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Center for Biologics Evaluation and Research (CBER)

125th Blood Products Advisory Committee (BPAC) Meeting

Zoom Video Conference

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This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

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Chair

Zbigniew "Ziggy" Szczepiorkowski, M.D., PhD., F.C.A.P.	Professor of Pathology and Laboratory Medicine, Professor of Medicine, Dartmouth's Geisel School of Medicine, Medical Director, Transfusion Medicine Service, Director, Cell Labeling Laboratory, Dartmouth-Hitchcock Medical Center	Lebanon, NH

Members

Sanjay P. Ahuja, M.D., M.Sc., M.B.A.	Professor, Case Western Reserve University, Dominic Piunno Endowed Chair in Hemophilia & Bleeding Disorders, Distinguished Physician, University Hospitals Clinical Director, Pediatric Hematology/Oncology, Director, Rainbow Hemostasis & Thrombosis Center, Rainbow Babies & Children's Hospital	Cleveland, OH
Mark Ballow, M.D.	Professor, Division of Allergy & Immunology, Department of Pediatrics, University of South Florida, Morsani College of Medicine at Johns Hopkins All Children's Hospital	St Petersburg, FL
Sridhar Basavaraju, M.D., FACEP (CDR-USPHS)	Director, Office of Blood, Organ, & Other Tissue Safety, Division of Healthcare Quality Promotion, National Center for Emerging & Zoonotic Infectious Diseases, Centers for Disease Control & Prevention	Atlanta, GA
Evan Bloch, M.D., M.S.	Associate Director, Transfusion Medicine, Johns Hopkins University School of Medicine, Department of Pathology	Baltimore, MD
Melissa A. Cumming, M.S., CIC	Senior Epidemiologist and HAI/AR Program Manager, Healthcare-Associated Infections and Antibiotic Resistance Program, Bureau of Infectious Diseases and Laboratory Sciences, Massachusetts Department of Public Health	Jamacia Plain, MA
Brenda J. Grossman M.D., MPH	Professor, Department of Pathology & Immunology, Division of Laboratory and Genomic Medicine, Washington University School of Medicine	St. Louis, MO
Frank Maldarelli, M.D., Ph.D.	Senior Investigator, Head, Clinical Retrovirology Section, National Cancer Institute, National Institutes of Health	Fort Detrick, MD
Traci Mondoro, Ph.D.	Associate Director, Division of Blood Diseases and Resources, Acting Chief, Blood Epidemiology and Clinical Therapeutics Branch, Program Director, NHLBI Cure Sickle	Bethesda, MD

	Cell Initiative, Chief, Translational Blood Sciences and Resource Branch, National Heart, Lung, and Blood Institute National Institutes of Health	
Richard Scanlan, M.D.	Professor, Vice Chair of Laboratory Medicine Transfusion Service, Medical Director Oregon Health & Science University	Portland, OR
Abdus Wahed, Ph.D.	Professor and Associate Chair, Department of Biostatistics & Computational Biology, University of Rochester	Rochester, NY

Guest Speakers

Susan A. Galel, M.D.	Global Senior Director of Medical Affairs, Donor Screening, Roche Diagnostics Solution	Pleasanton, CA
Seymour Williams, MD, MPH	Team Lead for the Domestic Response Team, Domestic Malaria Team, Malaria Branch, Division of Parasitic Diseases and Malaria, National Center for Emerging an Zoonotic Infectious Diseases, Centers for Disease Control and Prevention	Atlanta, GA

Consumer Representative

Susan Lattimore, R.N., M.P.H.	Assistant Professor Pediatrics, Associate Director, The Hemostasis & Thrombosis Center at Oregon Health & Science University	Portland, OR

Industry Representative

Suchitra Pandey, M.D.	Chief Medical Officer, Stanford Blood Center	Palo Alto, CA

CBER/FDA Participants

Peter Marks, M.D., Ph.D.	Director, Center for Biologics Evaluation and Research, Food and Drug Administration	Silver Spring, MD
Anne Eder, M.D., Ph.D.	Director, Office of Blood Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration	Silver Spring, MD
Sanjai Kumar, Ph.D.	Chief, Laboratory of Emerging Pathogens, Division of Emerging and Transfusion Transmitted Diseases, Office of Blood Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration	Silver Spring, MD

Jennifer Scharpf, M.P.H.	Associate Director for Policy, Office of Blood Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration	Silver Spring, MD

Designated Federal Officer

Christina Vert, M.S.	Division of Scientific Advisors & Consultants, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD

Director

Prabhakara Atreya, Ph.D.	Division of Scientific Advisors & Consultants, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD

Committee Management Specialist

Tonica Burke, B.S.	Division of Scientific Advisors & Consultants, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD

Committee Management Officer

LaShawn Marks	Division of Scientific Advisors & Consultants, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD

Open Public Hearing Speakers

Jeffrey Linnen, Ph.D.	Grifols Diagnostic Solutions Inc.	San Diego, CA
Jed Gorlin, M.D., M.B.A.,	America's Blood Centers	Washington, D.C.
Ralph Vassallo, M.D.	The Association for the Advancement of Blood and Biotherapies	Scottsdale, AZ
Cole Williams	Pride and Plasma	

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Opening Remarks

Dr. Szczepiorkowski: Good morning, everyone. It is my pleasure to welcome everyone to the 125th meeting of the Blood Products Advisory Committee. I would like to welcome all who will participate in today's meeting, the BPAC members, presenters, speakers from the public, and anyone from the public who may be viewing this remotely.

My name is Zbigniew Szczepiorkowski, and I have the privilege to serve as the chair of this committee. As my last name is rather complex, I prefer to be called Ziggy, but understand that for some it would be easier to call me Dr. Z. I'm a professor of pathology and laboratory medicine, and professor of medicine at Dartmouth-Geisel School of Medicine in Hanover, New Hampshire.

As we continue our meetings over the virtual platform, I would just like to remind the committee members and participants to use the raise your hand feature on the system if you have a question or comment to make, so I can call you to speak. Today we'll be reviewing information on transfusion-transmitted malaria and a newly approved test for malaria. And although we are not asked to vote, we'll work during open deliberations on providing CBER with our thoughts and responses to the proposed role of the test in the future efforts to mitigate the risk of transfusion-transmitted malaria. It might be also helpful to remind the committee members, but also the audience, the role of Blood Products Advisory Committee, which is to provide independent expert advice to the FDA on broad scientific topics or on certain products, to help the agency make sound decisions based on available science. Advisory committees make non-binding recommendations to the FDA, which generally follows the recommendations, but it's not legally bound to do so.

As we do not vote today, I hope that our deliberations will help CBER to continue to work on mitigation strategies for transfusion-transmitted malaria. I'd like to ask now to advance to the next slide.

Before we start our deliberations today, I would like to inform you that one of our BPAC most distinguished members, Dr. Ada Adimora, passed away on January first at the age of 67. Dr. Adimora was Sarah Graham Cannon Distinguished Professor of Medicine, and Professor of Epidemiology at the University of North Carolina at Chapel Hill. She was raised in Manhattan by both her parents, who worked in the field of medicine. She received her undergraduate degree from Cornell University, followed by the medical degree from the Yale University School of Medicine. She was an intern and resident in Boston City Hospital and an infectious disease fellow in Montefiore Medical Center, Albert Einstein College of Medicine in New York City. She ultimately settled in Chapel Hill, North Carolina. I would like to cite the University of North Carolina tribute published soon after her passing. A true pioneer, Dr. Adimora made history as the first African American woman in her department to achieve tenure. With over 35 years of clinical experience, she dedicated her career to treating patients with HIV disease and investigating the epidemiology of HIV and STIs. Her groundbreaking work shed light on the epidemiology of heterosexual HIV transmission among African Americans, emphasizing the role of sexual network patterns and addressing the impact on macroeconomic and social forces on racial disparities in the U.S. HIV epidemic. In 2019,

Dr. Adimora was elected National Academy of Medicine, a testament to her exceptional intellect and commitment to advancing healthcare. Her leadership extended to numerous state and national positions, including roles in the NCAA Department of Health Communicable Disease Control Section, NIH Prevention Trials Network, HIV Medicine Association, and the

U.S. Department of Health and Human Services Anti-Retroviral Treatment Guidelines Panel. She also served on prestigious advisory councils, such as the Presidential Advisory Council on HIV and AIDS, and the National Institutes of Allergy and Infectious Diseases Advisory Council. Notably, Dr. Adimora's tireless efforts did not stop with her research and leadership roles. Despite her demanding schedule, she generously gave her time to mentor and advise counseling students, trainees, and junior faculty. This commitment to nurturing the next generation of healthcare professionals reflects her deep passion for education and mentorship. Dr. Adimora, a brilliant and compassionate physician-scientist, left an indelible mark on her department and the broader medical community. End of the citation. We, the members of the Blood Products Advisory Committee and the FDA at large, were privileged to work with her and benefit tremendously from our interactions with her, both professionally and personally. I would like to ask for a minute of silent reflection on Dr. Adimora's passing. Thank you very much.

Please advance to the next slide. At this point, I would like to hand the meeting over to Christina Vert for administrative announcements, the roll call, and conflict of interest statements.

Administrative Announcements and Roll Call

Ms. Vert: Thank you, Dr. Ziggy. Good morning, everyone. This is Christina Vert, and it is my great honor to serve as a designated federal officer, DFO, for today's 125th Blood Products Advisory Committee meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, CBER, and the committee, I am happy to welcome everyone for today's virtual meeting. Today, the committee will meet in open session to discuss strategies to reduce the risk of transfusion-transmitted malaria, by testing blood donations from donors at risk of malaria exposure. Today's meeting and the topic were announced in the federal register notice that was published on March 11, 2024. Next slide. At this time, I would like to introduce and

acknowledge outstanding leadership, my division director, Dr. Prabhakara Atreya, who will be my backup DFO, and the excellent work of my team, whose contributions have been critical for preparing for today's meeting. My team includes Ms. Tonica Burke, Ms. LaShawn Marks, and Ms. Joanne Lipkind. I would also like to express our sincere appreciation to Mr. Gideon McMullan, Mr. Devante Stephenson, and Mr. Derek Bonner for facilitating the meeting today. The transcriptionist for today's meeting is Catherine Diaz. Also, our sincere gratitude goes to many CBER and FDA staff working very hard behind the scenes trying to ensure that today's virtual meeting will be a successful one. Next slide. Please direct any press media questions for today's meeting to FDA's Office of Media Affairs at fdaoma@fda.hhs.gov. Next slide. I would now like to acknowledge CBER leadership, including Dr. Marks and Dr. Eder. Dr. Eder will be giving the introduction and the charge to the committee this morning, and Dr. Marks may be joining the meeting later today. Next slide. We will begin today's meeting by taking a formal roll call for the committee members. When it is your turn, please turn on your video camera, unmute your phone, and then state your first and last name, organization, and expertise. When finished, you can turn your camera off so we can proceed to the next person. Please see the member roster slides in which we will begin with the chair, Dr. Ziggy. Dr. Ziggy, can we start, please?

Dr. Szczepiorkowski: Sure. Ziggy Szczepiorkowski. I'm coming from Dartmouth Hitchcock Medical Center in Lebanon, New Hampshire. My expertise is in transfusion medicine and cellular therapy.

Ms. Vert: Thank you. Dr. Ahuja.

Dr. Ahuja: Morning. Hi, I'm Sanjay Ahuja. I'm a pediatric hematologist at Rainbow Babies and Children's Hospital, which is part of Case Western Reserve University in Cleveland, Ohio. And

my expertise is in bleeding and clotting disorders in children, as well as in general hematology and pediatrics. Thank you.

Ms. Vert: Thank you. Dr. Ballow.

Dr. Ballow: Good morning. Mark Ballow, professor of pediatrics at Morsani College of Medicine, University of South Florida Department of Pediatrics, Allergy Immunology Division. My area of interest is clinical immunology, particularly immunoglobulin replacement therapy in patients with immune deficiency.

Ms. Vert: Thank you. Dr. Basavaraju.

Dr. Basavaraju: Hi, I'm Sridhar Basavaraju. I'm the director of the CDC Office of Blood, Organ, and Other Tissue Safety.

Ms. Vert: Thank you. Next slide. Dr. Bloch.

Dr. Bloch: Hi, I'm Evan Bloch. I'm an associate professor at Johns Hopkins University School of Medicine, and my area of interest is transfusion medicine and infectious diseases.

Ms. Vert: Thank you. Ms. Cumming.

Ms. Cumming: Good morning. My name is Melissa Cumming. I'm a senior epidemiologist and manager of the Healthcare Associated Infections and Antimicrobial Resistance Program at the Massachusetts Department of Public Health. And my area of expertise is epidemiology and hemovigilance.

Ms. Vert: Thank you. Dr. Grossman.

Dr. Grossman: I'm Brenda Grossman. I'm a voluntary professor of pathology, immunology, and hematology at Washington University in St. Louis. My area of expertise is transfusion medicine.

Ms. Vert: Thank you. Next slide. Ms. Lattimore?

Ms. Lattimore: Good morning, I'm Susan Lattimore. I'm serving as the consumer representative on this committee.

Ms. Vert: Thank you. Dr. Maldarelli.

Dr. Maldarelli: Yes, good morning. My name is Frank Maldarelli. It's not starting my video, but I don't blame it for that. I'm an investigator in the National Cancer Institute intramural program and the HIV Dynamics and Replication Program. My expertise is in infectious disease and the transmission of infections through blood. I'm delighted to be here today, and I feel the need to acknowledge the people who have the land that we work on now, the Piscataway and the Anacostia Indians.

Ms. Vert: Thank you. Dr. Pandey.

Dr. Pandey: Hi, good morning, everyone. My name is Suchi Pandey. I'm at Stanford Blood Center and Stanford University. My expertise is transfusion medicine with a primary focus in the blood center, and I'm serving as industry rep.

Ms. Vert: Thank you. Next slide. Dr. Mondoro.

Dr. Mondoro: Good morning. My name is Traci Mondoro. I'm in the blood division at the National Heart, Lung, and Blood Institute on the extramural side. I'm a platelet biologist by training, and my expertise is in the management of basic translational and clinical research in thrombosis, hemostasis, transfusion medicine, and cell therapy.

Ms. Vert: Thank you. Dr. Scanlan.

Dr. Scanlan: Yeah, my name is Richard Scanlan. I'm a professor of pathology at Oregon Health Sciences University in Portland, Oregon, and my areas of expertise are in transfusion medicine and laboratory accreditation.

Ms. Vert: Thank you. Dr. Wahed.

Dr. Wahed: Hi, my name is Abdus Wahed. I am a professor and associate chair of the Department of Biostatistics and Computational Biology at the University of Rochester. My expertise is in clinical trials, adaptive clinical trial designs, smart trials, and also longitudinal study of any biomedical nature. Thank you.

Ms. Vert: Great. Thanks, everyone. We have a total of 13 members attending the meeting today, 12 voting and one non-voting member. And now I will move on to, oh I need to make some other comments. Okay. Before I begin with reading the conflict-of-interest statement, I would just like to briefly mention a few housekeeping items related to today's virtual meeting format. For members, speakers, FDA staff, and anyone else joining us in the Zoom room, please keep yourself on mute unless you are speaking to minimize feedback. If you have raised your hand and are called upon to speak by the chair, Dr. Ziggy, please turn on your camera, unmute, state your name, speak slowly and clearly so that your comments are accurately recorded for transcription and captioning. Thank you.

Conflict of Interest Statement

Now I will proceed with reading the FDA conflict of interest disclosure statement for the public record. The Food and Drug Administration, FDA, is convening virtually May 9th, 2024, for the 125th meeting of the Blood Products Advisory Committee, BPAC, under the authority of the Federal Advisory Committee Act, FACA of 1972. Dr. Zbigniew Ziggy Szczepiorkowski is serving as the chair for today's meeting. The BPAC committee will meet in open session to discuss strategies to reduce the risk of transfusion-transmitted malaria by testing blood donations from donors at risk of malaria exposure. The topic is determined to be both a particular matter involving a specific party, PMISP, and a particular matter of general applicability, PMGA. The particular matter involving a specific party will include the discussion of a licensed product,

cobas malaria test, manufactured by Roche Molecular Systems and Company, approved to test for malaria in donated blood, while the particular matter of general applicability involves all potential future products that may be used for testing for malaria, in blood, that will all be affected equally by any recommendations made by the committee. With the exception of the industry representative member, all standing and temporary voting members of BPAC are appointed as special government employees or regular government employees brought in from other agencies, and are subject to federal conflict of interest laws and regulations. The following information on the status of this committee's compliance with federal ethics and conflict of interest laws include, but are not limited to, 18 U.S. Code Section 208, which is being provided to participants in today's meeting and to the public. Related to the discussions at this meeting, all members and regular government employees, and special government consultants of this committee, have been screened for potential conflicts of interest of their own, as well as those imputed to them, including those of their spouse or minor children, and for the purposes of 18 U.S. Code Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, credits, teaching, speaking, writing patents and royalties, and primary employment. These may include interests that are current or under negotiation. The FDA has determined that all members of this advisory committee, both regular and temporary members, are in compliance with federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts of interest when it is determined that the agency's need for a special government employee's services outweighs the potential for a conflict of interest created by the financial interest involved, or when the interest of a regular government employee is not so substantial as to be

deemed likely to affect the integrity of the services which the government may expect from the employee. Based on today's agenda and all financial interests reported by committee members and consultants, there has been one conflict of interest waiver issued under 18 U.S. Code Section 208 in connection with this meeting. Among the members, Dr. Evan Bloch, a special government employee, has been issued a waiver for his participation in today's meeting. The waiver was posted on the FDA website for public disclosure.

