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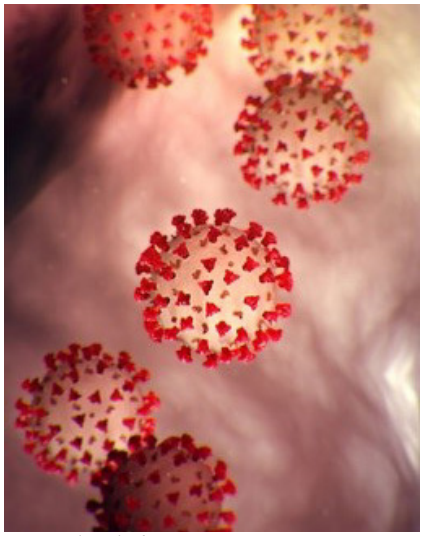
NEWS FROM THE SHERRILYN AND KEN FISHER CENTER FOR ENVIRONMENTAL INFECTIOUS DISEASES

Dedicated to the clinical research of environmental pathogens which improves the diagnosis and treatment of these infections.



Legionella (in red) infecting amoeba

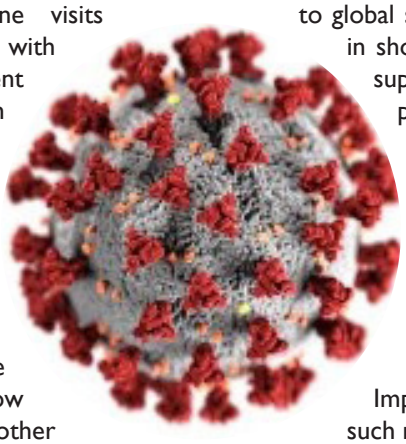
What's Inside

Fisher Center COVID-19 Responses

How our faculty is responding in the midst of a global pandemic

As with most individuals and businesses in the United States, the COVID-19 pandemic has dominated our research and clinical activities. As the Clinical Director of the Division of Infectious Diseases and Fisher Center Director, Paul Auwaerter, has been leading efforts at Johns Hopkins Medical Institutions for developing clinical guidelines in the face of rapidly evolving information to treat persons infected with SARS-CoV-2, the virus that causes COVID-19. Dr. Auwaerter's efforts include daily 7 am calls for clinical staff providing care in the hospital and weekly conferences to discuss clinical trial information that may be incorporated into the COVID-19 Treatment Guidance document for the Johns Hopkins Medical Institutions that has been revised over a dozen times since the start of the pandemic.

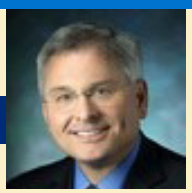
Responding to the need to limit in-person contact, clinicians have quickly pivoted to providing care using telemedicine, conducting outpatient visits utilizing the internet. Surveys of Johns Hopkins patients who have had telemedicine visits indicate great satisfaction with this mode of provider-patient interaction. Communication with our colleagues, fellow researchers and regular conferences have also all converted to online video conferencing. The success of online communication has led to a paradigm shift, which will most likely make some permanent inroads in how we communicate with one another post-pandemic.



Initially, during the first phase of the pandemic, limiting person-to-person exposure affected non-COVID-19 research. Employees who could work from home were mandated to do so. Research involving in-person visits was limited to only those studies offering critical treatments, such as cancer trials. Most laboratory-based research was also put on hold due to staffing and social distancing directives. In addition, the pandemic has led to global supply chain issues, resulting in shortages of lab chemicals and supplies. Disruption due to the pandemic delayed the onset of clinical and laboratory-based 2020 Fisher Center Discovery Program projects. Measures to counteract the delays, such as no-cost time extensions, were instituted.

Importantly, by mid-summer, such restrictions at Johns Hopkins are now lifted for almost all research projects across the institution. Special measures to protect both researchers and staff will allow research to resume, balancing safety with the customary imperatives to find new information to improve patient care.

MESSAGE FROM THE DIRECTOR



Influenza, tuberculous and other respiratory infections, since spread through human-to-human contact, have not been traditionally part of the Fisher Center For Environmental Infectious Diseases. Instead, the focus has been on vector-borne diseases such as those spread by ticks and mosquitoes or infections acquired through built structures.

