

Fisher FOCUS



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News from the Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases

Dangers of Antibiotic Use in Food Animal Production

Principal Investigator, **Christopher Heaney, PhD**, is a 2013 Fisher Center Discovery Program (FCDP) award recipient

Background In the last 70 years antibiotics have had tremendous impact on our world, decreasing death and disease in humans and animals. In the food production arena, therapeutic antibiotic use is defined as treating diseased animals with specific and appropriate antibiotics for a limited time, which may prevent the spread of pathogens to other members of the animal group. However, antibiotics also have non-therapeutic uses in food animal production such as increasing the weight of animals and increasing the speed of growth, thereby lowering the time to market. Based on 2012 data, the FDA estimates 80% of antibiotics sold in the US are for animals.

With cases of drug-resistant bacteria increasing around the world, over-use of antibiotics in food production impact both animals and humans and is a leading health threat. Food production workers who raise animals and workers in the food packaging industry are also exposed to antibiotics in the workplace, leading to antibiotic resistance. Solid and liquid wastes may contaminate the soil, air, and water in communities surrounding food animal production

areas, leading to drug-resistant bacteria spreading far into the environment.

FCDP Supported Study The FCDP supported project helped Dr. Heaney forge new collaborations with domestic and international researchers focused on food production associated antibiotic resistance. Relates Dr. Heaney, "This would not have been possible without FCDP support. These collaborations lead to new discoveries of antibiotic resistance, pathogenesis, and evolution of *S. aureus* that could have broad public health and clinical relevance." Preliminary findings show an association between carriage of livestock-associated *S. aureus* in the nose and increased risk of skin infections in hog workers. Nearly half of *S. aureus* strains carried by hog workers were multidrug-resistant.

Current Activities In May 2016 Dr. Heaney published a UK commissioned review of antibiotic resistance, *A Framework for Costing the Lowering of Antimicrobial Use in Food Animal Production*. This provides a published literature overview on costs associated with lowering or eliminating growth-promoting antibiotic use in food animal production. Proposed alternatives to



antibiotics include changing production practices, vaccines, or feed additives. Other suggested practice changes are to reserve specific drugs for human use, all of which are highlighted as key strategies in combating antimicrobial resistance. Bans on growth-promoting antibiotics in Denmark, Sweden, and the Netherlands have demonstrated the economic feasibility of antibiotic alternatives over time.

Additional Research The FCDP also supports the work of Brian Schwartz, MD, MS and Melissa Poulsen, PhD, who are examining the health impact of poultry farms in Pennsylvania communities over a 10-year period.

The FCDP recognizes the importance of food production safety and remains committed to examining issues related to environmental infectious diseases.

Image source: David Love, PhD

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Mission Statement

The Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases is dedicated to the clinical research of environmental pathogens which improves the diagnosis and treatment of these infections.



A word from our Director Paul Auwaerter, M.D., M.B.A.

Clinical Director, Division of Infectious Diseases

Global Action Now A Priority to Fight Antimicrobial Resistance

When focusing on infections and public health, media headlines are most often captured by something completely new such as Zika virus, Ebola virus striking in urban environments or pandemic influenza. Yet one of the most pressing problems has been evolving in a persistent and progressive fashion

since 1942. This was the year that penicillin was first used to treat human infections. Over the seven

decades since, bacteria in particular have developed considerable resistance to many of the commonly used antibiotics that physicians depend upon to routinely treat infections.

Nowadays, it is not uncommon to face situations where a common urinary tract infection is due to a bacteria that is resistant to any known oral antibiotic. Lung infections due to Mycobacteria abscessus, a distant relative of tuberculosis, are impossible to eradicate. Patients in intensive care units suffer from infections whereby we often rely on drugs such as colistin and amikacin not routinely used in decades due to their toxicities but are now the last lines of defense. It is estimated that 2 million in the U.S. are infected annually with 23,000 deaths as a result of resistant infections, that also adds significant costs to health systems estimated at \$20-35 billion.

Why are we in this situation? Among the factors, the success of antibiotic therapy has led to over-use in both human and animal health—in many countries such as the U.S., we use 3 to 8 times the amount of antibiotics that other countries such as the Netherlands employ to maintain similar well-being. The dynamics of global

travel and commerce mean that countries with high rates of resistance such as India, China and others “export” their resistance to others easily through foods and acquiring bacteria as part of normal human flora. Lastly, the pipeline of new classes of antibiotics has slowed to a crawl with

bacteria evolving far faster and outstripping our innovation—certainly compared to the glory days of antibiotic discovery in the 1950s through 1980s.