We have no special government employee or regular government employees' consultants serving as temporary voting members at this meeting. Ms. Susan Lattimore is serving as a consumer representative for this committee meeting. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee. Dr. Suchitra Pandey from Stanford Blood Center will serve as the industry representative for today's meeting. Industry representatives are not appointed as special government employees, and serve only as non-voting members of the committee. Industry representatives act on behalf of all related industry and bring general industry perspective to the committee. Industry representatives on this committee do not participate in any closed sessions if held, and do not have voting privileges. We have Dr. Seymour Williams from the U.S. Centers for Disease Control and Prevention, CDC, who was invited to serve as a federal speaker to make a presentation. Dr. Williams has been screened for his conflicts of interest and cleared to participate in today's meeting. Additionally, we have Dr. Susan Galel, from Roche Diagnostic Solutions, invited to serve as an industry guest speaker to participate in today's meeting. Disclosure of conflicts of interest for guests and federal speakers follows applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants, including open public hearing speakers, to advise the committee of any financial

relationships that they may have with any affected firms, its products, and, if known, its direct competitors.

We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFO and exclude themselves from such involvement, and their exclusion will be noted for the record. This concludes my reading of the conflicts of interest statement for the public record. At this time, I would like to hand over the meeting to Dr. Ziggy. Thank you.

Dr. Szczepiorkowski: Thank you very much, Christina, for reviewing the conflict of interest. I would like now to introduce Dr. Anne Eder, the Director of the Office of Blood Research and Review, and congratulate her on her recent promotion to this position. Dr. Eder, please turn your camera on and unmute, and the floor is yours.

Introduction: Dr. Anne Eder

Dr. Eder: Thank you and welcome. I'm Anne Eder, the Director of the Office of Blood Research and Review. I'm going to make a few introductory comments and provide an overview to frame the discussion for the committee today. You have the agenda, and I'll just comment that our Chair, Dr. Ziggy Szczepiorkowski, will introduce the speakers. We have four speakers today, who will make presentations. We'll take a brief break at about 10:40. We'll take a lunch break, and we'll reconvene in the afternoon for the open public hearing and the committee discussion, and adjourn around 3:10. FDA's responsibility is to determine the necessary measures to reduce the risk of relevant transfusion-transmitted infections, and today we're discussing transfusion-transmitted malaria. In the four presentations, you'll hear about malaria in the U.S. and public health considerations in the general population and among blood donors. You'll hear about

transfusion-transmitted malaria cases and the scientific basis of the current deferral policy and our proposed selective testing approaches. You'll hear about the first licensed blood donor screening test for malaria. And finally, you'll hear about the regulatory basis of our proposed recommendations to reduce the risk of transfusion-transmitted malaria by selective testing. As defined in the Code of Federal Regulations, or CFR, FDA determines that it is necessary for blood centers to perform testing for relevant transfusion-transmitted infections, when a licensed test is available, and testing will adequately and appropriately reduce the risk of transmitting malaria to blood transfusion recipients. Business case considerations or cost-benefit modeling does not factor into FDA policy.

However, I'll comment that in the issue summary, we do not recommend universal testing. That is, testing every donation every time, although blood centers may choose to do more. But rather we are recommending a selective testing strategy to reduce the risk of transfusion-transmitted malaria. And a selective strategy will also limit the testing burden and costs. Currently, today, for human immunodeficiency virus, HIV, for hepatitis B and hepatitis C, for example, universal screening for risk factors and testing of every donation with more than one test is performed. Selective testing strategies, in contrast, are used on other parasitic transfusion-transmitted infections. So these are the examples for Trypanosoma cruzi, or Chagas disease. For about two years, in 2007 and 2008, there was universal testing with a serologic test for T cruzi. This recommendation was changed to selective testing in the 2010 final guidance, because no new infections were found among previously tested negative donors. So, that one negative test qualifies an individual for all future donations, provided they meet the other eligibility requirements, without further testing for Chagas or questioning about a history of Chagas. Depending on the case definition, so what is the transfusion-transmitted infectious risk

to patients? Before testing, about seven cases of transfusion-transmitted Chagas were reported over about 20 years in the U.S. And after implementation of first universal and then selective testing, there have been no reported cases.

Another example is transfusion-transmitted babesiosis, caused by babesia species. Since 2019, FDA has recommended, in the babesia guidance, selective testing using a nucleic acid test for babesia in 14 highest-risk states, in the northeast, Minnesota, Wisconsin, and the District of Columbia, and in all other states, a screening question for a history of babesiosis. And just to comment, it's a selective testing strategy based on the state in which the blood is collected, and every donation in those 14 states and D.C. is tested. Before testing, there were more than about 20 cases each year reported to FDA, and after, now, about three full years of testing, there have been zero cases transmitted by NAT negative units, collected in the 14 states and D.C. that perform testing. However, there have been about two cases per year, in the states that do not perform testing, but only screen donors for a history of babesiosis. And just as an aside, we commented in the babesia guidance that we continue to monitor this risk and will modify and possibly expand these recommendations on evidence of continuing risk as it becomes available. For transfusion-transmitted malaria, this table summarizes the current recommendations that are based on donor screening and deferral.

And I'll just say on a high level, it's complicated. It does not prevent all cases of transfusion-transmitted malaria, and it results in significant donor and donation loss, as we'll discuss in the other talks today. Just suffice it to say that the current approach requires evaluating donors for travel, prior residency, and history of malaria. These terms, residency in a malaria-endemic country, malaria-endemic area, are all specifically defined in the guidance. So, it requires the health historian or phlebotomist to assess the date of departure from a country, the

amount of consecutive time spent in the U.S. spent in that country after departing, consultation of maps and review of travel itineraries for visits to malaria-endemic areas, and deferrals. And you'll notice in red, two different deferral durations, either three months, for residents of a non-endemic country, or three years for a resident of a malaria country. And the longer deferral reflects the possibility of partial immunity and chronic asymptomatic parasitemia, which we'll hear more about in the talk after the break. Deferral of U.S. travelers has been a point of concern raised by blood centers at prior BPACs and other public forums, because the risk is relatively low and it defers a significant number of donors. Even a short three-month deferral has been shown, consistently and repeatedly, to reduce the likelihood of future donations by that deferred individual. So you lose not only the donation on that day, but also future donations by that individual. And, as I said, it's complicated.

This is a flow chart that's in the current donor history questionnaire, or DHQ, when donors are asked the capture question, have you been out the U.S. or Canada in the last three years? And this is what's required to assess residency, travel, consecutive time spent in malaria-endemic countries, non-malaria countries. It's complicated, and it doesn't prevent all cases. We consider transfusion-transmitted malaria a risk to transfusion recipients that has not been adequately mitigated. There is about one transfusion-transmitted case reported to FDA about every two years. All cases have implicated donors who were prior residents of malaria-endemic countries and had chronic asymptomatic parasitemia. Almost all cases were plasmodium falciparum. And transfusion-transmitted malaria has a higher fatality rate in transfusion recipients compared to mosquito-borne transmission in the general population. Limitations of the current DHQ-based referrals reflect chronic prolonged asymptomatic parasitemia in prior residents of malaria-endemic countries, which comprise about 60% of transfusion-transmitted

malaria cases, or, staff errors in evaluating donor history of prior residents in malaria-endemic countries, the remaining 40%. In conclusion, we are recommending selective testing to adequately reduce the risk of transfusion-transmitted malaria and associated deaths and infectious complications among transfusion recipients.

Another risk to patients is the availability of blood. The yellow banner is a recruitment email from a large blood center that's been in use for about the last six months, and it reads, critical need for your O-positive blood type. Give blood now to ensure patients can get the treatment they need. As I said, the DHQ travel question defers a significant number of donors, estimated at 50,000 to 160,000 donors each year, or hundreds of donors a day. The range of this estimate reflects changes over time. So, of course, in 2020 and 2021, travel plummeted, so there were fewer deferrals. But travel has rapidly returned to pre-2019 levels, and we expect the estimate to be somewhere between 50,000 and 160,000. There have been urgent appeals for blood donation and reported shortages, usually locally, but especially of group O red cell units.

The Advisory Committee of Blood and Tissue Safety and Availability recommended, in partnership with blood centers, and HHS invested in, the Giving Equals Living public awareness campaign in 2021 to increase donor recruitment and increase diversity in the donor base. So, it only stands to reason that we would not consider an option for blood centers to continue to defer donors instead of testing, when a selective testing strategy would likely identify more infected donors, would make the blood supply safer, and would eliminate a significant number of history-based deferrals, and thereby improve safety and increase not only availability, but also the genetic blood group diversity of the blood supply.

So, CBER is recommending selective testing to reduce the risk of transfusion-transmitted malaria. We ask the committee to consider one-time testing, which could be part of a selective

testing strategy, to adequately reduce the risk of transfusion-transmitted malaria, and selective testing strategy of donors who report a risk of malaria, meaning former residence, prior malaria diagnosis, and travelers, based on responses on the DHQ. These approaches have both advantages and limitations. We are also asking the committee, in addition, to consider our recommendation for time-limited testing in regions with mosquito-borne malaria transmission.

So, the charge to the committee today is, please comment on FDA's proposed selective testing strategies for testing blood donations from donors at risk for malaria, using an FDA-licensed nucleic acid test, by selective testing based on the donor history questions for prior residence, history of malaria, and travelers, or, one-time testing of all donors, combined with selective testing based on the DHQ for travelers and history of malaria. And, in the later talk this morning, it'll be clear that we're not recommending a choice or an option, but rather, which of these selective testing strategies would be necessary to adequately mitigate the risk. We're also asking the committee to consider, and comment on, FDA's proposal that blood establishments should implement time-limited nucleic acid testing, NAT screening, of all donations collected in areas of the U.S. when a single case of local mosquito-borne malaria is reported by public health authorities. So, with that, I'll conclude my comments, thank the committee again, and turn this back over to the chair, Dr. Ziggy Szczepiorkowski, to introduce our first speaker. Thank you for your attention.

Dr. Szczepiorkowski: Thank you, Dr. Eder, for your excellent introductory presentation and presenting the committee with the charges. As per our prior agreement, we will not have a Q&A after your presentation, but we'll do it after the next one. So, I'd like to introduce our next speaker, Dr. Seymour Williams, who is a team lead to the Domestic Response Team, Domestic Malaria Team from Malaria Branch, Division of Parasitic Diseases and Malaria, National Center

for Emerging and Zoonotic Infectious Diseases at the United States CDC. Dr. Williams, please turn your camera on and unmute. The floor is yours.

Public Health and Clinical Malaria in the U.S.: Dr. Seymour Williams

Dr. Williams: Thank you, Dr. Ziggy. I'm Seymour Williams. Let me put up my slides. I'm Seymour Williams, as was mentioned, in the U.S. CDC. I was requested to present on the U.S. malaria public health data related to current epidemiology, recommendations for prevention, diagnosis and treatment, and a brief on the local outbreak last summer. The presentation will be in four sections. We'll talk about the biology, burden, and brief history, then a little bit on the U.S. malaria surveillance system so you understand the timing of the data. And describe some of the epidemiology findings.

I'll briefly describe the prevention, the diagnosis, the treatment, and the care of malaria cases in the U.S., and then end with the local malaria outbreak cases and cluster that occurred in 2023. There is time for additional questions after the presentation. So, let's start with a brief biology, and I know I have a lot of colleagues who already know this, but just to level set on the knowledge. There are five plasmodium species that can cause malaria in humans. Malaria is transmitted through the bite of an infective anopheles mosquito. The plasmodium parasites from the mosquito skin bite travel to the liver within hours, where they undergo initial replication. This asymptomatic phase of replication in the liver lasts an average of one to two weeks for most plasmodium species, but can take longer for some species. After an initial liver phase, the parasites are released into the blood, causing the blood stage disease. This is when people will first have malaria symptoms. Some parasites in the blood will develop into gametocytes, the form of the parasite which is able to infect mosquitoes and cause onward transmission. Please note, plasmodium vivax and plasmodium ovale are relapsing types of malaria, meaning that there

is a dormant liver stage of the parasite that is not cured during initial treatment and requires specific anti-relapse therapy.

Just a quick review again. Malaria is transmitted mostly through the bite of an infective female anopheles mosquito. Other very to extremely rare types of malaria transmission include congenitally, from mother to her unborn infant, before or during delivery. As we're discussing today, blood transfusions and organ transplant, very rarely shearing needles or syringes contaminated with malaria-infected blood. This map shown here illustrates the countries where in the world malaria is endemic, with over 249 million cases globally in 2022. Countries in red to yellow had one or more indigenous case in 2022, and they're mainly the countries in Africa, Southern and Southeastern Asia, and South and Central America. For reference, greater than 99% of malaria cases in the U.S. are among individuals who reported travel for malaria-endemic region within one year of presentation.

Most patients with malaria in the U.S. had traveled to visit friends and family members in these malaria-endemic areas. A brief history. Historically, malaria used to be endemic in the Southern U.S. with about 65,000 cases a year in approximately 12 U.S. states back in the 1940s. The U.S. government created an Office of Malaria Control in War Areas to eliminate malaria as a major public health problem. Using insecticides airily and indoor residual spraying, alongside active disease surveillance, especially around military bases in Georgia, malaria disease control was attained. By the early 1950s, malaria was no longer a formidable public health challenge, so much so that in 1970, the WHO certified the U.S. as malaria-free. And going forward since 1980, imported cases are the overwhelming majority, plus there have been sporadic local outbreaks that have since occurred. Let's switch now to the malaria surveillance system. Briefly, CDC collaborates with state and local health departments to investigate each case of malaria diagnosed

in the U.S. Shown here is the CDC Malaria Electronic Case Report form, not for you to read, but state health departments use it to conduct their malaria case investigation. The case investigations typically involve medical record review, a patient interview, and sometimes discussion with the healthcare provider. In addition to demographic data, the Case Report form collects information on the laboratory tests done, the travel history, the clinical information, and pertinent medical history, including prior malaria infections and blood transfusions. So how does the surveillance system work? CDC receives malaria reports from more than 55 jurisdictions. The complex process involves communication and coordination between the clinical, laboratory, and the public health systems and staff. Surveillance system begins when a person with malaria seeks care for their illness, a diagnostic malaria test is performed, and if it is positive, then an alert through the electronic laboratory reporting system is sent to the local health department. This is happening over hours to days. The local and state health department initiates a case investigation for every person who tests positive for malaria, by either the blood-sphere microscopy or PCR. This investigation takes place days to months. Reporting the case to CDC takes weeks to months, and for the traditional compilation and analysis, this actually can end up taking one to two years.

So let me mention that states provide another source of malaria data to CDC in a preliminary fashion. It's called the CDC WONDER system, which are counts of the notifiable diseases and are preliminary public sources for case counts, from the states and the jurisdictions, but not enough detail is provided. Another caveat. As you know, our communities have been severely impacted in recent years by public health responses, including COVID, Mpox, and also because of the local malaria outbreak. So this has caused a delay in us getting the publications out that are normally done. So what are the overall trends of malaria in the U.S. over the years?

This graph illustrates with case numbers on the vertical axis, and years on the horizontal axis, the total cases in red, which is increasing over time. And, because of time's sake, I won't break it down for you. There are sort of three components that feed into it. There is civilian, there is military, but it's driven mainly by the US civilian cases, traveling to areas where malaria is endemic. This graph is appended with the preliminary total cases for the years 2019 and 2020. That includes the estimates from the CDC WONDER table that I talked about earlier. So again, the upward trend over time, which got interrupted in 2020 due to disruptions of international travel with COVID, but you can see that we have a return to the reported numbers of cases that are heading back to 2023 levels. And the preliminary data is pointing that we're going to this, approximately 2,000 malaria cases per year, diagnosed and reported each year. And again, 99% were acquired after travel in a malaria endemic region. Most years, every state reports at least one person diagnosed with malaria.

This map from the last public surveillance summary highlights the 14 jurisdictions highlighted in darkest brown, where approximately 75% of all cases reside. Consistently, New York City is the highest burden jurisdictions, with the highest number of cases. This group of 14 high burden jurisdictions include Maryland, Texas, California, New Jersey, Pennsylvania, Florida, Virginia, Georgia, Illinois, New York State, Massachusetts, Ohio, and Minnesota. I will briefly just focus on the 2019-2020 preliminary surveillance data, because it brings out some of the principles that will be helpful for this discussion. In 2019, there were more than 2,050 cases, and the number of cases diagnosed in the U.S. in 2020 dropped to about 600 cases. In 2019, 86% of patients in the U.S. acquired malaria from Africa.

The next highest proportion of patients reported travel from Asia, with 4% of the cases. The region of acquisition was unknown for nearly 8% of the cases. Cases lost to follow-up, from

whom specific travel history details are unknown, may be classified as imported, with the country of acquisition indicated as unknown. In 2020, there was a statistically significant difference in the proportions for the regions of acquisition. However, although these were fewer cases, 78% were still acquired from Africa. More cases, 5%, were acquired from Asia, and there were more cases with an unknown region of acquisition. And we think some of this unknown is due to just, again, the burden on state health departments to do this full-on investigation in the midst of other priorities like Mpox and COVID.

Here's a histogram of cases by the month and year of illness onset. In 2019 we observed a typical pattern, with the highest number of cases diagnosed in summer months, and an additional peak in January after the December travel season. For 2019, 75% of all cases were P. falciparum, shown in blue, 10% were vivax or ovale, shown in purple, and 16% of cases were another species that were unknown. In 2020, the pattern of malaria cases got disrupted. While there was expected peak of cases in January, the cases really decreased in February and March.