However, with the novel coronavirus SARS-CoV-2, while a virus spread by respiratory droplets and sometimes by small particles (aerosols), it appears where you acquire the disease does matter. This is especially important since many COVID-19 illnesses arise when the virus transmitted most effectively in the earliest phases when an individual is not ill or only mildly so, yet has high levels of the virus.

For example, studies from China performed in the early phases of the pandemic, found that the virus was rarely acquired from exposure in the outdoors. So-called superspreader events, where one infected person may spread the virus to many others, have only been described indoors, such as churches, ski-chalets, cruise ships, public restrooms and restaurants. Though not fully proven, it appears such mass infection events with the coronavirus appear to be facilitated by spaces with many people and poor ventilation. As the virus is more stable in the cold rather than warm environments, meatpacking plants have become hotspots because of the many workers who perform their butchering and packing within refrigerated rooms.

While the focus on finding safe and effective vaccines to prevent SARS-CoV-2 infections will likely lead to decreased intensity of infection within countries, the coronavirus appears poised to become part of the typical set of viruses that cause disease such as influenza, respiratory syncytial virus (RSV), parainfluenza and rhinovirus. The intense focus and research brought about by the pandemic may have some collateral benefits.

We are learning how environments do contribute to the spread of such respiratory infections. I suspect we will have a milder and later influenza and RSV season than usual in the United States, something already seen in the Southern Hemisphere in countries such as Australia during their current winter. Taking greater care to wear masks, socially distance by six feet or more, avoiding crowded indoor environments and disinfecting high touch surfaces will help keep you healthy, from not only the coronaviruses, but other viruses as well.

Paul G. Auwaerter, MD, MBA

COVID-19 Convalescent Plasma Trials

Fisher Center staff lent a hand to COVID-19 research teams investigating convalescent plasma. ***Paul Auwaerter, MD, MBA****, provided consultation regarding study design, while Fisher Center Program Manager,* **Yvonne Higgins, MAS, MS***, assisted with the development of protocols, consents, recruitment plans and materials, and regulatory applications, helping to launch the COVID Plasma Trials.*

Convalescent plasma trial sites are in multiple locations across the United States.

For more information or to enroll as a study volunteer, please visit the website, CovidPlasmaTrial.org

COVID-19 RESEARCH PROJECTS

Immune Response Research

Yuka Manabe, MD

Paul Blair, MD

In support of critical COVID-19 research, **Sherrilyn Fisher** generously provided funding for a groundbreaking observational study, the Outpatient COVID-19 Cohort: Characterization of Immune Protection and Outcomes, led by **Yuka Manabe, MD and Paul Blair, MD**. The goal is to understand immune responses in patients who have a milder infection, not requiring hospitalization. Through intensive clinical visits specimen collection, these SARS-CoV-2 positive participants will report symptoms and collect samples from blood, nose and mouth swabs for one year.

This research will help determine the duration of positive antibodies and other immune responses as well as monitor for any evidence of reinfection. The reinfection question is one that worries many patients and medical personnel alike, but can only be answered through careful investigations over time.

Manabe and Blair are using oral fluids to detect both the virus and the antibody responses, which is attractive since it is non-invasive and a natural approach for self-collection. The team is investigating various platforms to detect both viral antigens (indicating acute infection) as well as the immune response in a single sample type, which will be useful as a larger proportion of the US population is exposed over time. With the support of the Fisher Center, the team plans to learn from this cohort to improve our understanding of the long-term course of the disease and to find non-invasive tests to determine immune protection.

COVID-19 RESEARCH PROJECTS

Plasma Donation

Evan Bloch, MD

Evan Bloch, MD, a former grant awardee of the Fisher Center Discovery Program, is leading a trial that qualifies persons who have recovered from COVID-19 as donors for the convalescent plasma trials. Blood samples are collected from volunteer participants. If SARS-CoV-2 antibodies are sufficiently elevated to a predetermined level, the participant is invited to donate their plasma, which is then transfused into persons as a prevention or treatment for COVID-19. "A donor qualification study has enabled the recruitment of convalescent individuals to support a series of clinical trials. Those trials are critical both to advance convalescent plasma as a therapy for COVID-19 as well as to further our understanding of SARS-CoV-2 testing and the immunopathogenesis of COVID-19," states Dr. Bloch.