While infectious diseases physicians and their societies have been arguing for some time to avoid what is now being called a “nightmare scenario” by both the Centers for Disease Control and the World Health Organization, there is increasing traction among governments for this global threat to human health that demands concerted action. For only the fourth time, this past September the United Nations passed by unanimous affirmation a health-related resolution to develop action plans in each country to combat antimicrobial resistance.

By this measure, each country is to focus efforts upon limiting misuse of antimicrobial agents in human health, animal health and agriculture; developing improved surveillance to monitor drug-resistant infections as well as use of antibiotics and driving innovation of new diagnostic and therapeutic agents. This will require local, regional, national and global collaboration and cooperation as well as research efforts to achieve the goal of continuing to effectively treat infections.

Infectious disease physicians and researchers are among the needed leaders in these efforts. Antimicrobial resistance research is among the highest priorities of research in the Fisher Center focusing on ways to improve recognition and limit spread of such resistant organisms in humans and

animals as well as methods to better treat resistant pathogens. To date, ten Fisher-

funded studies have focused on these areas.

Without such efforts to maintain our antibiotic armamentarium, there could be a day that a routine joint replacement surgery or cesarean section cannot be carried out without high risk of infection—harkening to the pre-antibiotic era of our forefathers.

“Drug resistance imposes huge costs on health systems and is taking a growing—and unnecessary—toll in lives and threatening to roll back much of the progress we have made.”

Ban Ki-moon, United Nations Secretary General [September 2016]



Paul Auwaerter, MD, President-Elect of the IDSA and Helen Boucher, MD of Tufts University School of Medicine, Treasurer of the IDSA, attended the General Session and Resolution of Antimicrobial Resistance (AMR) on September 21, 2016 at UN Headquarters in New York

Thank you to those who contributed so generously to Environmental Infectious Disease research in the past six months. Such gifts help facilitate innovative research, especially targeted to younger investigators.

In particular we would like to acknowledge:

- Leonard Hartwig
- Thomas L. Owsley
- Robert Bank

Fisher Center Discovery Program 2017 Awards

On December 1, 2016 the Fisher Center Advisory Board reviewed 14 grant applications for the 2017 Fisher Center Discovery Program. The following four projects were awarded grants totaling \$ 178,693.23. Congratulations to the research teams on their outstanding efforts.



Aaron Milstone, MD and Katherine Goodman, JD **Impact of Heterogeneous Resistance Mechanisms on Hospital Transmission of Carbapenem-Resistant Enterobacteriaceae (CRE)** The CDC has assigned its highest antibiotic resistance threat level to carbapenem-resistant Enterobacteriaceae (CRE). CRE infections impose mortality rates approaching 50 percent and have caused numerous outbreaks in US healthcare facilities. These highly drug-resistant organisms bring us to the brink of a “post-antibiotic” era, as there are extremely limited antibiotic options remaining to treat CRE infections. Preventing hospital CRE infections by limiting organism spread in the hospital environment is critical. This proposal intends to evaluate which patients are asymptotically bringing CRE into high-risk hospital environments and once hospitalized, what transmission risks asymptomatic carriers pose. This research will address which patients should be screened for CRE, and once carriers are identified what infection control practices are appropriate. Our goal is to maximize hospital transmission prevention while simultaneously ensuring that CRE policies are cost-effective and implementable.



Evan Bloch, MD **African BAOBAB (Babesia Observational Antibody) Study** *Babesia* is a genus of tick-borne protozoan parasites found in red blood cells. The overwhelming majority of human disease is ascribed to

Babesia microti, which is endemic in the United States. While most *Babesia* infections are subclinical or mild, severe complications and even fatal disease occur in selected patient subsets (i.e. those at extremes of age, the asplenic and the immunocompromised). *Babesia* also poses a risk to transfusion recipients. An increase in tick-borne and transfusion-transmitted babesiosis in the US has prompted its designation as a notifiable disease and development of new assays for blood donor screening. However surveillance to date has been constrained by lack of availability or access to diagnostic assays. A pilot evaluation in Tanzania, using an antibody assay suggests that *Babesia* may be present in a cluster of participating villages. The BAOBAB study plans to revisit one such affected village to conduct comprehensive laboratory testing and clinical evaluation, to characterize risk of *Babesia*, and propose prevention measures. The study offers an opportunity to expand the global epidemiology of *Babesia*, a neglected infection and possible mimic of malaria. It could also refine newly developed diagnostic tools by showing how test performance is affected by species diversity.