The fewest cases were diagnosed in the U.S. in 2020 was in June, and the summer peak never occurred, as global travel was disrupted from COVID. In 2020, a lower proportion of cases were P. falciparum, and there was a higher proportion of the relapsing species P. vivax and ovale. In 2020, there were more infections with other or unknown species determination. Let me explain this graph among imported cases in 2018, which shows the number of days between arrival in the U.S. and illness onset. The duration categories range from less than zero, meaning illness onset began before return to the U.S., to more than a year. The proportion of cases in each interval is compared between cases reported with P. falciparum and P. vivax species. So let's start with P. falciparum. And what we see is that nearly all cases of P. falciparum, 99%, when you add the 15 plus 79 and 4.2, have an illness onset starting less than 90 days from arrival in the U.S.

However, for P. vivax species, only 43% of cases develop symptoms 90 days or more after their arrival in the U.S. The range of difference in illness onset for each plasmodium type is likely because some patients who live in endemic areas may have asymptomatic parasitemia, and the illness onset difference between species further highlights the effect of being infected with a relapsing species. So, it's important to consider malaria among persons who have not recently traveled.

A case of malaria with one or more of the following manifestations, logic symptoms, acute kidney injury, severe anemia, acute respiratory distress syndrome, or 5% or higher parasitemia, are classified as severe. Cases are also counted as severe if this person received treatment for severe malaria, was a fatal case for which malaria was the cause of death. In 2020, we observed an increase in the proportion of severe malaria compared to 2019. In addition, despite a 70% decrease in the number of cases from 2019 to 2020, the same number of people died from malaria. In 2019, the malaria fatality rate was 0.3% and in 2020, it was 1%. Quickly, let me briefly touch on malaria prevention and recommendations. As most of you may know, CDC has its chemoprophylaxis recommendations by country, and they are published in the Yellow Book and on our website.

The recommendations are reviewed every two years, before the publication of the next Yellow Book. However, there may be updates more frequently on the website if there is a new area of concern between publications. We review various sources of information, including the WHO reports. We also reach out to malaria control programs and CDC country offices. Our malaria branch is present in about 30 countries as part of the U.S. President's Malaria Initiative. We review our surveillance data to see where travelers are acquiring malaria, and we conduct a literature review. In general, we take a low-risk conservative approach for chemoprophylaxis. We

want to avoid malaria in travelers, as they are challenges with diagnosis and treatment here in the US. As we have been reminded this summer, we have competent vectors that are capable of transmitting malaria here in the U.S. So, malaria prevention consists of a combination of primarily chemoprophylaxis by country of travel, and mosquito avoidance measures, and I won't go through them for time's sake. So let's move on to diagnosis and treatment recommendations, and this I'll do rather quickly.

All patients suspected for malaria need to be tested as soon as possible. Microscopic examination of a thin and thick blood smear is the gold standard for malaria diagnosis. On the thick smear, the red blood cells are lysed, allowing visualization. As a result, even infections with a small number of parasites can be detected. On the thin smear, the RBCs are spread out to a single cell layer and are left intact, so it's easier to see parasite morphology, even though fewer cells are visible. This allows for determination of the species, the parasite density. Species may not be reported on the initial read, but a positive result is adequate to initiate treatment. There is one rapid diagnostic test, RDT, that is FDA-approved for use in the U.S. The use of an RDT can decrease the time to diagnosis and initiation of treatment, but it is not a replacement for the blood smear. A blood smear is still required to confirm the results, determine the species, and provide parasite density. There are other tests for malaria, but these are generally not recommended for malaria diagnosis in the clinical setting. PCR is the most sensitive, can be used to detect a very low level of parasitemia. It can also identify or confirm the species. However, it tends only to be performed in reference labs, and they have a long turnaround time. Serology tests detect antibodies to malaria parasites, depending on which target is selected. These tests can remain positive for several years after treatment, so it cannot distinguish between an acute or prior infection. It has a lengthy turnaround time. So there are several key considerations when treating

malaria in the U.S., that differ from treatment in endemic areas. U.S. residents are at high risk of progressing to severe malaria, even if their initial symptoms are mild, so hospitalization should always be considered when malaria is diagnosed. This is true for all plasmodium species, and particularly for P. falciparum infections. An individual's malaria treatment is dictated by several factors: disease severity, parasite species, expected drug-resistant patterns, depending on where they acquired their infection, drug availability at the treating facility, the age, and the pregnant status of the patient. These are the medications available in the US to treat uncomplicated malaria.

Again, for time's sake, won't go through each of them. Standard of care for the treatment of severe malaria in the U.S. is IV artesunate. It is the only IV anti-malarial medication available in the U.S., and it is effective against all species, and can be used in all ages, and during pregnancy, and for those with liver and kidney disease. IV artesunate is now FDA-approved. It's commercially available and does not require CDC approval. CDC no longer distributes IV artesunate.

Let me finish up with an overview of the 2023 locally acquired malaria outbreak. Let me set the stage for describing the 2023 outbreak. Let me remind you that although recent data are limited, anopheles mosquitoes are native and widespread in the U.S. They are most active at night, and they are seasonal. Here are four examples of the anopheles species, and they are able to spread malaria through their bite, when infected, to an uninfected person. So as long as there are travelers to endemic countries who become infected with malaria and are aparasitemic, when competent anopheles mosquitoes are prevalent, there will always be a risk of local transmission in the U.S. Historically, there have been about 30 outbreaks of local malaria transmission, from 1980 to 2003. 87% of these outbreaks were due to P. vivax, relapsing species.

Between 2003 until 2023, this was the longest stretch without locally acquired malaria cases reported. So let's talk what happened last summer, where 10 cases of locally acquired malaria were identified in four states. Nine of the 10 cases were P. vivax. To start, between May and July last year, seven cases were identified in a focal area of Sarasota County, Florida. The affected counties are marked in red on the map. In June one, P. vivax was identified in Cameron County, Texas. And in October one, cases of P. vivax malaria were identified in Saline County, Arkansas. On August 1, one person was identified with P. falciparum in the National Capital Region of Maryland. Genetic analyses suggested that each of these four outbreaks had an independent introduction. The investigations conducted for the four outbreaks were complex, and encompassed lab, epi, and environmental components, as well as public health communications. So, the lab studies confirmed all cases, and the species were identified with molecular typing. The epi investigations included detailed interviews to assess all the transmission risk factors, and active case findings that included alerting providers and community members on the symptoms and signs of malaria to be on the lookout for. The environmental investigations required visiting all households of cases for mosquito habitat assessment and trapping, and then deploying vector control activities.

Communications were done through the health department via the local media and other channels to providers and members of the affected community. For the epi investigation, malaria surveillance data was reviewed to identify cases in temporal and geographical proximity. The health department investigators revealed that none of the cases had recent international travel to an area with malaria, nor did they have a blood transfusion or organ transplantation. Three cases in Florida reported experiencing homelessness. This is a figure that was published after the Florida and Texas investigation, and it shows a duration timeline between illness onset and date

of definitive health care, for the 75 max cases identified in Florida, shown in blue, and one Texas case shown in a black triangle. At least three patients had symptoms for a week or more before their definitive diagnosis, and at least one patient sought care earlier, but no diagnosis was made at that visit. As these were plasmodium vivax cases, gametocytes, a form of the parasite which can be transmitted to mosquitoes, develop just before symptom onset, and are killed by the antimalarial given for treatment of the blood stage. So the time periods represented here show when the patient would have likely been infectious to any mosquitoes that may have bitten them.

The next two slides show characteristics of the nine of the P. vivax cases identified in Florida, Texas, and Arkansas. 67% were among men. 44% were among individuals ages 20 to 39. All nine patients reported a history of fever. Two-thirds reported vomiting. A little more than half reported abdominal pain, and a third reported diarrhea. On presentations, all patients had low platelets, and more than three-quarters had anemia. Providers were not usually thinking about malaria in individuals without any travel. Some of these patients were diagnosed because of an abnormality on the complete blood count test, with a manual differential, or a smear looking for another diagnosis like babesia. All six cases who had an RDT performed all were positive for malaria. Blood smears and PCR confirmation for all patients were positive for P. vivax. Six patients received Artemether-lumefantrine and three received Atovaquone or Proguanil for the acute blood stage infection, and all received primaquine for anti-relapse therapy.

All but one of the nine patients were hospitalized. None developed severe anemia, and there were no deaths. All cases were promptly reported by providers to the local or state health department, or to the CDC malaria hotline. For the 2023 outbreak, CDC provided guidance to field teams in each of the four states for mosquito vigilance, which included anopheles trapping

and surveillance, mosquito control, and testing any trapped anopheles that were sent to CDC to assess for parasites. The anopheles trapping approaches varied by site. Again, I won't go into that. Mosquito control over the sites varied by resources available locally. Our key lessons coming out of this outbreak is that the U.S. remains at risk for sporadic mosquito outbreaks.

Therefore, we need sustained awareness and strengthening of response and readiness around these several areas, both at the federal, state, and local levels. For surveillance, we really need it to be enhanced, and do more rapid reporting for laboratory – strengthen the confirmation and molecular methods, and for entomology for mapping and testing. I've covered a lot of material about biology, the burden, and the history of malaria, the epidemiology and the surveillance, prevention and diagnosis, and again, the local malaria outbreak last year.

The key things I want this committee to take away is that the U.S. has eliminated endemic malaria, and the significant majority of the 2000 cases per year are mainly among returning travelers, visiting friends and families, especially in Africa, and they are unfortunately not taking prophylaxis at all or properly. However, the risk of sporadically local malaria transmissions, though low and geographically restricted, this risk still exists, and will result in local outbreaks given the presence of competent vectors and delay in prompt recognition, presentation, and diagnosis of malaria in the U.S. And yes, we do have effective medications that are available by prescription to prevent and treat malaria. However, challenges, as I mentioned, to prophylaxis and even adherence to treatment, and prompt availability of the medications, these challenges exist. Thank you.

Dr. Szczepiorkowski: Thank you, Dr. Williams, for that wonderful presentation, a very comprehensive one. I'd like to open the presentation to any questions from the committee members. Please raise your hand and I will call to turn on your camera and unmute your

microphone prior to your question. We have about seven or eight minutes for questions. Please do not be bashful. So, I'm not seeing any hands up, but Dr. Williams… Okay, great. So we'll start with Dr. Ballow, who's the first.

Dr. Ballow: So the question I have is, in the cases in Florida, because actually I live in Sarasota, on the vigilance on mosquito control, were they able to identify any mosquitoes during that period of time that actually carried the disease or carry the malaria?

Dr. Williams: That's a great question. And I have the slide, but just for time's sake, yes. So, there were mosquitoes that were collected and were sent to CDC and dissections were done, and they did identify plasmodia in the abdomen of the mosquito. And so yes, they confirmed the presence of plasmodia species in the mosquitoes in Florida.

Dr. Szczepiorkowski: Thank you so much. And next I'd like to recognize Frank Maldarelli and unmute and ask a question.

Dr. Maldarelli: Yes, hi. That was just amazing. Thank you so much for all the information. My question has to follow on with that. Is there good evidence from other countries about the relationship between anopheles screening positivity and frequency of infection, as things are implemented to try and eliminate the disease? And then the second question is about asymptomatic transmission potential. And is there any screening either here or elsewhere for antibody positivity and transmission?

Dr. Williams: Wow, you're pulling me out of my subject here, but just sort of to frame the question, if I understand it. Anopheles screening, so vector screening. And then the second part of your question, remind me.

Dr. Maldarelli: The second part was about, how much, in other countries, asymptomatic transmission, are we missing cases that may not be reported or recognized?

Dr. Williams: So, let me tackle the first part. After malaria was eliminated, I think one of the challenges we've had is we've not kept our vector maps current. So, a lot of the activities have been devolved down to the states. And it's only now, with all the other vector-borne diseases, that we're really trying to, I call it, improve the occurrence of our vector screening in the various parts of the country, especially where this is a problem. So the Floridas, the Texas, maybe even as far as Maryland. So, is vector screening systematically done?

And I think the quick answer is no, but I'd have to get back to you on the specifics. Individual states might be collecting mosquitoes, then speciating them, but as to whether they are looking for plasmodia in them, I don't think that is happening. I can get back to you to confirm that. As far as antibody screening for asymptomatics in other countries, I'm sort of out of my depth with that, but I think for the little that I know, is that there are folks that are coming from other countries that show evidence, and you know this maybe better than I do, they are asymptomatic carriers. And the point I wanted to make with that is because of P. vivax and P. ovale having those hypnozoites, the dormant stage in the liver, we don't have a test for that. So yes, there are people that have malaria, but they're not showing any symptoms. Which countries are doing the screening, when you would need a serologic test that would show evidence of infection? I don't know enough about that to comment on the other countries. But yes, asymptomatics are occurring. Which countries are screening, I don't know.

Dr. Maldarelli: Thank you so much.

Dr. Szczepiorkowski: Thank you. And Dr. Ahuja, I recognize you.

Dr. Ahuja: Yes, thank you. That was a great presentation. I had a couple questions. One was, I saw that you mentioned 100% of the vivax patients have thrombocytopenia or had thrombocytopenia in the U.S. I think that data was in 78% anemia. So my question is, do the

blood related symptoms like thrombocytopenia or anemia exist without the other symptoms of vivax? For example, can you eliminate patients or donors based on anemia or they have anemia because they have asymptomatic vivax? Does that happen? And my second question was kind of related to what the previous questions were. Is there a CDC alert that is given out for the activity of anopheles in certain areas? So, would I come to know if I'm in an area that is high activity, I need to be careful?

Dr. Williams: Let me answer your second question first. Yes. So, well, let's start with Florida Texas, and then Maryland, the three counties initially. Yes, alerts go out. The issue, as you can imagine, is because it's not expected to have local cases, the state wants to be absolutely sure that it's locally spread. So there might be a delay in notification, but yes, yes. So if you lived in an area, there will be notification. They need to confirm that it is being spread. So back to your sort of question on, should we screen for anemia. In my experience, both in review of the literature, anemia is too general to screen people out. The thrombocytopenia might have an interesting way to look at it, but again, I don't know the numbers to say, go with thrombocytopenia, low platelets, versus, I don't think anemia would be the better screen. It's thrombocytopenia that seems to be a recurring pattern for people with malaria.

Dr. Szczepiorkowski: Thank you, Dr. Williams for your answer. And I have Ms. Cumming.

Ms. Cumming: Yes. I actually had a question for Dr. Eder, regarding one of the slides where she was summarizing the deferral periods based on responses to the DHQ. And I was just looking for some clarification as far as how that translates to use of pathogen reduced products. And I didn't know if she could clarify that.

Dr. Eder: Sure. Okay. Sure, I didn’t mention that. It will be described in another talk today, but in the recommendations, we do – let me see if I can bring up this slide. We do recognize that

pathogen reduction can be used in lieu of the questions, however… let me bring up the slide. So, on this slide, if blood centers are pathogen reducing plasma or platelets, they do not have to ask the question. However, an FDA-approved pathogen reduction system is only available for plasma or platelets, not for red cell components or whole blood. And, you know, malaria is primarily transmitted by infected red cells or whole blood. So we're not going to be talking about pathogen reduction. We will consider it the same way we do currently, for plasma and platelets.

Ms. Cumming: Okay, thank you

Dr. Eder: Yeah.

Dr. Szczepiorkowski: Thank you so very much. And thank you for the questions. Now we're going to have a break until 10:50, and at 10:50 a.m. Eastern EDT we'll be back. Thank you very much.

Transfusion-Transmitted Malaria in the United States: Dr. Sanjai Kumar

Dr. Szczepiorkowski: Okay. Now it is 10:50, and I have the pleasure to introduce our next speaker, Sanjai Kumar, who is the Chief Laboratory of Emerging Pathogens, Division of Emerging and Transfusion-Transmitted Diseases in the Office of Blood Research and Review. And Dr. Kumar, please turn on your camera and unmute. The floor is yours.

Dr. Kumar: Yeah, hi, good morning. Thank you, Dr. Ziggy, for the introduction. Can you hear me clearly?

Dr. Szczepiorkowski: Yes, we can.

Dr. Kumar: Okay, alright, thank you. So this morning, I'm going to summarize various aspects of transfusion-transmitted malaria in the United States. Why can't I progress it? Okay, so I will provide a brief introduction to – I think I jumped one slide here. Okay. After providing a brief discussion or introduction to discussion issues, I will provide some scientific rationale behind the

current FDA's measures to mitigate transfusion-transmitted or TTM risk in the United States. I will touch upon parasite and host factors that contribute towards TTM, donor characteristics and clinical presentation of TTM, effect of malaria risk differences on donor availability, some of these things you heard in Dr. Eder's presentation, and then nucleic acid test as a tool to screen blood donors for malaria risk. And finally, the conclusion.

Okay, so in the United States, currently we don't test blood donors for malaria risk. In the absence of testing, the safety of blood supply against the risk of TTM is currently maintained by different individuals who have had a history of malaria or have had traveled or lived in different countries. While effective, the current strategy fails to capture all asymptomatic infected donors, resulting in infrequent but continued cases of TTM and loss of otherwise healthy donors, who are not actually infected with the plasmodium parasite. So, in view of the technological advances in malaria detection technology, we think a more robust strategy based on testing of at-risk donors would adequately reduce the risk of TTM while allowing more donations by eligible healthy donors.