COVID-19 RESEARCH PROJECTS

Convalescent Plasma Research

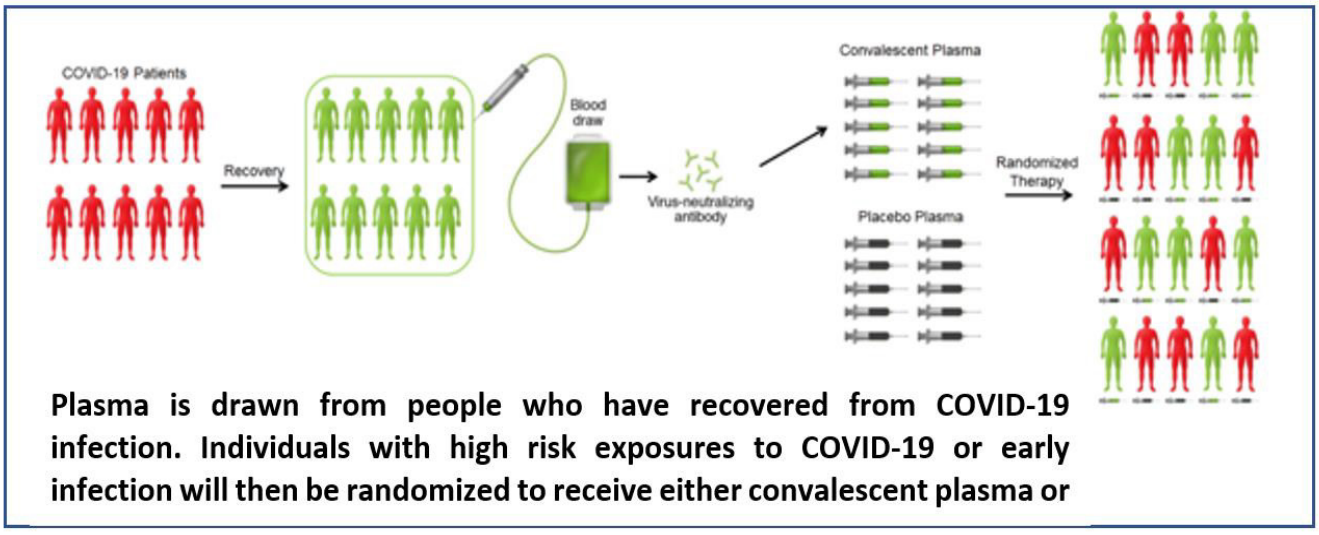
Fisher Center staff also assisted research teams examining the use of COVID-19 convalescent plasma for the prevention or treatment of COVID-19 illness. Plasma, which is similar to serum, is the clear yellow component of blood that contains antibodies. Antibodies are proteins the body produces in response to infections that may prevent or help clear pathogens.

Currently, there is no fully FDA-approved treatment or vaccine for COVID-19. However, some important studies have suggested clear roles for severely ill patients with the antiviral drug remdesivir and the anti-inflammatory corticosteroid, dexamethasone.

At the time of this writing, the Food and Drug Administration (FDA) is considering whether COVID-19 convalescent plasma taken from patients who have recuperated may be given an emergency use authorization (EUA) for treatment. While the FDA has approved the use of convalescent plasma for COVID-19 as an investigational agent, the agency also authorized the **National COVID-19 Convalescent Plasma Project,** https://ccpp19.org/, wherein multiple studies are in progress. Johns Hopkins physicians are leading three of the national, multi-center convalescent plasma studies.

Convalescent Plasma: *Using standard blood bank technique, the liquid part of blood, plasma, is drawn from adults who have recovered from COVID-19. The plasma is transfused into adults who have been exposed to or have early COVID-19 illness, providing SARS-CoV-2 (the virus that causes COVID-19) antibodies to the recipient. Figure reprinted with permission of the Journal of Clinical Investigation and the authors.*

FIGURE 1:



Plasma is drawn from people who have recovered from COVID-19 infection. Individuals with high risk exposures to COVID-19 or early infection will then be randomized to receive either convalescent plasma or

COVID-19 RESEARCH PROJECTS

A team led by **Shmuel Shoham, MD** will test whether a transfusion of plasma containing antibodies from persons who have recovered from COVID-19 can prevent others from getting COVID-19 after exposure. The study will target for recruitment adult household contacts of COVID-19 positive persons. It is hoped the transfusion of SARS-CoV-2 antibody-laden plasma will prevent or lessen the severity of subsequent COVID-19 illness. Per Dr. Shoham, "We are trying to find out if plasma, which is available now, can prevent infections, keep people out of the hospital and stop transmission. Volunteers have stepped up to become study participants. We need many more here and across the country to make sure we get the science right."