Kevve Nachman, PhD **Building a baseline for assessing the human health impact of a landmark legislative intervention on antibiotic use in industrial poultry production** Non-therapeutic antibiotic use in industrial livestock production promotes antimicrobial-resistant (AMR) bacteria, which can leave the farm via environmental routes (food, air, water, and soil) and infect humans. In early 2018, California will implement legislation to ban non-therapeutic antimicrobial use in livestock. This natural experiment presents an opportunity to evaluate whether reductions in livestock antimicrobial use lead to subsequent AMR reductions in meat-source and clinical *E. coli* isolates. We propose to leverage electronic health record data and prospectively-collected clinical and retail meat *E. coli* isolates to develop the baseline data

necessary to determine whether a policy to reduce livestock antimicrobial use will benefit human health. This will allow us to better understand the contribution of antibiotic use in industrial poultry production to the growing problem of human AMR infection. Our team stands to make critical contributions to this field, in part because we represent a paradigm shift in multi-disciplinary thinking, combining expertise in livestock-associated AMR, veterinary medicine, clinical infectious diseases, causal inference statistical methods, and big data electronic health records.



Sabra L. Klein, PhD and Meghan Vermillion, DVM **Identification of early detection biomarkers and candidate therapeutics for congenital Zika virus infection** Zika virus (ZIKV) is a mosquito-borne virus endemic in regions of Africa and Asia, and is an emerging as a significant public health threat in South, Central, and North America. Infection during pregnancy has severe consequences for the fetus, causing congenital Zika syndrome, which includes microcephaly, intrauterine growth restriction, and miscarriage. In the absence of an available vaccine, there is an urgent need to identify and test early detection markers and candidate therapeutics for congenital ZIKV infection and disease. Because studies in humans cannot readily be performed, our group has developed a novel model of transplacental ZIKV transmission using mice. We have discovered that the mouse placenta expresses high levels of a candidate ZIKV entry receptor, Axl, which may contribute to fetal transmission. Using this *in vivo* infection model in parallel with *in vitro* placental cultures, we seek to characterize the early inflammatory and hormonal markers of placental and fetal ZIKV infection and test the efficacy of a selective Axl inhibitor as a candidate therapeutic for preventing or limiting congenital infection and disease.

Funding Our Future

Thanks to all of you that believe in the mission of environmental infectious disease research. As always, we are extremely grateful to those who have contributed. To donate, please consider the following options and designate the **Fisher Center for Environmental Infectious Diseases**

Online: To make a gift or pledge online, please complete our secure online giving form, <https://secure.jhu.edu/form/infdis>

Phone: To speak to someone directly about making a gift, please call 410-550-9893

Recent Publications

Plasma Tryptophan and the Kynurenine-Tryptophan Ratio are Associated with the Acquisition of Statural Growth Deficits and Oral Vaccine Underperformance in Populations with Environmental Enteropathy. **Kosek MN**, Mduma E, Kosek PS, Lee GO, Svensen E, Pan WK, Olortegui MP, Bream JH, Patil C, Asayag CR, Sanchez GM, Caulfield LE, Gratz J, Yori PP. *Am J Trop Med Hyg.* 2016 Oct 5;95(4):928-937. Published online August 8, 2016, doi: 10.4269/ajtmh.16-0037 *Am J Trop Med Hyg* 2016 16-0037. PMID: 27503512

Environmental Exposures and the Risk of Central Venous Catheter Complications and Readmissions in Home Infusion Therapy Patients. **Keller SC**, Williams D, Gavvani M, Hirsch D, Adamovich J, Hohl D, Krosche A, Cosgrove S, **Perl TM**. *Infect Control Hosp Epidemiol.* 2016 Oct 4:1-8. PMID: 27697084

Occurrence of methicillin-resistant Staphylococcus aureus in surface waters near industrial hog operation spray fields. Hatcher SM, Myers KW, **Heaney CD**, Larsen J, Hall DJ, Miller MB, Stewart JR. *SSci Total Environ.* 2016 Sep 15;565:1028-36. doi: 10.1016/j.scitotenv.2016.05.083. Epub 2016 May 31. PMID: 27261430.