So, what are the FDA current measures to mitigate the risk of TTM in this country? In 2013, FDA issued major guidance on recommendations for questioning deferral, reentry, and product management to reduce the risk of TTM. In 2020, FDA issued revised guidance to our recommendations to reduce the TTM risk. And there were two major elements to this revised guidance. The first was the change, the deferral for travel to malaria endemic area from 12 months to 3 months, after departure from an endemic area. And the other was they allowed, for the first time, the use of pathogen reduction devices or pathogen reduction technology, PRT, that demonstrate effective reduction of plasmodium falciparum in view of certain questions. But there had been some discussion earlier this morning on this in detail. So, currently, PRT or pathogen

reduction is available only for plasma and platelet components. And, so far, there's no FDA-approved PRT system for whole blood or RBCs. On March 19, 2024, FDA licensed the first test-screened blood donors for plasmodium infection. And it's this regulatory action why we are here this morning before the committee.

So TTM in the U.S., or in any non-endemic country for that reason, is the consequence of asymptomatic chronic infections in blood donors acquired during travel or prior residence in endemic countries. It's the complex and multistage plasmodium lifecycle, the inherent parasite biology, and partial immunity in hosts resulting from multiple exposures received during living in malaria endemic areas or countries, are the major determinants of chronic malaria infections. So that's the basic premise behind transfusion-transmitted malaria. In addition, parasite virulence factors, course, and duration of infection, both acute and chronic infection, and host immunity and pathogenesis, all of these vary by infecting plasmodium species. So it's very much plasmodium species-dependent. So, let me see if my cursor works.

Okay. So in a human host, there are two distinct lifecycle stages for malaria parasite. The first one incoming is porous virus and parasite residing within the liver cell. These collectively constitute the pre-therapeutic stage malaria. And the second stage is the blood stage or the therapeutic stage cycle. So, this first stage here, pre-therapeutic malaria, is clinically silent and cannot be transmitted to another host. But this stage here, the blood stage, is responsible for all clinical malaria, malaria pathogenesis. And also another feature is this form can exist as a chronic long-term infection. And there's another feature. So, there are two stages during the lifecycle of blood stage malaria, where infection can exist in asymptomatic silent form. And those are stages which are risk for transfusion malaria. So the first one is upon the release of this liver form parasites. And before they reach a certain parasite threshold that requires to trigger

clinical symptoms, the parasite burden may be too low and asymptomatic. And also during this chronic stage here. And if the blood is collected from such an infected individual during these asymptomatic phases, that is major transfusion risk. So, pre-therapeutic cycle, depending on plasmodium species, it takes 7 to 30 days post-infectious mosquito bite for the liver from parasites to be released in circulation. But there's a complication here. For plasmodium biovax (phonetic) malaria and plasmodium ovale malaria have dormant liver form stages. You briefly heard about this in the CDC presentation. Causing relapse infections which may last from months to several years. In terms of asymptomatic chronic blood stage infection, the majority of chronic blood infections are cleared in about 12 months. But in rare instances, chronic blood stage infections may persist for years, or lifelong, mostly owing to the partial host immunity or inherent parasite biology of infecting plasmodium species.

For example, for falciparum malaria, this period has been shown to be at least 13 years. And for plasmodium malaria, it has been demonstrated to be 40 years or even longer. So the interval between departure from an endemic country, and inability to donate blood, is a major consideration in mitigating TTM risk. It's the driving force behind the current policies. Okay, so you have seen this slide from Dr. Eder's presentation. So just very quickly here, travel to a malaria endemic area. If someone has been resident of a non-endemic country or resident of a malaria endemic country, prior resident, who has lived three years or more consecutively in a non-endemic country, the three-month deferral for such individuals after each travel to endemic area. And also the option of PRT is available, but only for plasma or platelet products. For these two categories, a resident of a malaria endemic country who has lived less than three consecutive years is deferred for three years. No PRT option available. Resident of a malaria endemic country is deferred for three years. Again, no PRT. And someone with clinical malaria is deferred for

three years. So that's the current policy. So, there have been, I think this question was raised earlier, there have been no systematic studies in this country or elsewhere to determine the duration of how long asymptomatic chronic infections can persist. So, in the absence of such data, we use as surrogate the duration of onset of clinical illness after leaving an endemic area.

This is CDC data from 2018. This is cumulative data for all plasmodium species, and no distinction between prior residents or travelers here. So the only thing I want to focus on here is more than 90% of clinical cases reported within three months of departure from an endemic area. Hence the current policy of three-month deferral. And 1% or less of the cases of clinical malaria are reported after one year after return from an endemic area or country. So that's the three-year policy. So, the longer period is to take care of any residual lingering parasitemia.

Okay, so this is looking at the historical data, the characteristics of donors implicated in TTM in the U.S. This is, again, CDC data from 1963 to 1999. And the data are stratified based on the origin of residents of donors implicated in causing TTM. So the first column here is the first seven years, ‘63 to ‘99, and thereafter decade-wide distribution of data here. So, what's evident here is only two things I will focus on here. The prior residents of endemic countries are becoming the dominant group who have been implicated in transmission of malaria. And the second is the relatively or actually diminishing contribution of U.S. civilian travelers, those who had no prior immunity from non-endemic countries. So, in fact, actually, in the past four decades, only a single case of TTM has been caused by a U.S. civilian traveler, that was traveling to Nigeria in 1990, I believe. So, what's evident here is this allows us to identify the risk groups of donors who are primary contributors of transfusion malaria, that helps us to devise our different policies.

This is, again, historical data of transmission of malaria in the U.S., between 1963 to 1999. Total 93 TTM cases over a 36-year period, about less than three TTM cases each year. But the important features here are the four major human plasmodium species are represented here. Falciparum is the dominant species. 35% of our cases were caused by falciparum infection. Then the next is the vivax and ovale. But what is surprising is the higher proportion of ovale cases compared to their global contribution to malaria. But it's not surprising given their hypnozoite dormant form stages, which become clinically relevant during long residency. So then plasmodium malaria is also implicated, I think, because of the virtue of their ability to persist for a long time.

This is more recent data from 2000 to 2021. Overall, 13 cases of TTM over two decades, a little more than two decades. About one case of TTM every other year. Plasmodium falciparum has become the dominant species now. Ten of 13 cases. Two cases of plasmodium malaria and one case of plasmodium ovale was seen. So it allows us to just do some parsing of the data a little bit more. It allows us to look at the limitations of current FDA recommendations in capturing asymptomatic malaria in donors. So obviously, the current approach has not been completely foolproof. There have been cases of transfusion malaria. 13 TTM cases reported, more than two decades. So, from looking at the data from all sources, it's clear that all implicated prior residents were prior residents of a malaria endemic country. So there may be less than clarity here, in how to attribute these cases. Seven cases where donor eligibility was evaluated correctly, but donor had chronic asymptomatic infections. So the criteria failed, the deferral period was too short. And obviously, I guess any reasonable deferral period may not be able to capture all asymptomatic infections. In four cases, the donor did not disclose risk about prior travel or residence, or there was a staff error involved. So the process failed either on the donor

side and the staff side. And we're still trying to find more clarity in two cases. These cases are not published so far.

So, the clinical presentations of a transfusion-transmission malaria, the signs of symptoms are not distinguishable compared to those from mosquito-borne malaria infections, fever, chills, malaise, which may progress to severe disease, including severe malarial anemia and other clinical complications, and may lead to death if not treated. Clinical features and disease severity in TTM, and which is quite obvious, depends on the causative plasmodium, infective plasmodium species. The incubation period of TTM may vary between one to 12 weeks post-transfusion, which is longer than what is known from mosquito-borne infection. And probably this relates to many things. One could be the lower inoculum size coming through infected blood unit.

The other thing is fatality rate of TTM is approximately 11% historically, which is much higher than what is seen in severe malaria cases, important malaria cases in this country, who were admitted in the hospitals in the United States, which is 1% or less. And again, there could be many reasons. One is the comorbidity associated with the individual who already is receiving blood transfusions. And also, there are often delayed diagnoses of TTM in the U.S., one to 80 days, resulting in delayed treatment and adverse outcomes, because malaria is not always on the mind of clinicians treating blood transfusion recipients. Blood components that cause TTM. So, basically, TTM is caused by only one blood component, that is infected red blood cells present in whole blood or blood components. But in a few instances, all blood-derived platelets containing residual infected RBCs, all in rare cases, fresh plasma, or organ transplantation, have been implicated in causing TTM. Plasmodium parasites can survive at four degrees for more than 14 days. In banked RBCs, this is data both from the transfusion of stored blood units in the patient

and also from laboratory studies. Cryopreserved RBCs can also cause TTM. And leukocyte reduction and irradiation do not remove and do not inactivate infected red cells, and thereby do not prevent TTM.

Also, this has been touched upon this morning, the effect of malaria risk difference on donor availability. So historically, about 1% of all blood donors have been shown to be deferred because they are identified to have malaria risk. But if you look at the more current data from different sources, those numbers fall now somewhere between 50,000 to 160,000 blood donors are deferred. But this is not a simple issue of blood supply and number of donors deferred. There are other issues involved here. Individuals deferred from malaria risk are ethnically and racially diverse and often have rare blood group types. So they feel a very special need also in the transfusion recipient populations. Such donors feel a critical need in transfusion medicine, particularly among the U.S. minority population, who have distinguished genetic characteristics, such as transfusion-dependent patients with sickle cell disease or thalassemia. Individuals might self-defer and not present to donate because they are aware of the policies, so they don't bother to show up. Deferred donors are less likely to return to donate blood. So, all these things are rather unknown, their effect. So, I would like to talk a little bit now about the value of nucleic acid tests and that best testing for malaria because that's the reason why we are here today. So, microscopy, I mean, this is looking at the historical data published through dozens of publications in the literature. Microscopy and antigen detection tests, which are used in routine malaria diagnosis, both in non-endemic countries and endemic countries, are a thousandfold or greater less sensitive than NAD-based assays. Another issue is the microscopy and antigen detection methods are not amenable for high-throughput adaptation to serve as donor screening assays.

Now coming to the licensed plasmodium NAD. This is the cobas malaria test, recently licensed by FDA. The sensitivity and specificity were demonstrated in preclinical and clinical studies for five plasmodium species, plasmodium falciparum, vivax, malaria, ovale, and nolzi. The specificity of the licensed NAD assay, that's based on large clinical specificity with very few false positives. So the false positives are negligible, but the next presentation will be by Dr. Susan Galel, and I would like to let her speak for herself, and she will present the raw data. I will not go any further on that. The other thing I would like to mention is that the licensed plasmodium NAD is available in high-throughput format.

So, we can consider some things more scientifically. The question being NAD in detecting asymptomatic phases of malaria infection. And the model where the most data is available right now, these are laboratory studies done by different investigators, in this country and in Europe, for falciparum malaria only. So in controlled human malaria infection studies, where human volunteers are infected with infected falciparum infected mosquitoes, in malaria, nine volunteers. The average time for the release of liver from merozoites is five to seven days, and I think one group has precisely mapped it to 6.75 days, that's the time. So then one has to worry about the window period when the merozoites are released. They are present in the blood and infectious, and before the clinical onset of disease, one may present for donation. How long it will take before NAD or any other test can detect them. So NAD could detect pre-falciparum.

There are multiple studies, but I'm summarizing data from one study only. Could detect pre-falciparum parasite blood samples in the majority of volunteers by seven post-exposure challenge. Actually, in another study, it was mapped to 7.6 days. Compared to microscopy, NAD reduced the window period of detection by an average of 3.7 days. So, predict a short window period before NAD detection among travelers. So this is, I think, very important data here

because one has to worry about how effective the test will be in travelers. But I would like to have the big qualifier here. These are investigator-driven, well-controlled studies where the sporular burden in the muscle is well-defined, and these are malaria-naive individuals.

And also, this data exists only for falciparum malaria, not for other plasmodium species. The other thing is, there are dozens of studies where they have shown that NAD detects low-level parasitemia in asymptomatic carriers in endemic settings. Again, one could argue about the effectiveness of that, but generally, NAD has been shown to be effective in detecting low-level parasitemia. So, based on that, we predict the ability to detect asymptomatic individuals carrying low-grade plasmodium infection who were prior residents of endemic countries. I mean, that's the extrapolation.

So, I would like to conclude. The current FDA's recommendations are insufficient to identify and defer all blood donors with asymptomatic plasmodium infections. Consequently, TTM continues to occur in the U.S. Loss of otherwise eligible donors, particularly those at low risk of being exposed to plasmodium parasite, adversely affects the blood supply. And published reports indicate the effectiveness of NAD-based assays in detecting asymptomatic low-grade plasmodium infections among U.S. travelers. This is again by extrapolation. And prior residents of malaria-endemic countries, availability of an FDA-licensed NAD-based donor screening assay offers the opportunity to further augment blood safety and availability against TTM risk. So, I would stop here and take questions.

Dr. Szczepiorkowski: Thank you, Dr. Kumar, for your presentation. Very thoughtful and illuminating. I would like to open the presentation to any questions from the committee members at this point. Again, please raise your hand, and when called, turn on your camera, and unmute your microphone prior to asking a question. Actually, I will start with the first one. So, I'm a little

confused, so hopefully you will excuse me for that. So in 2020, FDA was perfectly fine with moving to three-month deferral, yet yourself and CDC presenters showed us that some of the malaria species actually reside for longer than three months. So now, the thinking goes, because of that change in our approach, would you expect to see an increase in malaria transmission, especially not falciparum, but others, over the last three years? And was that modeled prior to making a decision in 2020 for the changes?

Dr. Kumar: So, I mean, one could answer that question in many ways. But one assumes that the U.S. traveler is well-informed. Usually, sometimes, they do follow CDC advice and chemoprophylaxis for malaria. And also, if they become clinically ill, they do undergo testing and don't present for blood donation. So overall, I think that's the pattern we looked at, really, in the last 40 years. Not a single person who has been a resident of a non-endemic country was implicated in transfusion-transmitted malaria. So overall, that's the low-risk group. I mean, that's the best I think we can infer at this point. And we have not seen any uptick of transfusion malaria caused by U.S. travelers. I think that has been contention at the blood centers for a long time, really, actually. And so far, so good, actually. The policy has been holding. Yeah, Dr. Eder.

Dr. Eder: So, if I could just make one comment about 2020. So 2020, during the public health emergency, was a very challenging time. So we did consider the effect of shortening the travel deferral to three months. And it is still expected. Dr. Kumar had the slide of detecting about, I think, 95%. So we did consider it very carefully during the pandemic. We did weigh the issues, and we did still feel that it was sufficient. And we've seen no increase from the three-month shortening of the one-year deferral.

Dr. Szczepiorkowski: Yeah, I think that's great. And I think my understanding is that what we're trying to accomplish is basically zero risk of transmission, because the outcome of the readout of any decision, basically is based on the transfusion transmission of malaria. Is that correct?

Dr. Eder: Yeah.

Dr. Szczepiorkowski: Thank you. Okay, Dr. Ahuja, you're next.

Dr. Ahuja: Thank you. Great presentation. Sanjay. I was a little unclear about the window period for NAD testing, and maybe this will be covered in the next presentation. So say so if you feel like we can wait for that, Because I think one of the points you mentioned was it was a healthy volunteer study, that post-sporozoite challenge detected by day seven, you said, right? And then you shortened the window by three-and-a-half days or so. So, can you explain a little bit better, as to who are we missing by the NAD testing?

Dr. Kumar: Okay, so people have spent their lives studying this, really. And there has been mathematical modeling. So in controlled human challenges for infectious disease, they use three to seven plasmodium falciparum-infected mosquitoes, those are laboratory rigor. So usually the 10,000 to 40,000 liver-formed merozoites, they come out in circulation. And then you can calculate the five liters of blood, 5,000 ml in a healthy adult. So, I mean, you give and take, you know the number of parasites present there, okay? Each amplification cycle is 12.2 days in humans, they have calculated. So log-4 increase for falciparum is 48 hours. Somebody also has done calculations. There are about 11 infected liver cells. Those numbers come down to 280,000. So what's happening probably is there should be no overlap. From the time of instant release, NAD should be able to detect it, given the current sensitivity of NAD. But then there are multiple studies in the U.S., that Walter Reed Army Group has been doing. There have been studies done at Johns Hopkins. So, they all point towards the same thing. But then, again, as a

big qualifier, these are very well-controlled studies in human volunteers. So the overlap, there should be no window period with the sensitive NAD. But what will happen in people who had multiple exposures, most of these parasites will get neutralized before they get to – there will be some cellular immunity. So those numbers will vary. So those things will be known in the real-life setting only. I hope I answered your question.

Dr. Ahuja: Yes, thank you.

Dr. Kumar: And then people have done meta-analysis of all these studies, also, and come up with these numbers.

Dr. Ahuja: Thank you.

Dr. Szczepiorkowski: Thank you. Dr. Sridhar?

Dr. Basavaraju: Yeah, thanks. So, I just wanted to go back and make a comment about the discussion earlier, Ziggy, when you posed about how FDA changed the travel deferral to three months in 2020, and would we have expected to see more cases of transfusion-transmitted malaria. When we counted travel deferrals for the NBCOS in 2019, we counted, I think, 170,000 travel deferrals. And in 2021, when we did the NBCOS, it was only 27,000. So, assuming that there was not really much travel to malaria-endemic areas by U.S. travelers in 2020, 2021, 2022, I don't know if I would have expected to see any adverse impact of the malaria deferral change if there was to be one, at least in those three years, because people, probably the blood donor population, wasn't really traveling to begin with.

Dr. Ahuja: Thank you very much for the clarification. Appreciate that.

Dr. Szczepiorkowski: Any other questions? Okay. Dr. Kumar, thank you so very much for your presentation.