Prevention

Shmuel Shoham, MD

COVID-19 RESEARCH PROJECTS

David Sullivan, MD, a current Fisher Center grant awardee investigating the parasite Babesia, leads a team to test whether a transfusion of plasma containing antibodies from persons who have recovered from COVID-19 is an effective treatment for early COVID-19 illness not yet severe enough to require hospitalization. Some small studies suggest that giving antibodies as treatment is most effective in the early stages of illness. Therefore, recruitment will concentrate on adults within eight days of symptom onset. "Presently, there are no outpatient COVID-19 therapies. Immediate transfer of immunity to SARS-CoV-2 delivered to outpatients by convalescent plasma is the foundational step in returning Americans back to work and protecting the military by eliminating the fear of hospitalization," explains Dr. Sullivan.

Both are randomized, double-blind trials, which are considered the scientific gold standard upon which the FDA decides whether to approve a given therapy. These trials are critical to understanding whether convalescent plasma should be routinely used to treat COVID-19 illness. The research teams led by Drs. Shoham and Sullivan recently received $35 million in funding from the **U.S. Department of Defense (DOD)** Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND) to test the effectiveness of convalescent plasma for outpatient treatment. Trials sites will include the Navajo Nation, military installations, and civilian medical centers. The full press release may be found here.

Treatment

David Sullivan, MD

FORMER FISHER CENTER FELLOW AUTHORS CANDIDA ARTICLE

Takaaki Kobayashi, MD, a former Fisher Center research fellow, has a manuscript accepted for publication in Open Forum Infectious Diseases, on behalf of the Infectious Diseases Society of America. As the lead author of Impact of Infectious Disease Consultation in Patients with Candidemia: A Retrospective study, Systematic Literature Review and Meta-analysis, Dr. Kobayashi and colleagues found Infectious Diseases consultation (IDC) was associated with a 59% reduction in mortality in patients with candidemia (a yeast bloodstream infection). This is the first systematic literature review and meta-analysis to evaluate the association between IDC and candidemia mortality. IDC was associated with significantly lower mortality and should be considered in all patients with candidemia. *Dr. Kobayashi is completing his ID fellowship and MPH at the University of Iowa Hospitals and Clinics in Iowa City. He and his wife, Nao, are the parents of two children.*

BreakOut

The Fisher Center Discovery Program (FCDP) has awarded grants to Johns Hopkins faculty to facilitate clinical or translational research related to environmental infectious diseases. Since 2013, the FCDP has distributed more than $1.4 million to investigators. FCDP grants are usually used as pilot grants, providing proof-of-concept and generating data used to apply for larger grants. Researchers used FCDP grants to obtain additional grants totaling $41 million, a substantial return on investment from the investment in their innovative, pilot research.

The Fisher Center congratulates the following research teams on the 2020 awards.

Keira A Cohen, MD

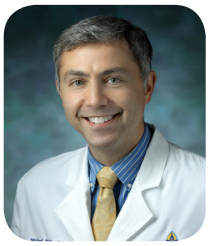
Early bactericidal activity of standard drugs used to treat Mycobacterium avium complex: a pilot study

Nontuberculous mycobacteria (NTM) are environmental bacteria found in soil, water and in biofilms. These bacteria can cause human disease, most frequently in the form of a chronic lung infection similar to pulmonary tuberculosis (TB). The number of people in the US with NTM lung disease has been increasing at a rapid rate and outnumber the patients infected with TB. This trial design may provide a reliable method to determine which drugs or combinations are most active at killing these bacteria in humans.

Gyanu Lamichhane, PhD

Developing antibiotic regimen to treat M. abscessus disease based on whole genome mining

Mycobacteriodes abscessus (Mab) complex is a rapid-growing nontuberculous mycobacterium (NTM) that is ubiquitous in the environment. It causes opportunistic infections in humans, especially in the setting of cystic fibrosis, bronchiectasis and COPD. Mab is an emerging pathogen with a rising US incidence that far exceeds that of TB. The cure rate for Mab lung disease is only 30-50%. A computer-based algorithm will analyze the whole genome sequence and recommend the most potent oral antibiotic regimen that the patient can take at home.



