to antibiotics for use in agriculture.

www.ars.usda.gov/alternativestoantibiotics

Thank you!

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OIE *ad hoc* Group on prioritisation of diseases for which vaccines could reduce antimicrobial use in animals

- "Provide guidance on prioritisation of disease for which the use of already available and new vaccines could reduce antimicrobial use in animals, focusing the first step on pigs, poultry and fish "



- Identify actions to improve utilisation of such vaccines

- To support the WHO Global Action Plan on AMR which makes provision for such approach

Table 2: Infections for which new or improved vaccines would significantly reduce the need for antibiotic use in swine

Key syndrome	Primary pathogen(s) (disease)	Antibiotic use	Commercial* vaccine exists	Major constraints to use of vaccine / vaccine development	Vaccine research priority
Systemic (respiratory)	*Streptococcus suis*	High	Yes	• Strain coverage too narrow • Lack of cross-protection • Poor immunogenicity due to being a capsule based vaccine	High
	Haemophilus parasuis	Medium	Yes	• Serotype specific with variable cross-protection • Maternal antibody interference	Medium
Respiratory	*Pasteurella multocida (for pneumonic disease)*	High	No	• No vaccine with approved label claim for pneumonia (There is a vaccine for atrophic rhinitis)	High
	Mycoplasma hyopneumoniae	High	Yes	• Does not completely prevent lung lesions • Animals continue to shed pathogen • Diagnostics not always accurately done	Low
	Actinobacillus pleuropneumoniae	High	Yes	• Limited coverage • Good immunity only if serotype specific • Sub-unit vaccine which affords cross-protection	High
	Porcine Reproductive and Respiratory Syndrome virus (secondary bacterial infections)	High	Yes	• Strain coverage limited • High virus mutation rate • Modest cross-protection • Vaccine evasion	High
	Swine Influenza Virus (secondary bacterial infections)	High	Yes	• Strain matching • Vaccine-associated enhanced respiratory disease (VAERD) • Lack of cross-protection • Efficacy in piglets limited	High
Enteric – neonatal	*Escherichia coli*	High for the syndrome, Low for *E. coli*	Yes	• Maternal vaccine provides effective lactogenic immunity • Coverage of enterotoxigenic *E. coli* may occasionally need to be updated	Low
Enteric (weaners/finishers)	*Escherichia coli*	High	Yes	• Maternal antibody interference • Short window for induction of immunity	High
	Lawsonia intracellularis	High	Yes	• Other pathogens in the syndrome (*Brachyspira*) not included • Antibiotic-free window for vaccination required (live attenuated oral vaccine)	Low (see also *Brachyspira*)
	Brachyspira spp *B. hyodysenteriae,* *B. pilosicoli*	Medium-high	No	• Low current research investment as changes in husbandry largely eliminated the disease • Technical barriers to vaccine development	High
	Rotaviruses (secondary bacterial infections)	High	Yes	• Reasons limiting wider adoption unknown	High

Report Conclusions

Vaccine research could have a significant impact, particularly if it addressed the following four priority gaps:

- Maternal antibody interference
- Cross-protection or inclusion of relevant strains in vaccine formulations
- Occurrence of immunological interference in multivalent vaccines
- Innovative delivery systems to enable mass-vaccination

frontiers in Veterinary Science

PERSPECTIVE
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Strategic Priorities for Research on Antibiotic Alternatives in Animal Agriculture—Results From an Expert Workshop

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[1] Foundation for Food and Agriculture Research, Washington, DC, United States, [2] Pew Charitable Trusts, Washington, DC, United States, [3] National Pork Board, Clive, IA, United States, [4] Agricultural Research Service, U.S. Department of Agriculture, Beltsville, MD, United States, [5] College of Veterinary Medicine, Iowa State University, Ames, IA, United States, [6] Department of Veterinary Pathobiology, Texas A&M University, College Station, TX, United States*

The emergence, spread, and expansion of antibiotic resistance and increasing restrictions on the use of antibiotics in animal agriculture have created a need for efficacious alternatives that remains unmet. Prioritizing research needs in the development of alternatives is key to ensuring that scarce research resources are dedicated to the most promising approaches. However, frameworks to enable a consistent, systematic, and transparent evaluation of antibiotic alternative candidates are lacking.