Dr. Kumar: Thank you.

Dr. Szczepiorkowski: No further questions. So now we come to the next presentation. I would like to introduce the next speaker, Dr. Susan Galel. She's a global senior director of medical affairs, donor screening, at Roche Diagnostic Solutions. Dr. Galel, please turn your camera on and unmute. The floor is yours.

Molecular Testing for Detection of Asymptomatic Plasmodium Infections: Dr. Susan Galel

Dr. Galel: Put this in presentation mode. There we go. Thank you, Ziggy, and many thanks to the committee for the opportunity to speak with you today. First, some disclosures. As mentioned earlier, I'm an employee and shareholder of Roche Diagnostics. The cobas malaria assay just mentioned by the previous speaker was licensed by the U.S. FDA for donor screening in March of this year, and is not yet commercially available. As other speakers have covered, malaria is an infection caused by plasmodium parasites, which are usually transmitted to humans through anopheles mosquitoes.

The parasites infect red blood cells, and the infection can cause severe anemia, but other organ systems can also be impacted, and the infection is sometimes fatal. Recurrent infections that occur in individuals who live in endemic areas can result in asymptomatic chronic infection with a low level of parasitemia that is sometimes referred to as a semi-immune state. There are many plasmodium species. Most human infections are due to five species, P. falciparum, vivax, malaria ovale, and nolzi. Transfusion transmission of malaria can occur in both endemic and non-endemic areas. In non-endemic areas, transfusion transmission is due to individuals who have traveled to or resided in endemic areas. As mentioned, there are chronically infected immigrants from endemic areas, and these individuals can have sustained infection for more than the current three-year deferral period in the U.S. And additionally, recent concern has been raised about the potential for local transmission, given the identification of anopheles mosquitoes in

multiple locations in the United States. As Sanjay reviewed, the current mitigation strategy in the United States is to use a donor screening questionnaire to identify donors at risk and to assign temporary deferrals. Donors are asked about a history of malaria and travel to and former residence in endemic areas.

The challenges with the current policy, as Sanjay reviewed, are that there is an imperfect reliability of the donor information, there are a large number of potential donations lost from individuals who are unlikely to be infected, and the current policy provides incomplete protection from chronically infected former residents. Another pain point that we have heard from blood banks around the world is that the deferral of former residents from endemic areas can impair access to certain red cell phenotypes needed for patients with hemoglobinopathies, and many blood banks are looking toward molecular testing as a tool to help them improve the diversity of the blood supply and better support patients from these regions.

And finally, there is no current strategy for blood safety in the context of local transmission episodes. As Seymour mentioned, microscopy and antigen tests have been the classical tests used for malaria diagnosis. The sensitivity of these tests is typically estimated at about 100 parasites per microliter, which translates to a sensitivity of 100,000 parasites per milliliter, so obviously these are not very sensitive tests. These tests are intended for use in febrile patients in order to determine whether plasmodium is the cause of the fever. Now, some reference laboratories in the U.S. offer laboratory-developed PCR tests that detect the DNA of plasmodium, that is, they detect plasmodium genes, and typically these targets are present in one to five copies per parasite. As I mentioned, these are all laboratory-developed tests. Their sensitivity is typically estimated in the range of 1,000 to 6,000 parasites per milliliter. The sensitivity is limited both by the small number of copies of a target in every parasite, as well as

the sample volume, which is usually some fraction of a milliliter. Nevertheless, despite the somewhat limited sensitivity, there is documented improved detection of asymptomatic infections by these molecular DNA-based PCR tests, compared to microscopy or antigen. Most recently, a more sensitive form of molecular testing has been used by some research laboratories.

These tests detect ribosomal RNA. Ribosomal RNA has been estimated to be present in approximately 7,400 copies in every parasite. So with the huge number of copies of target per parasite, the predicted sensitivity for these assays is that if one parasite is present in the sample, it would be detected. And Sanjay mentioned controlled human malaria infection studies. These ribosomal RNA assays have been primarily used in the setting of the controlled human malaria infection studies. And there's quite a bit of modeling, as Sanjay mentioned, quite a bit of modeling using these assays, showing how rapidly the infection can be identified with these tests.

But I should mention that, in these studies, typically the sample volume that is used is 50 microliters. So it's one twentieth of a milliliter, which again somewhat limits the sensitivity of the assays used in these studies. Now, so far I've been talking about sensitivity in terms of the detection of parasites. But there is a lot of evidence for extracellular plasmodium nucleic acid and the detection of plasmodium nucleic acid in plasma or serum. I've provided just two references here. One is referring to a study that showed the utility of using stored frozen serum samples for retrospective diagnosis for prevalence studies. And a recent study from Brazil. Now, some of you may be aware that some public blood banks in Brazil have implemented donor molecular testing for plasmodium, using a DNA-based assay, performed on plasma samples from donors that are tested in pools of six. And using these plasma-based DNA PCR assays, they are finding what appear to be true positive donations. Now, in these studies that I mentioned, the

nature of the nucleic acid that was detected in the plasma is unclear. We don't know if these were parasite fragments or extracellular vesicles, and there is a lot of literature about extracellular vesicles in plasmodium infection.

So, I mention these findings because it is possible that nucleic acid could be detected in a donor whole blood sample, because whole blood contains both plasma and red cells, even if no parasite is captured in the sample. So our goal in designing the cobas malaria assay was to develop a high-sensitivity five-species plasmodium nucleic acid test. And our intention was that this tool could enable preservation of blood safety while increasing donor availability and diversity. The design of our assay is based on detection of ribosomal RNA as well as DNA, again, because of the high copy number of ribosomal RNA in every parasite.

The sequences used in the assay are intended to detect the five main species known to infect humans. And because plasmodium parasites are primarily found inside red blood cells, the sample type for this assay is whole blood, not the plasma that's used for, say, HIV or HCV NAT. For this capturing of whole blood, we used the Roche whole blood collection tube, which was initially developed for the cobas babesia test and is currently used in the United States for that assay. And I should mention that the same sample can be used for both cobas malaria testing and cobas babesia testing. The workflow for this testing is that approximately 1.1 ml of donor whole blood is collected into tubes that contain a lysis buffer and preservatives. When the red cells enter this lysis medium, the red cells and any parasites present are immediately lysed, and the parasite nucleic acid would be stabilized. Then this tube can be placed on our Cobas 6800 and 8800 systems, and tested with our ready-to-use cobas malaria reagents. The sensitivity of malaria molecular tests can be measured in a variety of ways.

This slide shows analytical sensitivity of the cobas malaria assay for detection of intact infected red blood cells, or IRBC. For this experiment, P. falciparum cultures of infected red blood cells were used, where the infected red blood cell concentration was quantitated by microscopy. And this culture material was serially diluted in plasmodium negative whole blood. Then 1.1 ml aliquots of specific concentration levels were transferred into Roche whole blood collection tubes, and the lysate tested by cobas malaria on the Cobas 6800 and 8800 systems. The observed concentration for detection of plasmodium with 95% probability was 2.9 infected red blood cells per ml, and this is exactly the concentration that you would need to have, to have a 95% probability of capturing one infected red blood cell in the test sample, based on Poisson distribution. So, this essentially confirms that if you capture one infected red blood cell in the sample, it would be detected.

We have also assessed the sensitivity of the cobas malaria test for isolated ribosomal RNA. The analytical sensitivity for the ribosomal RNA of each of the five species was assessed using recombinant particles that encode a single copy of plasmodium target ribosomal RNA, encapsulated by bacteriophage protein. This protein protects the ribosomal RNA from degradation. These protein coated RNA particles are called armored RNA or ARNA. Armored RNA particles were serially diluted and then tested with cobas malaria. Similar sensitivity was demonstrated across the five species, and the differences in detection between the five species are negligible compared to the thousands of copies present in every parasite. Now the reliable detection of positive samples begins with assay design. Cobas malaria utilizes a dual target PCR design that targets two highly conserved regions of ribosomal RNA sequences. In silico analysis predicts robust detection of all of the species claimed. Detection of the five species was further

confirmed by wet lab testing, using clinical samples, culture supernatants, and armored RNA constructs.

These studies are described in the package insert. We performed a large clinical specificity study in U.S. blood donors. Whole blood samples from volunteer donors in the United States were collected in the Roche whole blood collection tube and tested by cobas malaria. 20,187 donations were tested by individual sample testing, with no reactive donations, so 100% specificity.

Now, in order to confirm that the assay would detect asymptomatic infections, we conducted a study in Nigeria. The study population for this study included asymptomatic study participants in the Edo state of southern Nigeria, which is a highly endemic region for malaria. The samples were collected in August and September of 2021, which is the rainy season or the high season for malaria. Fresh blood from subjects was tested locally by microscopy and antigen tests, and 1.1 ml of EDTA whole blood from each participant was inoculated into a Roche whole blood collection tube, and the lysate then was frozen and shipped to the United States for molecular testing. These samples were tested in the U.S. by cobas malaria, as well as an in-house alternative nucleic acid test with similar sensitivity. Samples from 199 study participants were evaluable. There were four participants who were positive on local testing by microscopy and antigen testing, and a total of 76 samples that were reactive by cobas malaria and confirmed by the alternative nucleic acid test. So, of the 76, these included the four samples that were positive by microscopy and antigen, and an additional 72 samples that were negative by microscopy and antigen but confirmed positive for molecular testing.

But what about the detectability of asymptomatic plasmodium infections in non-endemic areas? Well, the challenge here is that asymptomatic plasmodium infections are rarely identified

or diagnosed in the United States and other non-endemic areas, and much of what we know about the laboratory detectability of these infections is from donors who have been identified as the cause of transfusion-transmitted malaria. So, I sought to determine the laboratory detectability of the donors who have been identified as the source of transfusion-transmitted malaria in the U.S., Canada, and Europe. I identified all published cases of transfusion-transmitted malaria in these countries since 2010. I contacted the authors and laboratories in order to solicit missing details about the sample types that were used for testing, and the laboratory methods. And the next few slides summarize the results of the testing that was performed on samples, either retained from the donation that caused the TTM, and/or laboratory testing performed on fresh follow-up samples.

So, in this time period, there were 12 cases of transfusion-transmitted malaria and one case of bone marrow transplant-transmitted malaria. Seven of the cases were in the U.S., one in Canada, and five in Europe. The results of molecular testing, which was all performed by DNA-based PCR assays, were reported for 12 of the 13 implicated donors. This slide shows the eight cases from U.S. and Canada. I show these together because donor eligibility criteria for these countries are similar. So, there were a total of eight cases in U.S. and Canada in this time period. In all eight cases, the donors' malaria exposure was in Africa. Seven of the eight donors were stated to be former residents of Africa. With one case, the bone marrow transplant-transmitted case, the former residence is not mentioned and only travel is mentioned, but I do not have further information about that case. The time since last potential exposure to malaria ranged from 16 months to 15 years, with four donors, that is half of the cases, involving former residents of endemic areas whose last exposure was more than three years prior to the time of donation. So

they would have been eligible by current criteria. Molecular testing is available for all of these cases.

In all cases, the molecular testing was performed by laboratory-developed PCR assays with an estimated sensitivity in the range of about 3,000 to 6,000 parasites per milliliter. In most cases, the PCR testing was performed on a fresh follow-up sample, and this follow-up sample was positive by PCR in all cases except for one. In this case, that shows a negative result, the publication actually reports reactivity with a late CT value that could be consistent with nucleic acid below the limit of detection of the assay. This donor was positive on PCR testing of the retained blood segment from the donation. PCR testing was negative in two donors who were tested only on retained segments from their blood donation that had been stored for multiple weeks in the refrigerator, which is not ideal for nucleic acid testing. This slide shows the TTM cases reported from Europe, and PCR testing was performed in four out of five of these donors.

In all cases, the PCR performed was a DNA-based PCR, and the reported sensitivities appear similar to the sensitivities of the U.S. CDC testing. In all cases, the fresh follow-up sample was positive by PCR. In three cases, a frozen retained segment of plasma was tested from the implicated donation, and interestingly, in one case, this frozen plasma sample was positive by PCR. So, in summary, the PCR assays used in these case investigations were able to detect plasmodium infections in all donors tested except for two donors, who were tested only on samples likely to have deteriorated from prolonged refrigerated storage. And cobas malaria is approximately 1,000-fold more sensitive than the assays that detected infection in these cases. So I have been asked by some people whether there is a potential for using our test to test lysates in pools, and first I should clarify that for pooled testing for malaria, similar to babesia, the pooling is performed on the lysates, not the donor whole blood sample. And this is, again, because if a

parasite is captured, thousands of copies would be released into the lysate, and therefore aliquots of the lysates can be used for pooled testing, without a significant loss of sensitivity. And yes, we have performed studies using cobas malaria in lysate pools or simulated pools, and we plan one additional study to further support a pooling claim.

Now, there's reason for optimism for the potential for testing lysates in pools. As Dr. Eder mentioned, the testing of pooled lysates appears to be sufficient for babesia. Babesiosis, like malaria, is caused by parasites that infect red blood cells, and the donor screening tests for babesia are, like cobas malaria, ribosomal RNA-based tests. FDA guidance in May of 2019 requires testing of donations collected in regions of the U.S. where babesia is endemic. The workflow that is utilized for this testing is similar to that which I've described for malaria, except that testing is permitted on pools of lysates. And as Dr. Eder mentioned, there has been no transfusion-transmitted malaria identified from donations that have been tested in lysate pools. Sorry, testing of babesia.

So, in summary, molecular methods are more sensitive than antigen or microscopy for the detection of asymptomatic plasmodium infections. Molecular tests have been able to detect infection in donors implicated in transfusion-transmitted malaria. And a highly sensitive automated five-species nucleic acid test that detects ribosomal RNA and DNA may provide a useful tool for further reducing the risk of transfusion-transmitted malaria. Again, I'd like to thank the committee for the opportunity to speak with you today. I'd also like to thank Dr. Brian Raphael from the U.S. CDC, who helped me gather information about the CDC PCR testing, from the transfusion-transmitted malaria case investigations, and all of the authors who supplied additional information about their cases. Thank you.

Dr. Szczepiorkowski: Thank you, Dr. Susan, for your informative presentation. I'd like to now open the presentation to any questions from the committee members. Again, please raise your hand, and when called, turn on your camera and unmute your microphone prior to asking your question. Just a clarification. So, Susan, you mentioned that the same tube can be used for both malaria and babesia, or they can be tested from the same tube? Is that what you mentioned?

Dr. Galel: Yes, it's two different assays, but the two assays can be performed on the same 1.1 ml sample that's collected into the Roche whole blood collection tube.

Dr. Szczepiorkowski: So, what we need requires two tubes. Is that correct?

Dr. Galel: No, one tube.

Dr. Szczepiorkowski: One tube.

Dr. Galel: One 1.1 mL into the lysate tube, and then that lysate can be used for either or both assays.

Dr. Szczepiorkowski: Thank you so much for clarification. Sridhar?

Dr. Basavaraju: Yeah, thanks. Is there actually a consideration to do pooled malaria testing, or was that just something that you were just addressing, because that sounds <unintelligible> for babesia. Because I would think operationally it would be difficult to implement that, right? Because these donors would be sporadic, right? It's not like in a babesia endemic area where every donation collected in some state is tested. I mean, you would have a smattering of donors from here and there, periodically, I would imagine.

Dr. Galel: Yeah, I agree with you. If you have just a small number of samples, it doesn't seem to make a lot of sense to pool the samples together. Operationally, it would probably be easier to test them individually. I would imagine that in a local outbreak setting where you may be testing all collections from a particular area, then it would make a lot more sense.

Dr. Basavaraju: That would depend on the size of the outbreak, right? Because I would think in a local outbreak you would want to be even more careful about identifying even in any case. So even in a local outbreak, wouldn't you still recommend these to be done individually?

Dr. Galel: Yeah, I think it's not clear. Again, if you capture one parasite, you've got thousands of copies there. So, theoretically, you should not be losing sensitivity by pooling. Again, we're pooling lysates. We're not pooling the whole blood samples.

Dr. Szczepiorkowski: Thank you. Dr. Pandey?

Dr. Pandey: Hi, thanks Dr. Galel for all the information. Excellent presentation and summary. So, I actually have two questions. So, one has to do also with the sample tube. Wanting to understand, I know you said 1.1 ml, is that the actual tube size or is it actually like a 3 ml tube, but only 1.1 ml is used for the testing?

Dr. Galel: Yes. So, the tube actually comes prefilled with 7.7 ml of the lysis and storage medium. And it has a vacuum in it. So the tube automatically collects approximately 1.1 ml of whole blood from the donor sample pouch. So the tube contains a total of 8.8 ml of lysate. That's the 1.1 ml of whole blood and the 7.7 ml of the medium already in the tube. So the total volume in the tube is 8.8 ml. And that's why this one tube is plenty to be used for either the cobas malaria testing or cobas babesia testing or both.

Dr. Pandey: Okay. And the reason I ask these questions is there is very limited volume in that diversion pouch for some of the blood bags that are being used. But my other question is that, if, let's say there is an issue with even 1.1 residual volume, could blood centers aliquot from an already taken, a tube drawn into that Cobas tube, or residual sample, from tubes already collected?

Dr. Galel: Yes. So, first I should say we have not heard concerns for the blood banks that are using our test routinely for babesia testing. I'm not aware of any concerns about being able to find the 1.1 ml in the sample pouch for that tube. But yes, there is an alternative in the package insert that allows the laboratory to aliquot 1.1 ml of whole blood from an EDTA tube into the Roche whole blood collection tube. So the laboratory would then, you know, keep a stock of the tubes and they could create the lysate there in the lab. But the most efficient workflow would be to collect the whole blood into the tube at the collection site, and then the laboratory can test those tubes directly on the system.