Michael Melia, MD
Saman Nematollahi, MD

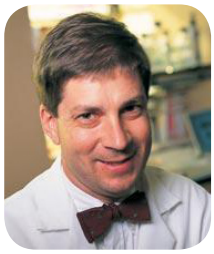
Beta-d-glucan and galactomannan curriculum

Environmentally-based fungi such as Candida, cryptococcus and histoplasmosis may be unfamiliar names but are ubiquitous, leading to 1.5 million deaths annually. Physicians sometimes inappropriately order tests for fungal infections. This project will create a fungal diagnostics educational curriculum to improve resident knowledge of environmentally-based fungi and appropriate test ordering practices. In turn, reductions may ensue regarding unnecessary antifungal use and unneeded imaging or testing. The length of hospital stay stays also are anticipated to be less after the intervention

Heba Mostafa, MD, PhD

Genomic Surveillance of Enteroviruses Polymorphic Events that Correlate with Disease Severity and Neuro-virulence

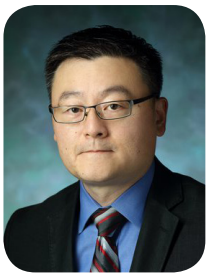
Enteroviruses are environmental pathogens that cause a wide spectrum of disease ranging from respiratory, cardiac, gastrointestinal to neurological. Non-polio enteroviruses, with the capability of causing polio-like disease, have emerged and periodically cause outbreaks of acute flaccid paralysis in children more than adults. This research will look closely at genomic changes that associate with severe disease or paralysis. Such research will be instrumental in developing strategies for disease prevention, molecular diagnosis, and management.



David Sullivan, MD

Murine Babesia Combination Chemotherapy

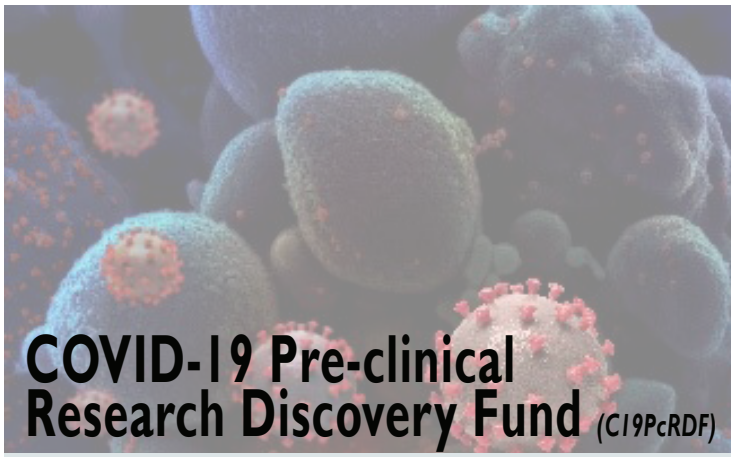
Babesia is an emerging tick-borne, a single-celled parasite that lives inside red blood cells. It can be lethal in persons who lack a spleen or have compromised immunity. The recommended drugs used to treat this infection are based on limited studies. There may be improvements gained with more intensive studies of new drugs and in different mixes. This study will test combination drugs in an immune-compromised Babesia mouse model. The expected outcome is curative combination therapy superior to current drugs used for Babesia. The preclinical animal work can easily be translated directly to the clinic after human efficacy trials.



Sean Zhang, MD, PhD
Wen Hsieh, PhD

POC.auris: A 15-minute point-of-care detection of multi-drug resistant Candida auris

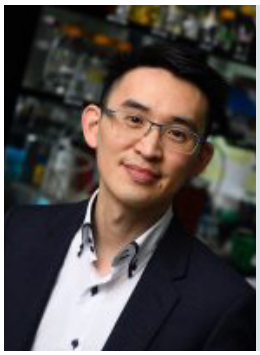
Candida auris (C. auris), a newly discovered "superbug," can cause deadly infections. It is challenging to identify and treat. C. auris can cause life-threatening bloodstream infections in the elderly, newborns, and chronically ill patients, killing more than 60% of infected patients. According to the CDC, more than 90% of C. auris infections are resistant to commonly used antifungal drugs, and it can stay alive on the surface of medical devices and furniture for up to 14 days. Patients can carry the bug without any clinical symptoms, becoming new sources for spreading the disease. This study will develop a point-of-care device to detect C. auris within 15 minutes in hospitals and long-term care facilities. This would trigger the rapid initiation of treatment for patients and effectively control and prevent C. auris from spreading in healthcare facilities.