Role of Suppressive Oral Antibiotics in Orthopedic Hardware Infections for Those Not Undergoing Two-Stage Replacement Surgery. **Keller SC**, Cosgrove SE, **Higgins Y**, **Piggott DA**, Osgood G, **Auwaerter PG**. *Open Forum Infect Dis.* 2016 Aug 30;3(4):ofw176. PMID: 27747252

Geophagy is associated with growth faltering in children in rural Bangladesh. Perin J, Thomas A*, Oldja L, Biswas S, Sack RB, Ahmed S, Haque R, Parvin T, Azmi IJ, Bhuyian SI, Talukder KA, Faruque AG, **George CM**. *J Pediatr.* 2016 Aug 2. pii: S0022-3476(16)30506-6. doi: 10.1016/j.jpeds.2016.06.077. [Epub ahead of print]. PMID: 27496267

Learning from the patient: Human factors engineering in outpatient parenteral antimicrobial therapy. **Keller SC**, Gurses AP,

Arbaje AI, Cosgrove SE. *Am J Infect Control.* 2016 Jul 1;44(7):758-60. doi: 10.1016/j.ajic.2016.01.010. Epub 2016 Mar 2. PMID: 26944005.

Defining Clinical Excellence in Adult Infectious Disease Practice. Chida NM, Ghanem KG, **Auwaerter PG**, Wright SM, **Melia MT**. *Open Forum Infect Dis.* 2016 Jun 16;3(3):ofw122. doi: 10.1093/ofid/ofw122. eCollection 2016 Sep. Review. PMID: 27419186

Unsafe Child Feces Disposal is Associated with Environmental Enteropathy and Impaired Growth. **George CM**, Oldja L, Biswas S, Perin J, Sack RB, Ahmed S, Shahnaj M, Haque R, Parvin T, Azmi IJ, Bhuyian SI, Talukder KA, Faruque AG. *J Pediatr.* 2016 Jun 15. pii: S0022-3476(16)30243-8. doi: 10.1016/j.jpeds.2016.05.035. [Epub ahead of print]. PMID: 27318380

Evaluation of Multiple Methods for Detection of Gastrointestinal Colonization of Carbapenem-Resistant Organisms from Rectal Swabs. Simner PJ, Martin I, Opene B, **Tamma PD**, **Carroll KC**, **Milstone AM**. *J Clin Microbiol.* 2016 Jun;54(6):1664-7. doi: 10.1128/JCM.00548-16. Epub 2016 Apr 6. PMID: 27053674

A Framework for Costing the Lowering of Antimicrobial Use in Food Animal Production. Commissioned Report. Anthony D, Ramachandran R, Love DC, Korinek A, Fry JP, **Heaney CD**. A commissioned paper for the United Kingdom Review on Antimicrobial Resistance, May 2016.

Recent Presentations

Antimicrobial Resistance Hits Global Stage at UN Summit. **Paul Auwaerter, MD, MBA**. Medscape Infectious Diseases. <http://www.medscape.com/viewarticle/870953>. November 2, 2019

More of Everything: Characteristics of Those Seeking Opinions Regarding Lyme Disease. Takaaki Kobayashi, **Yvonne Higgins**, Sarah Salter, Gayane Yenokyan, Paul Lantos, **Michael Melia**, **Paul Auwaerter**. Poster Session: ID Week in New Orleans, Louisiana. October 27, 2016

Infectious Mononucleosis and Mononucleosis Syndromes. **Paul Auwaerter, MD, MBA**. 11th Infectious Diseases Update for Primary Care and Hospital Medicine, at the Johns Hopkins University, School of Medicine, in Baltimore, MD. October 20, 2016

Vertebral Osteomyelitis: Is 6 Weeks of Treatment Not Enough? **Paul Auwaerter, MD, MBA**. Medscape Infectious Diseases. <http://www.medscape.com/viewarticle/869317>. September 29, 2016

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