Dr. Pandey: Okay, thank you. And one last question is, you talked a little bit about the data from Nigeria. And what I wanted to ask is, is there any other real-world data, especially in endemic countries? I'm not sure if this assay is being used in other countries routinely on blood donors. If there's any more information about testing in more of an endemic, and identifying those low, you know, the potential chronic infections with low parasitemia.

Dr. Galel: Yeah, it's hard to identify chronic infections in endemic areas because people are constantly acquiring and clearing infections. So, it's probably not the best place to understand what the level of parasitemia is in these people who have sustained chronic infections. So, you know, in our malaria study, in our Nigeria study, people could have had malaria three weeks before they participate in the study. I mean, we have no way of knowing when their last infection was. And so I think most people believe that the sustained parasitemia that occurs in chronic infections is probably different from the asymptomatic infections in those countries, like Nigeria, where people are chronically acquiring and clearing infections. I don't think one is a good model for the other.

Dr. Pandey: Thank you.

Dr. Szczepiorkowski: Thank you. Dr. Ballow.

Dr. Ballow: Thank you. A couple of questions. I saw the slide where it was 100 percent sensitivity of this new asset, correct?

Dr. Galel: I don't think I reported… I reported specificity was on 100 percent.

Dr. Ballow: Oh, specificity.

Dr. Galel: Yeah.

Dr. Ballow: I'm sorry, yeah.

Dr. Galel: And sensitivity was also 100 percent, but I didn't report that on my slide.

Dr. Ballow: Right. So, false positives then would be negligible?

Dr. Galel: Right. So, more than 20,000 samples tested individually, we did not have any reactives. So false positives. We also reported at last year's ABB meeting that we performed a specificity study in pooled lysates, as well. And more than 67,000 donations were tested in pools, with no reactive pools and no reactive individual samples. So, 100 percent specificity in 67,000 donations tested in pools.

Dr. Ballow: And false negatives. You think you need more studies to define what the false negatives are?

Dr. Galel: So we're not aware of false negatives in terms of failure to detect specific sequences. So as far as we can tell, we would detect all of the species that we intend to detect, and the published sequences for the five species. I think what Sanjay brought up is whether… two cases, one is what he referred to as the window period. And that is from the time of releasing the parasites from the liver and their detection in the blood. And as Sanjay mentioned, in the controlled human malaria infections using these the ribosomal RNA-based assays, it looks like they're detected essentially on release from the liver. The assays used in these studies, as I

mentioned, use typically 50, that's five oh microliters of blood. So, one twentieth of an ml. So they would have some limitation in terms of the number of parasites that could be captured in that volume. So, as Sanjay mentioned, it's not anticipated that there is a significant window period between the time of the liver phase and detection in the blood, because there's a huge amount of multiplication that occurs in the liver.

The other question has to do with the detection of these asymptomatic chronic infections. And as I mentioned, the transfusion transmitted malaria cases provide, I think, a high level of optimism that that these infections, although they're usually not detectable by microscopy, they do seem to be detectable by much less sensitive PCR assays. That is the DNA-based PCR assays that are a thousand-fold less sensitive than ribosomal RNA assays. So, it looks like these asymptomatic chronic infections should not be difficult to detect. But, how do you how do you do a study in people that you can't find, right?

Dr. Ballow: Yeah. Thanks. Because one of the outside groups, I think from Canada, suggested that more data has to be obtained with this new assay in order for them to feel comfortable. But I think you answered a lot of the questions that address that criticism and ones that I had. Thank you.

Dr. Szczepiorkowski: Dr. Maldarelli .

Dr. Maldarelli: Yes, just following on those questions, thank you very much for this presentation, so comprehensive. In terms of the false negative rate or cross reaction rate. Forgive me if I missed it. How much cross reaction is there with babesia samples?

Dr. Galel: Yeah, we did test. So, by in silico analysis, there is not cross reactivity. And we did do wet lab testing and verified no cross reactivity with babesia.

Dr. Maldarelli: And with how many samples was that done?

Dr. Galel: That was just with a high concentration culture, or high concentration sample of babesia. And again, there are some plasmodium assays that by design have some cross reactivity. And we were careful in our assay design to exclude the detection of babesia species.

Dr. Maldarelli: But in natural or authentic samples from babesia-infected individuals, how many of those were tested with this assay and found… were there any false positives for malaria?

Dr. Galel: I don't think we did a systematic study of a large number of clinical samples. But again, we would not expect detection.

Dr. Maldarelli: Right. Okay, thank you. I think in terms of the way you characterize it, it was such an exhaustive analysis. But in general, I think there's no such thing as 100 percent. So, it's less than one positive in 20,000 rather than 100 percent. I've seen that in most package inserts, where the numbers of samples tested is not as extensive as what you've done. And I think it's probably a better idea to use a denominator. And I think that's going to speak to the false negatives that that we've already discussed, or Dr. Ballow raised.

Dr. Galel: Yes, in terms of specificity there, we do express that with confidence intervals. So just in the interest of time, I didn't state those orally.

Dr. Maldarelli: Thanks so much.

Dr. Szczepiorkowski: Thank you. Any other questions? Just one more question to clarify. So Susan you worked the most with those TTMs. You look at Canada, U.S., and Europe, and it sounds like you were able to detect them. But looking at the characteristics of those donors and maybe I’m going out on a limb right now. Do you expect that testing 20 million people or 10 million people who are not at risk, would identify infections which we didn’t tag by TTM?

Dr. Galel: That's a good question. You know, are there additional asymptomatic donors, and we're not detecting who are transmitting infection and we don't know about it. Is that the question?

Dr. Szczepiorkowski: Yeah, that's the question. Yes.

Dr. Galel: I mean, it's certainly possible, because many transfusion recipients die of their underlying disease. And we don't know if they have acquired some transfusion-related infection. Also, as I think Sanjay mentioned, there's typically a delay in diagnosis of TTM cases because the recipient hasn't been in an endemic area, and therefore nobody considers malaria as the cause of whatever their symptoms are. So, it is possible that there have been additional transmissions that have gone unrecognized.

Dr. Szczepiorkowski: Okay, thank you so very much. And thank you for a wonderful presentation. We're moving to the next speaker. I'd like to introduce Ms. Jennifer Scharpf, Associate Director of Policy at the Office of Blood Research and Review. And Ms. Scharpf, please turn your camera on and unmute. The floor is yours.

FDA's Policy Considerations for Testing Blood Donations for Malarie Infection: Dr. Jennifer Scharpf

Ms. Scharpf: Good afternoon. Thank you, Dr. Ziggy. And thank you to the committee for your participation in today's meeting. The objectives of my presentation are to describe FDA's regulatory framework that addresses blood safety against transfusion-transmitted malaria, review FDA's current recommendations for reducing the risk of transfusion-transmitted malaria, present FDA's proposals for selectively testing blood donations for malaria, and discuss advantages and limitations of the proposed selective testing strategies. And I'll conclude my presentation by presenting the charge to the committee. Over the next few slides, I will be presenting the

regulatory framework that guides FDA's policy development. The Code of Federal Regulations, or the CFR, sets FDA's approach to blood safety. The CFR contains regulations that have the force and effect of law. The CFR defines relevant transfusion-transmitted infection, or RTTI, as well as the actions that blood establishments must take to address the risk of relevant transfusion-transmitted infections.

Under this framework, plasmodium species, or malaria, is enumerated as an RTTI, and certain requirements flow from this designation. The first is with respect to assessing donor eligibility through questioning. As shown on the slide, blood establishments must conduct a medical history interview to determine if the donor is in good health, and to identify risk factors closely associated with exposure to, or clinical evidence of, an RTTI. FDA's current approach to addressing malaria risk falls under this regulation. And we recommend questioning and deferral for risk factors for malaria. Elsewhere, the CFR contains requirements for testing blood donations for RTTIs. Currently, there are specific requirements in the CFR for testing donations for certain RTTIs, including HIV, HCV, and HBV. However, at the time the regulations were finalized in 2015, tests were not available for certain RTTIs, including malaria. So our regulations are forward-looking, and establish the conditions for testing RTTIs for which tests were not available in 2015, as well as for emerging infectious diseases that may be designated as RTTIs in the future. So, specifically, the regulation states that blood establishments must test for certain RTTIs, including malaria, when the following conditions are met.

One, a test is licensed, approved, or cleared by FDA for use as a donor screening test and is available for use. And two, testing is necessary to reduce adequately and appropriately the risk of transmission of the RTTI by blood, or blood components, or a blood derivative product manufactured from the collected blood or blood component. So it's this regulation that sets the

stage for our discussion today. Because as you've heard from our speakers, there is a licensed test now available, and transfusion-transmitted malaria continues to affect blood safety in the U.S. However, the regulations also anticipate that testing every donation may not always be necessary. The regulation means, in part, that testing must be performed on each donation unless testing of each donation is not necessary to reduce adequately and appropriately the risk of transmission of such infection. And when evidence supports this determination, that testing each donation is not necessary, blood establishments may adopt an alternative testing procedure that has been found acceptable for this purpose by FDA. The supporting evidence may include the epidemiology of the RTTI, such as seasonality or geographic risk, as well as the effectiveness of manufacturing steps, for example, pathogen reduction technology, that may reduce the risk of transmission of the RTTI. We've interpreted this testing regulation to mean that FDA makes the determination for when testing an RTTI is necessary, and issues guidance to describe acceptable procedures. So, this framework allows FDA to consider selective testing strategies for an RTTI, in which not every donation must be tested. As you've heard, to date, we've applied this approach to testing two RTTIs, T. cruzi, the causative agent of Chagas disease, and babesia, which causes babesiosis.

In 2010, we recommended one-time testing of each donor for T. cruzi, and under this strategy, donors who test non-reactive are qualified for subsequent donation without testing. Blood establishments review records to determine history of testing of each donor, and test accordingly. More recently, in 2019, we recommended a regional testing strategy for babesia. When a licensed donor screening test became available, we recommended that blood establishments test each donation in the states with highest babesia risk. Alternatively, blood establishments can pathogen-reduce platelet and plasma components using an FDA-approved device. Currently, we recommend testing in 14 states and Washington, D.C. In states that do not

test for pathogen-reduce components, donors are asked about a history of a positive test for babesia and deferred accordingly. However, we continue to review the available data, and our recommendations may change over time as the epidemiology or risks of RTTI evolve. I'll transition now to review FDA's current recommendations to reduce the risk of transfusion-transmitted malaria. Our recommendations are contained in the 2022 guidance that's listed in the first bullet on this slide, and as you know by now, they're based on donor questioning and deferral. The guidance recommends that the donor history questionnaire assess donors for malaria risk, namely for a history of malaria in the past three years, a history of prior residence in a malaria-endemic country, a history of travel to a malaria-endemic area in the past three months, and a history of travel to a malaria-endemic area in the past three years if the donor was a previous resident of a malaria-endemic country.

To capture these risk factors, the FDA-recognized donor history questionnaire includes two questions. One, have you ever had malaria? And two, in the past three years, have you been outside the United States or Canada? The second question is a capture question, and if a donor answers yes, the health historian follows a flow chart with subsequent questions to determine eligibility. One exception, which is noted in a footnote at the bottom of the slide, is that blood establishments are not required to assess source plasma donors for malaria risk. And this is because, in part, source plasma is used for the manufacture of plasma-derived products, and pathogen inactivation methods that are used in the manufacture of these products are sufficient to reduce the risk of malaria transmission.

Dr. Eder showed this flow chart previously, but I'll just remind the committee that this is the flow chart that is utilized to assist the screeners in assessing a donor's eligibility to the question of, in the past three years, have you been outside the U.S. or Canada? And I'm sharing it

just to illustrate the complexity of the current process for determining donor eligibility based on prior residency in a malaria-endemic country, and assessing travel to a malaria-endemic area. And this is the table that summarizes our current recommendations based on donor questioning and deferral. Donors are deferred for travel to malaria-endemic areas, prior residence in a malaria-endemic country, and for a history of malaria. For donors that report travel, the deferral period depends on the length of time spent in a non-endemic country. And as shown in the third column, and as discussed previously, as an alternative to the three-month referrals for travel to a malaria-endemic area, we do permit collection of platelet and plasma components without a deferral period, provided the components are pathogen-reduced using an FDA-approved device.

As discussed in previous presentations, there are limitations associated with our current recommendations. Significant donor loss is associated with deferrals for malaria risk. Although the exact number is not known, some estimate that approximately 1% of all presenting donors are deferred for travel to a malaria-endemic area. And we presented that approximately 50,000 to 160,000 donors may be deferred annually. This number may be reduced slightly as our donor deferral policies have changed over time. And further, recent data reflects a significant reduction in travel in the early part of the decade because of the COVID-19 pandemic. Importantly, the deferrals associated with malaria risk, particularly for prior residence of malaria-endemic countries, reduce the diversity of blood types needed for patients.

Also, transfusion-transmitted malaria continues to occur because of the inherent limitations in donor questioning. Because the questioning is complicated, there exists a potential for errors by collection staff in assessing donor eligibility, as well as with donors in recalling or disclosing risk. As you've heard, the deferral periods may also not be sufficient to identify asymptomatic infections. And this is particularly true in prior residence of malaria-endemic

countries with partial immunity, or those who have had a history of malaria. And finally, the FDA-approved pathogen reduction devices are currently only available for platelet and plasma components, and not for whole blood or red blood cell collections, which are primarily implicated in transfusion-transmitted malaria. The information on this slide demonstrates how the current approach fails to adequately capture malaria risk in donors, resulting in TTM. Thirteen cases of TTM have been reported since 2000. In seven of those cases, donor eligibility was evaluated correctly, but the donors had chronic asymptomatic infections. So in these cases, the criteria failed, namely that the deferral period was too short to capture this risk. In four cases, the donors did not disclose their risk or there was staff error in assessing donor eligibility. And in this case, the process failed. And the reason for the TTM in two cases has not been described in the literature.

So we recognize a selective testing strategy based on donor questioning alone may not impact the cases where the process failed, but it has the potential to intercept infectious units where the criteria failed because the donor had a chronic asymptomatic infection. However, we also recognize that a one-time testing strategy, in addition to selective testing, has the potential to reduce the number of cases where the process fails.

So this slide provides a high-level overview of the proposed selective testing strategies for which we're seeking the committee's advice. With the first approach, labeled here as Strategy 1A, we propose selectively testing blood donations from donors at risk for malaria exposure, as determined solely by donor questioning. Blood establishments would assess donors for a history of malaria, travel to a malaria-endemic area in the past three months, and prior residency in a malaria-endemic country.

In the second approach, labeled here as Strategy 1B, we propose testing all donors at least one time, and then selectively testing blood donations from donors at risk for malaria exposure as determined by the donor questioning. And in this strategy, donors would be assessed for a history of malaria as well as travel to a malaria-endemic area in the past three months. And in this strategy, I want to point out that we would not recommend assessing donors for prior residence in a malaria-endemic country.

This third proposal, labeled as Strategy 2, should be considered separately from Strategies 1A and 1B, because it's intended to address risk in areas of the U.S. with local malaria transmission. Under this approach, we propose blood establishments test all donations in regions of the U.S. with local mosquito-borne malaria transmission. Testing would be triggered by public health authority reporting of local cases, and would be limited to the risk period only. And similar to our current approaches for donor questioning and deferral, the proposed testing strategies, all three that I presented, would not apply to the collection of source plasma or the collection of pathogen-reduced platelets or plasma components. So now I'll go into a little bit more detail about each of the testing strategies.

This flowchart illustrates the first element of Strategy 1A, in which we propose testing all donations from individuals with a history of malaria at each donation. Donors who report a history of malaria would be asked three additional questions to assess for ongoing infection. Specifically, since your last malaria diagnosis, have you been evaluated by a physician or healthcare provider? And have you completed any prescribed treatment for malaria? And are you now asymptomatic and free of malaria? If a donor answers yes to all questions, the donor would be eligible and the donation would be tested. If a donor were to answer no to any of these questions, the donor is not eligible and would be deferred for at least one year. Donors with a

history of malaria would be asked the same questions at each donation, and if eligible, their donations would be tested. So under this approach, there would be repeat testing of donors with a history of malaria, regardless of new risk. However, we anticipate that this testing burden would be small. And on the left-hand side of the chart, donors without a history of malaria would continue with the donor history questionnaire to be evaluated for prior residence in a malaria-endemic country and travel to a malaria-endemic area.

So, this flowchart illustrates the second element of Strategy 1A, which entails selective testing for donors with a history of prior residence in malaria-endemic countries and travel to malaria-endemic areas. Under this strategy, we propose testing all donations from individuals who report a history of prior residence in a malaria-endemic country, and this is defined as a continuous stay of five years or more. Donors who report a history of prior residence would not be asked about recent travel history, so that would be a change from the current donor history questionnaire and eliminates some complexity in evaluating travel history and prior residence.

The donations would be tested regardless of the length of stay of the donor's residency in a non-endemic country or recent travel history. We believe that testing each donation addresses the risk of partially immune donors with chronic asymptomatic malaria infections. These donors, again, would be asked the same questions at each donation, and if eligible, their donations would be tested. Again, there would be repeat testing of all prior residents regardless of new risk, but again, this testing burden would be small. All other donors, as shown on the other side of the flowchart, would be assessed for recent travel history, and we propose testing donations from individuals who report a history of travel to a malaria-endemic area in the past three months. So FDA's second selective testing proposal, labeled here as 1B, includes one-time testing of all donors for malaria risk. This one-time testing would be performed on all donors regardless of

reported malaria risk, and donors who test non-reactive would be qualified for subsequent donation without testing, subject to their responses to the donor history questionnaire. Blood establishments must review their records to determine history of testing, and if the blood establishment does not have a record of testing, then the establishment must test that donor.