COVID-19 Pre-clinical Research Discovery Fund *(C19PcRDF)*

Paul Auwaerter, MD, Fisher Center Director and Clinical Director, Division of Infectious Diseases and **Mark Sulkowski, MD**, Chief, Division of Infectious Diseases Johns Hopkins Bayview, are the Therapeutics team leaders for the Johns Hopkins University COVID-19 Research Response Program.

In response to the COVID-19 pandemic, Johns Hopkins University funded the COVID-19 Pre-clinical Research Discovery Fund (C19PcRDF), which awarded four grants of $50,000 each. These awards are meant to stimulate innovative research that may lead to further translational or clinical efforts. Under the leadership of the COVID Therapeutics Team, applications were received from 46 investigators across the University, resulting in a highly competitive review. The following four proposals received funding.



ANTHONY K. L. LEUNG, PH.D.

Anthony K. L. Leung, Ph.D. of the Department of Biochemistry & Molecular Biology in the Bloomberg School of Public Health, will build on his prior award from the Fisher Center Discovery Program in which he studied macrodomain. Using a team developed a biochemical-screening assay for identifying potential chemical lead compounds, the team proposes to develop a macrodomain inhibitor for the treatment of COVID-19.

SUSAN MICHAELIS, PH.D.

Susan Michaelis, Ph.D. of the Department of Cell Biology in the School of Medicine, will focus on the integral membrane zinc metalloprotease ZMPSTE24. The hypothesis is that ZMPSTE24 will prevent cell entry of SARS-CoV-2, the virus that causes COVID-19. Findings could reveal therapeutic cellular targets, providing a potent defense against SARS-CoV-2 and thus prevent COVID-19 or diminish its severity.

LINDA RESAR, M.D.

Linda Resar, M.D. in the Department of Medicine, Division of Hematology in the School of Medicine, will focus on the rapidly progressive, atypical pneumonia associated with COVID-19. By studying HMGA1 epigenetic regulator as a key hub to foster uncontrolled inflammation, the team hopes to describe the inflammation further and to begin testing drugs to disrupt these aberrant inflammatory pathways. These studies could reveal novel therapeutic opportunities to prevent excessive inflammation and lethal pneumonia in COVID-19.

MAXIM ROSARIO, M.D., PH.D.

Maxim Rosario, M.D., Ph.D. in the Department of Pathology in the School of Medicine, proposes a T cell vaccine that targets the most conserved regions of the SARS-CoV-2 virus. This type of vaccine may stand-alone or work in conjunction with a B cell vaccine. The proposed vaccine may be able to withstand viral changes, be applicable to other future SARS viruses, and may synergize with a vaccine designed to generate antibody responses.

FUNDING OUR FUTURE

Thank you to those who contributed so generously to support environmental infectious disease research and education in the past six months. Such gifts help facilitate innovative research, especially targeted to early-career investigators. In particular, we would like to acknowledge

Mrs. Martha Bartlett
Mr. Frederic M. Bryant III
Mr. Michael Butler
Mrs. Sherrilyn Fisher
Dr. Morton Goldberg
Mr. Len Hartwig
Mr. Louis Hogan
Ms. Ann Jacobson
Ms. Andrea Laporte
Mr. Jeff Legum
Mr. Park Miller
Mr. Thomas Owsley
Mr. George Sherman
Scott L. Sherman and Julie Rothman
Ms. Ann B. TenHoopen

IF YOU ARE INTERESTED IN SUPPORTING OUR WORK, PLEASE CONTACT DONNA BOLIN AT 410-550-9893 OR DBOLIN1@JHMI.EDU

+ RECENT PRESENTATIONS

Infectious Diseases in 2020: 5 Areas of Concern. Paul G. Auwaerter, MD. Medscape Infectious Diseases. https://www.medscape.com/viewarticle/923388. January 14, 2020

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FisherFocus
Johns Hopkins University, School of Medicine
Department of Medicine, Division of Infectious Diseases
The Fisher Center for Environmental Infectious Diseases
Pre-Clinical Teaching Building | 725 N. Wolfe Street, Suite 211
Baltimore, MD 21205
fishercenter@jhmi.edu | 443-287-4840

Managing Editor: Yvonne Higgins | yhiggins@jhmi.edu
Design: Stephanie Cohen | scohen58@jhmi.edu