Blood establishments under this strategy would continue to assess donors for a history of malaria and travel to a malaria-endemic area in the past three months. And under this approach, blood establishments would not assess donors for prior residence in a malaria-endemic country. Once the one-time testing is performed, donors would only be assessed for new malaria risk because of travel. I'm not going to walk through this flowchart. You've seen this, but I just wanted to highlight the difference with this strategy. On the one side, of course, a donor that reports a history of malaria would be evaluated using the same algorithm I presented previously. If the donor does not have a history of malaria, they would then be evaluated for travel to a malaria-endemic area in the past three months.

So, this is simplified somewhat, in that there's no assessment for prior residence in a malaria-endemic country. Over the next few slides, I'll summarize the potential advantages and limitations of the proposed selective testing strategies. This slide highlights potential advantages for both strategies 1A and 1B. First, we anticipate that using a selective testing approach would be more robust than the current approach that uses donor questioning and deferral alone to address risk. Selective testing would likely identify donors at greatest risk of transmitting malaria, and potentially improve blood safety. Secondly, and importantly, selectively testing donors at risk for malaria would reduce donor deferrals associated with malaria risk. This could contribute to a diverse blood supply, for example, for patients with sickle cell disease that are

dependent on transfusions, and also help to address potential shortages and reduce urgent calls for blood donation.

And finally, a selective testing strategy reduces overall testing burden when compared to a universal testing of all donations. There are some additional considerations for one-time testing that we would like the committee to consider. A potential benefit of strategy 1B is that one-time testing of all donors would likely identify more at-risk donors with asymptomatic ongoing malaria infection than strategy 1A in the current deferrals. In addition, this approach also reduces some reliance on the donor history questionnaire to identify risk. It would require testing based on donor questioning, only for history of malaria and recent travel. And importantly, it eliminates a complicated algorithm to identify prior residents of malaria-endemic countries. Another potential benefit of strategy 1B would be that it eliminates the burden of repeatedly testing prior residents with no recent travel history at each donation. And finally, we note that blood establishments since 2010 have experience with one-time donor testing for T. cruzi.

Over the next two slides, I'll discuss the limitations of selective testing strategy. Notably, there are operational challenges in identifying only certain donations for testing. These challenges include potential issues in updating blood establishment computer software, failure of staff to follow standard operating procedures, and the use of unique collection equipment with the testing. Biological product deviations reported to FDA reflect the potential for error in identifying donations for selective testing. Between 2019 and 2023, 34 blood establishments reported the distribution of over 1,000 units that were not tested for babesia or T. cruzi, under the required selective testing strategy. And we recognize that potential for error may be greater for the proposed selective testing strategies for malaria, when compared with the regional testing approach for babesia or one-time testing for T. cruzi**,** because we've added donor questioning to

identify the donations for testing. To continue the discussion of limitations, we recognize both strategies for selective testing are dependent on donor history questionnaires, donor history questions to identify malaria risk, and donations for testing. Therefore, these strategies do not fully eliminate the challenges with nondisclosure of information by donors, and staff errors in assessing eligibility.

Although, as I noted, some questions would be simplified with both strategies. And a one-time testing strategy further reduces these risks. And finally, a limitation of any testing is a potential risk of false positive test results and required deferrals in a population at low risk for malaria. But based on the performance of the tests that you've heard earlier today, and our experience with testing using similar technology, we do expect this risk to be negligible. I'll now change course slightly and discuss testing strategy two, for regions in the U.S. with mosquito-borne malaria transmission. So under this strategy, we propose testing all donations in geographic regions in the U.S. with local mosquito-borne transmission, when reported by public health authorities. Testing would be initiated when a single case is reported, and discontinued when no new case is reported within a three-month rolling period.

We propose the region for testing could be defined by zip code initially and expanded as appropriate. And this strategy is intended to address the rare but potentially increasing risk of local mosquito-borne transmission in the U.S., as described by Dr. Williams earlier today. An advantage of this approach is that establishments could continue collecting in at-risk areas and avoid potentially local shortages. This approach, however, does require monitoring of local mosquito-borne malaria transmission and communicating with local public health authorities. And again, there is the risk of false positives, but we do think this is a negligible risk. So finally, I'll briefly discuss FDA's expectations for managing units and donors on the basis of reactive test

results for malaria. These considerations apply to all the testing strategies I presented. So, whenever testing is performed, there are certain actions blood establishments must take. Reactive donations must not be released for transfusion or further manufacturing use. And donors with reactive screening tests for RTCIs must be deferred and notified of their deferral and counseled appropriately.

We propose deferral for at least one year and until completion of medical evaluation and all prescribed treatment, if applicable. And donors would be requalified after the one-year deferral period and would be tested accordingly. In other words, a donor with a history of malaria would be tested at each donation under the proposed strategies. Currently, there's insufficient information to propose a testing algorithm for requalification before the one-year deferral period ends if false positive results are suspected. This could change over time, however, depending on the availability of future donor screening tests or confirmatory tests for malaria. So that concludes my presentation, and I'll just repeat the charge to the committee. We ask that the committee please comment on FDA's proposed strategies for selectively testing blood donations from donors at risk for malaria, using an FDA licensed NAD. Please consider Strategy 1A that involves selectively testing donors for a history of malaria, history of prior residence in a malaria-endemic country, and history of travel to a malaria-endemic area. We ask that you also comment on Strategy 1B, which entails one-time testing of all donors and selective testing for history of malaria and history of travel to a malaria-endemic area.

Finally, we ask that the committee comment on FDA's proposal that blood establishments should implement time-limited NAD screening of all donations collected in areas of the U.S. when a single case of local mosquito-borne malaria is reported by public health authorities. Thank you.

Dr. Szczepiorkowski: Thank you so much, Ms. Scharpf.

Ms. Scharpf: Yes, thank you for your attention. I'd be happy to address questions.

Dr. Szczepiorkowski: Yes, absolutely. We have about five minutes, and I'd like to now open to presentation and questions from the committee. So please raise your hand, and when called, turn your camera on and unmute your microphone prior to asking your question. Okay, Dr. Grossman, please.

Dr. Grossman: Thank you for your presentation. Just to put it in perspective, can you tell me the number of biologic product deviations that were reported for malarial history violations or errors?

Ms. Scharpf: I don’t have that, but we can look at, maybe over the lunch break, I can look and see what has been included in the report, the last published report. I can pull that up and report back to you after lunch.

Dr. Grossman: Thank you.

Dr. Szczepiorkowski: Okay. Dr. Bloch, next one.

Dr. Bloch: Hi, thanks. Also a really great presentation. I'll probably save comments for the discussion, but just to understand the charge a little bit more, are we just restricted to the proposed strategies? We can't talk about comments more broadly on what we think are the rationale for selective testing in general?

Ms. Scharpf: No, we welcome all comments. We're not limiting to the questions I posed. They're just to guide the discussion, but we welcome all comments.

Dr. Bloch: Thanks very much.

Dr. Szczepiorkowski: Any other questions? So let me just, again, clarification. So, in the context of individuals who lived in endemic countries over five years, for all practical purposes, they might be tested many times, or this is only for those who actually had malaria?

Ms. Scharpf: In strategy 1A, we would recommend testing their donations at each donation. Strategy 1B, after the one-time testing is performed, those donors would not be tested for that risk factor. Only for new travel to a malaria-endemic area.

Dr. Szczepiorkowski: Thank you so much for the clarification. Dr. Pandey?

Dr. Pandey: Hi, thank you so much for the summary. And so my question is about the strategy related to local cases, and I wanted to better understand the reasoning or the decision for basically to have the testing done, if there's a single case, you know, often I think a single case may not indicate necessarily a cluster or, you know, so that's one question, is why one case? And then also the three months, I think, was my other question. What led to the recommendation or proposal, I should say, of testing for three months if there's a local case?

Ms. Scharpf: Yep, we put forward this proposal, but we welcome the committee's comments, on the trigger of one case, as well as the timeframe that you would recommend is more appropriate for that timeframe.

Dr. Szczepiorkowski: Thank you so much. Ms. Cumming?

Ms. Cumming: Hi, yes. Just a question to make sure I'm understanding Strategy 1B correctly. Is it a correct statement to say that if Strategy 1B was in place, I know we've talked about the 13 cases that occurred over a 21-year period. Would the six cases that were missed due to process failure and unknown reasons theoretically have been captured if that one test strategy was in place? Is that a correct statement?

Ms. Scharpf: Yes. We do think that the process failures would also be captured by testing all donations at least once, or all donors at least once.

Ms. Cumming: Okay. Thank you.

Dr. Szczepiorkowski: Any other questions? Yes.

Dr. Maldarelli: Just a quick one. Thank you very much for the presentation. Was the three-month interval determined by the clinical data that's available or was that also tested in scenarios, and maybe done by predictive methods as well? So, estimating what might be able to be done with that test.

Ms. Scharpf: Yeah, no, I'm not sure we went into that much detail in proposing the three months. Again, we welcome the committee's comments. Yeah. And we'd consider other timeframes that could be more appropriate.

Dr. Maldarelli: Yeah, I wasn't clear. No modeling data went into that three-month deferral.

Ms. Scharpf: That's correct.

Dr. Maldarelli: Thanks.

Ms. Scharpf Thank you.

Dr. Szczepiorkowski: I don't see any more questions. So, this is the time for our 25-minute off to lunch. And at 1 o'clock, we'll reconvene and have the open public hearing. We have four presentations. And after then, with no break, we're going to move to deliberations by the committee. Thank you very much and enjoy lunch.

Open Public Hearing

Dr. Ziggy: Good afternoon again, it is 1:00, and we are restarting our meeting. I think the slide can go off. Thank you very much. Welcome to the Open Public Hearing session. Please note that both the FDA and the public believe in a transparent process of information gathering and

decision making. To ensure such transparency the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentations. For this reason the FDA encourages you, the Open Public Hearing speaker, at the beginning of your oral statements to advice the committee of any of your financial interests developments to this meeting. Such as financial relationship in a company or group that may be affected by the topic of this meeting.

In addition FDA encourages you to advise the committee of any financial relationship that you may have with the sponsor of the product being discussed at today's meeting, and if known other firms or products that may directly compete with the product being discussed.

For example, this financial information may include the sponsor's payment of expenses in connection with participation in this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude your from speaking. That's the important statement.

I would like to remind the committee members that they can ask short clarifying questions which are scientific in nature, and relevant to our deliberations today. I would also like to thank all individuals in organizations which provided thoughtful comments and suggestions to the docket. Your valuable time and input is greatly appreciated by BPAC and CBER. I would like now to had over the meeting to Ms. Christina Vert, who will lead our Open Public Hearing.

Ms. Vert: Thank you Dr. Ziggy. Before I begin calling the registered speakers, I would like to add the following guidance. FDA encourages participation from all public stakeholders in its decision-making process. Every Advisory Committee meeting includes an Open Public Hearing session, during which interested persons may preset relevant information or views. Participants

during the OPH session are not FDA employees or members of this advisory Committee. FDA recognizes that the speakers may present a range of viewpoints. The statements made during the open public hearing session reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate agency agreement with the statements made. Now I will introduce the first open public hearing speaker. Next slide, Dr. Linnen, go ahead.

Dr. Linnen: I appreciate the opportunity, go to the first slide, please, to give this talk today. I'm going to provide some information on the Procleix Plasmodium assay on the Procleix Panther system. This is a molecular assay that has been developed for screening blood. It is not approved in the US, but it is CE marked, and it's approved in a number of countries outside the European Union. And as indicated by this slide, I am an employee of Grifols Diagnostic Solutions based in San Diego, California. As I mentioned, this assay is not approved in the US. I will mention the MESIA assay, which is US licensed and CE marked.

Okay, so the Procleix Plasmodium assay qualitatively detects five species. This is really important for an assay like this. Probably the most important thing to stress about the design of the assay is that it targets 18S ribosomal RNA. And I have to thank Susan Galel. I think she made a number of excellent points and makes it easier for me, and I'll expand on some of those points. So everything that I talk about in terms of performance is related to the CE marked assay. So that assay is intended for screening blood donations in individual whole blood lysates and in lysate pools. And I want to point out here that according to one publication, the average, a number of copies of 18S ribosomal RNA, about 10,000 copies on average per parasite. And I think that's very relevant to the design of the assay. And I think it's key for the potential use of lysate pools as an effective screening approach. Other very important point that I wanna make is that we intend to pursue licensure in US and Canada. And so that effort is underway.

This slide shows some detail of the workflow for the assay. So the important thing to realize is that this assay requires a whole blood sample. So in the case of this assay, we use a number of different standard whole blood tubes have been validated. The assay uses 0.9 mls of whole blood. It is added to something we call parasite transport medium. This is a proprietary solution that lysis the red cells, opens up the parasites, and releases thousands of copies of ribosomal RNA. So you can see then we can create an individual donor lysate but aliquots from that can be used to create pools of lysate. So again, to repeat the point that was made earlier in the day of ribosomal RNA. So either the individual donor sample or the pooled lysate then can be tested on the panther system. I'll point out that these steps of adding the whole blood to the lysate can be automated. And this is the other shown there, the Procleix Express system, or for very low volumes, it can be done manually. And really very important point to make about this.

This is not a new workflow. This is the same workflow that is used for the Procleix Babesia assay, which I would guess that maybe over 10 million donations have been screened. So this is a workflow that is used every day in the US. Now, if you go to the next slide and add a little bit more detail to this slide to really emphasize the point of, because it may be counterintuitive that testing an individual lysate or pooled lysate could have equivalent clinical sensitivity.

So if you assume that around 10,000 ribosomal RNA copies are present in each parasite, if there is at least one parasite present in that 0.9 mL sample, there would be, based on the dilution factor, almost 2,800 ribosomal RNA copies present. So that's a very high level. So if that, and you'll see what I mean when I show some of the analytical sensitivity data. Even if that's pooled, and we outside the US have a claim for up to 16 lysate pools, the concentration still is 174 ribosomal RNA copies. And if you consider an average value for the LOD of the assay of

around 10 copies of RNA, you can see that that is 15 to 17 times the LOD. So we think that you could expect detection in a pooled sample with the same reliability as a individual lysate. So this will be a little bit clearer on the next slide.

I want to highlight a manuscript that came out the beginning of this year. So Laura Tonetti was the senior author. So this was done in collaboration with Laura Tonnetti and Susan Stramer, both at the time, the American Red Cross. In this paper, we described some of the performance characteristics of the CE-marked assay, and then some interim results from a research study that is still underway today. So in terms of analytical sensitivity, it's very important to look at the analytical sensitivity in two ways. What's the LOD for detection of RNA copies, based on what I showed you on the previous slide, and also what's the LOD for infected red blood cells per ml? So you can see, what I'm showing is the range for the 95% limit of detection, and that's the range across the five clinically relevant species. And then I'm also showing similar data for the infected red blood cells with the clinically relevant species also. So very sensitive for detection of ribosomal RNA, ranging from 8.5 to just under 12 copies per ml. And for red blood cells, we typically see in experiments two to three copies. These experiments are highly dependent on the original value assignment of the stock, but what we showed here was around two to 6.8 infected red blood cells per ml, 95% detection.

As I mentioned before, we would expect clinical sensitivity to be equivalent in the two testing formats that we're using for the CE-marked product, and that's what we saw in our testing, 100% in both individual and 16 donation pooled lysates. And so this represented 50 clinical specimens, known positive samples, and then there was a replicate testing to show the reliability. And so in every case, all replicates were reactive in the study. So this clinical

sensitivity was very reliable. Specificity is very similar to other NAT assays, range from 99.99% to 100% in testing 16 donation pooled lysate pools.

We also tested deferred donors. These were all US deferred donors. What was reported in the manuscript is 862 deferred donors. All of these were under a three year deferral. We detected one confirmed positive, so 0.12% for this data set. This was an infected donor that was a prior resident of a malaria endemic area in West Africa, and was confirmed positive individually and in all pooled lysates that were tested. This donor remained NAT positive for 13 months. And I'll just point out that through the entire study with this donor, and this donor participated in a huge number of follow-up visits, I think a total of 19 follow-up donations were tested, remained antibody positive over the follow-up testing, but all samples were antigen negative. So the rapid test that was used was just simply not sensitive enough to be used in this context.

So I think I can just, this is a very brief presentation. So just to reemphasize, I've described a CE marked assay, and we intend to complete a clinical trial to support licensure in the US. And hopefully between Susan's talk and my talk, you realize that this new class of assays that detect 18S RNA really increase the sensitivity of the assay. So the detection of 18S ribosomal RNA is a critical aspect of the assay's design, and is expected to substantially enhance clinical sensitivity, and may allow screening in whole blood lysate pools. You can see in some situations where that could be very useful. It certainly streamlines the amount of work needed in the blood testing lab. So the other really important point to emphasize: this assay workflow is, the actual workflow is identical to what is used for Babesia in a routine basis every day in the US. And just to point out that, and I think this point was made by Dr. Eder earlier in the meeting, that the intervention for Babesia with NAT testing has been very successful. There have been no cases of transfusion transmission of Babesia of tested blood. Okay, and so for our product,

almost all of the testing maybe exclusively is done in 16 lysate pools for Babesia. So to sum things up, we believe that highly sensitive plasmodium nucleic acid testing can play an important role in both blood safety and availability.

And so that concludes my presentation. I just would like to thank you again. So if you go to the next slide, we'd be happy to answer any questions if there are any.

Ms. Vert: Okay, I don't see any questions. I think we can move on to the next speaker, Dr. Gorlin.

Dr. Gorlin: Thank you so much. I have no financial disclosures to make. I am presenting on behalf of America's Blood Centers. First, I thank the FDA for using the Blood Products Advisory Committee to review evidence to determine how the newly approved malarial NAT screening test may best be used.

ABC recommends delaying publication of a draft guidance on malarial testing until real world modeling studies help determine the clinical sensitivity of available tests in specific donor populations. Virtually all US cases of transfusion transmitted malaria in the last two decades were from asymptomatic donors, originally from endemic countries. Those individuals are known to have relatively low levels of parasitemia relative to symptomatic cases. So we want to ensure the assay's sensitivity is sufficient. While clinical studies may not be feasible, we recommend waiting for completion of modeling studies demonstrating adequate clinical sensitivity, as well as the approval of more than one test prior to issuing guidance. In any case, we applaud FDA's consideration of allowing multiple future options for usage of this assay. We heartily agree with FDA that universal testing at this time would be quite cost ineffective. ABC encourages FDA to ensure that any testing-based strategies for blood safety apply evidence and risk-based decision-making and are justified by commensurate increases in safety. ABC

recommends that FDA maintain allowing the current deferral options, given the fact that there's only been 13 cases in the last 21 years out of over 200 million donations.

We recommend they allow current deferral options while also allowing for a selective testing strategy to qualify a donation after returning to the US following a short incubation period for individuals who travel to an endemic country, but who are not prior residents of a malarial endemic country. These donors are not transmitting malaria via transfusion and are unlikely to have ongoing low-level parasitemia. One-time testing of all donors is even less likely to have additional yield given Dr. Galel's data that she just shared of zero out of 60,000 yield today. Furthermore, our centers support the option for collection centers to use the test to qualify donors by former residents of malarial endemic countries, assuming modeling predicts no decrease in safety.

That said, this option also requires careful consideration of the logistic challenges, given the off-changing map of which countries and which regions were historically endemic. Certainly, many countries within Sub-Saharan Africa have changed names and borders over the indefinite look-back period.

Given the recent cases of autochthonous malaria in Florida and other states at our southern borders, ABC supports the potential for testing strategies for donations in regions with local mosquito-borne malarial transmission, but recommends having a higher minimum threshold than a single case for triggering testing determined through the recommended modeling studies. ABC also recommends FDA follow CDC guidelines starting a rolling eight weeks of testing after the diagnosis. ABC concurs with the strategy of defining geographic regions by zip code, recognizing the diverse array of sizes those zip codes actually represent.

In short, we appreciate FDA's willingness to consider multiple options for utilizing the malarial screening after completion of modeling studies. And I thank you very much for this opportunity to share America's Blood Center's thoughts on this endeavor. Thanks again.

Chairperson Vert: Thank you, Dr. Gorlin. We will now move on to the next speaker. Dr. Vassallo.

Dr. Vassallo: Hello, I'm Ralph Vassallo, incoming chair of AABB's Transfusion Transmitted Diseases Committee. I'm also chief medical and scientific officer for Vitalant, which is a co-owner of Creative Testing Solutions, a large US blood testing organization. That's my only financially relevant discussion.

On behalf of the Association for the Advancement of Blood and Biotherapies, AABB, America's Blood Centers, and the American Red Cross, I appreciate the opportunity to present this statement in support of FDA's consideration of strategies to reduce the risk of transfusion-transmitted malaria. Our organizations believe an FDA-licensed nucleic acid test for malaria holds promise to maintain or improve blood safety. The testing strategies may improve availability by removing unnecessary donor deferrals, which will also support a more diversified blood supply, particularly among subsets of donors with uncommon phenotypes, such as donors from Latin American, Asian, or African countries. We do note that there are no clinical studies demonstrating the licensed assay does in fact reduce the risk of transfusion-transmitted malaria, and some members have expressed concerns that the analytic sensitivity of that test may not detect levels of parasitemia sufficient to transmit malaria to transfusion recipients, especially asymptomatic donors with semi-immunity. FDA should support formal modeling studies designed in consultation with malariologists using the best available assumptions about parasite levels during asymptomatic infection before issuing final guidance. Assuming the results suggest

good clinical sensitivity of the test and donor populations, a substantial likelihood that transfusion-transmitted malaria will be reduced, and reasonable cost-effectiveness, our testing recommendations follow here. They are ninefold.

Number one, our organization strongly support FDA's consideration of multiple strategies to reduce the risk of transfusion-transmitted malaria to meet the unique operational and budgetary challenges of blood collectors, large and small.

Two, we support flexible testing selected strategies for donors with material risk of malaria identified by revised donor screening questions to establish donor eligibility using an FDA-licensed nucleic acid test, which will protect blood safety and remove unnecessary deferrals.

Three, with respect to the selective testing of donors with material risk of malaria, we urge FDA to provide flexibility, specifically permitting blood establishments to continue current questions and deferrals without testing. The operational considerations will vary, and it is clear that some facilities might opt to continue use of the current donor history questionnaire, avoiding testing except in the setting of local transmission reported within the US. So we ask to please clarify the path for a deferral-only strategy as an alternative to testing in all other circumstances.

Four, we support consideration of the option of universal testing with removal of all malaria risk screening questions as one of several strategies that may be available to blood establishments to address all three failure modes of current donor history questionnaire screening.

Five, we support FDA's approach to permit the use of an FDA-approved pathogen reduction device effective against Plasmodium falciparum according to manufacturer's instructions for use instead of the use of the screening questions followed by nucleic acid testing.

Six, we support time-limited nucleic acid testing of all donations collected in defined zip codes to address local mosquito-borne malaria transmission reported by public health authorities. This approach offers an alternative to substantial donor losses and or complex donor qualification interventions at centers affected by locally acquired malaria. However, since many individual cases have historically not been associated with clusters, consideration should be given to a higher trigger for testing than a single reported case. FDA should also comment on the use of alternative approaches such as enhanced post-donation surveillance as currently practiced in Florida.

Seven, we support resources to develop and maintain a reporting platform similar to the West Nile Virus Biovigilance Network to provide effective malaria risk mitigation through timely notification to all centers impacted by local transmission and FDA's consideration of recommendations in guidance to address inevitable questions on donor travel to U.S. geographic areas reporting local malaria transmission.

Eight, we support an extended implementation timeline to promote blood safety by providing adequate time to complete complex changes, including time to assess budgetary implications, planning for changes in donor screening and testing processes, blood establishment, computer system modifications and validation, extensive staff training and implementation of new screening assays.

And last, we recommend FDA review our written statement with additional information on background and other details that should be considered by FDA.

Thank you for the opportunity to present this statement.

Chairperson Vert: Thank you, Dr. Vassallo. All right, our next speaker. Mr. Williams.

Mr. Williams: Hi, we at Pride and Plasma and myself have no financial relationships to disclose. We understand that the committee did not intend to discuss gender diverse blood donors today and we appreciate the committee's allowing us to speak despite this.

With the transition from a lifetime deferral for MSM, men who have sex with men blood donors in 2015, the FDA included language endorsing gender affirming practices for transgender and gender diverse blood donors who identified as either male or female. Although this does not represent all gender diverse blood donors, namely non-binary, gender non-conforming and other identities, it was a step in the right direction and was included in the 2020 update that reduced the 12 month deferral to three months. When we say gender diverse, we mean gender non-conforming, transgender, non-binary, and other identities other than cisgender men and women. Current blood donation practices are not inclusive of these individuals. The experience of donors can vary greatly from state to state and from facility to facility.

The issue at hand is not that gender diverse people want to help their communities, but instead the current practice guidelines do not acknowledge their existence. This fails to intentionally promote welcoming spaces for all donors, resulting in underutilization of certain donors as well as potential recipient risk. Current practices may limit donors with a history of pregnancy from donating platelets and or plasma due to a risk of HLA antibodies that leads to a risk of Transfusion Related Acute Lung Injury (TRALI). If blood donor facilities only ask female or female presenting donors questions related to a history of pregnancy, transgender men and other gender diverse donors who have a history of pregnancy could give platelets and or plasma that have increased concentrations of HLA antibodies.

The prevalence of TRALIs is also difficult to assess using available data on TRALI mortality. Even if a patient does not die from a TRALI, they could end up on ventilators

requiring prolonged hospitalization or suffering additional adverse effects. One of the most common side effects of exhaustion is testosterone administration that is increased by blood self-production. This is significant enough for cisgender men undergoing testosterone replacement therapy to be prescribed therapeutic phlebotomy to donate blood at intervals more frequent than the typical minimum of eight weeks between appointments. These same side effects will likely be seen in a similar effect in non-cisgender recipients of the same prescriptions. These donors could be some of the safest donors from a donor risk perspective.

Further, transgender women and other gender diverse donors who have not been pregnant may be deferred from donating plasma or platelets. These individuals could not have the same risk for HLA antibodies and therefore TRALIs. Some of these facilities are not limited by intent or a lack of interest in inclusive practices, but by the computer systems that they use. We saw delays in updated policies and implementation of the new individual risk assessment due to the limitations in these computer systems. These delays and limitations will continue to affect the care and speed of implementation by blood banks and employees. As a registered nurse who not only donates blood, but administers blood products, I understand the necessity of ensuring safe donors being able to donate, as well as welcoming them into environments that promote repeat donations.

We recommend that the FDA recommends to all donors to be asked for a history of pregnancy to ensure that no donors fall through the cracks when assessing for risk of HLA antibodies related to TRALIs. Similar to the advanced study, we support the research on the current practices, potential changes, and the impact of said changes on donor populations, as well as recipients.

Lastly, in an era of chronic national shortages, fully utilized donors of all blood products, especially those with unique conditions that can elicit safer donating, such as transgender men undergoing HRT with testosterone and transgender women donating platelets and plasma.

Thank you for the opportunity, and we hope to see more inclusive policies and recommendations via new guidelines from the FDA, CBER, and VBAC.

Ms. Vert: Thank you, Mr. Williams. This concludes the open public hearing. I now hand the meeting back over to Dr. Ziggy.

Open Committee Discussion and Recommendations

Dr. Szczepiorkowski: Thank you so much. Thank you for all those who participate in the public open hearing. We appreciate your time and thoughtful analysis of the FDA approach. So now, we've decided not to have a break because we're about half an hour ahead of the time. So we'd like to present the slides, which will be our questions for the committee.

Before that even, I can say one more thing. This is the update from CBER regarding number of BPDRs, which were related to malaria testing or malaria.dhq. There are currently about 4,000 to 6,000 of those per year. So that obviously caused a lot of trouble in our industry. So in that the most common area of BPDRs. But having said that, we can move to the first question discussion. Correct? Okay.

So I will read that slide first, and then we'll go to individual questions. So I'll read both of them first, and then we'll go individually and discuss. So to remind all of us, we've seen those slides a couple of times today. Please comment on the FDA's proposals or charges. Comment on FDA's proposed strategies for selectively testing blood donations from donors at risk for malaria using an FDA-licensed NAT.

Strategy 1A, selective testing for history of malaria, history of prior residence in malaria-endemic country, history of travel to a malaria-endemic area, and then tests. We've seen those algorithms.

And then strategy 1B, the difference is that's a one-time testing for all donors and selective testing strategy for history of malaria and history of travel to a malaria-endemic area to follow. Now, the second group or second component of our deliberations today is to please comment on FDA's proposal that blood establishments should implement time-limited NAT screening of all donations collected in areas of the U.S. when a single case of local mosquito-borne malaria is reported by public health authorities. So I think, is the next slide just a brief number of strategies? I'm sorry. Exactly, perfect. All right, thank you. So it's a bit of a complication because there are many of us, 13, and I'd like to hear from all of us so we can divide it and slice it different ways. I would presumably suggest if the committee agrees that I'll ask individually, unless there's any comment before that, internal comments from anybody, maybe start with that. Anyone has a comment, a general comment for the question number one at this point? Please raise your hand. Okay, I see Dr. Grossman, please.

Dr. Grossman: Okay, so the reason I asked the question about the biologic product deviations is because I know it was huge. And with strategy 1A, if I understand correctly, we would not be testing those 4,000 to 6,000 because they made it through the system, wrongly so. Is that correct?

Dr. Szczepiorkowski: That's a good question. I wish we had the graph. Because we're focusing on malaria first. Is Jennifer maybe on? Yes, so someone from CBER. Can you clarify for us? Ms. Scharpf?

Ms. Sharpf: Oh, yeah. Sure.

Dr. Szczepiorkowski: Anne, thank you.

Dr. Eder: So Dr. Grossman, you are correct. That's how we're thinking about it.

Dr. Szczepiorkowski: Okay, thank you. That was the question. Amber, anything else? Dr. Bloch, you were for a moment raising your hand. Are you still having a question?

Dr. Bloch: I was just, sorry, are you gonna go around individually at NCR and are you gonna do this?

Dr. Szczepiorkowski: Yeah, I think at this point, given something that nobody's raising hand, it's good for you, Dr. Grossman, I think we just go individual one by one and allow people to opine on the discussion with question number one. I think that will help us to identify the at least sentiment of the committee. So if that's okay. You could be first, if you'd like.

Dr. Bloch: Who's going first, me?

Dr. Szczepiorkowski: Yeah, how about that?

Dr. Bloch: Brilliant. So first thanks to speakers, really superb presentations. So just from what I've taken away from that, I think the testing is robust, really exquisitely sensitive sensitivity and specificity. But I think that the question seems to be less about whether selective testing will be effective and rather whether the risk actually merits the cost and complexity of intervention. So just looking at the data, the CDC, well, the first one was presented was the Mungay data from New England Journal which is almost 25 years old. At that point, there was probably one to two cases per year of transfusion transmitted malaria.

The more recent data is actually less than one case per year. So I think in some of the materials that were circulated, it's looking at a risk of about one in 10 million. People have cited Babesia as an example. It's a related parasite and there are certainly parallels, but there's also significant differences. So for one, Babesia is highly endemic in the US. So there were numerous cases prior to intervention.

And the second piece is a risk-based deferral was ineffective, which accounted for why there was such high residual risk. Given the current strategy of risk-based deferral, that's not the case. There seems to be pretty effective at safeguarding the blood supply. So the question is, is this really worth it? There's a lot of, you know, the counter arguments is certainly there's a lot of donor loss. A lot of those donors who are deferred are never going to return. I think it's about 30% don't return and that should be considered. And then there are questions about diversity of the donor pool, which is also merits attention. But, you know, it probably needs some sort of modeling study on both sides to look at what is the cost per case averted versus the associated negative health effects of the current strategy. So those are a couple of things.

There was some other, you know, the projected number of donations per year from what we've said is probably 50 to 150, 160,000. And, you know, just as a kind of, just maybe this is a little bit lateral, but having one manufacturer, if we are going to proceed with a selective testing strategy, are they committed to support that market, which seems to be pretty small compared to conventional screening. So for considering Babesia, which is regional versus the major viruses. So just a couple of, you know, initial thoughts.

Dr. Szczepiorkowski: Can you also comment on the strategy 1B?

Dr. Bloch: So strategy 1B, I think is going to be enormously expensive and low yield. Again, when one's looking at preventing one, at best, one case per year. And so, you know, just, there is certainly changing epidemiology, climate change will affect things, but I don't think that that's linear or predictable. As in, if you look at I know this more from kind of the tech literature, is that with climate change, it can adversely or favorably affect vectors. So it can go in either direction. So I think we potentially conflating two different issues. So one is background risk of malaria and other vector-borne diseases. And the other is specifically transfusion focused. And

there's a long history of where those are kind of mixed up, where it doesn't necessarily translate. So I think strategy 1B would be really excessive.

Dr. Szczepiorkowski: Thank you. So thank you very much. That's very helpful. I think in summarizing what I'm hearing is that 1B, and again, the cost as we learn from FDA is not our consideration. Our consideration is potentially ability to improve the transfusion safety, but also in a reasonable way. And what I'm hearing from the exertion 1A, you believe that there's also an issue there and the current scenario, which is kind of testing, well, not testing, lack of testing, but we're doing relatively well.

Dr. Bloch: So, yeah, if unless there's a change in incidence, it's going to be very difficult to actually show an improvement on current strategy. That's kind of my gut feeling on that.

Dr. Szczepiorkowski: Thank you. Okay. Dr. Ballow, I think you raised your hand, so.

Dr. Ballow: Yeah, I wasn't really going to comment on A or B, but I just wanted to follow up on this issue. What we haven't discussed, and that's climate change and what we saw in Florida in 2023. So I'm not an expert in infectious disease in this area, but I'm wondering exactly whether we're going to see more malaria in warm climates, tropical, subtropical climates in the Southern United States because of climate change and therefore an increase in risk as we saw in 2023 in Florida. So I think it, you know, it behooves us to perhaps gather more data. And one way of gathering more data is by implementing the recommendations of the FDA.

Dr. Szczepiorkowski: So could you now mind commenting on both the strategy 1A and strategy 1B. It sounds to me like you are a potential proponent of actually implementing something, but which model?

Dr. Ballow: I think 1A is fine.

Dr. Szczepiorkowski: Thank you so much. Sridhar, I think I have a few, actually, Dr. Ahuja, I'll go to Dr. Ahuja first. I think I missed. Sorry.

Dr. Ahuja: Yes, hello.

Dr. Szczepiorkowski: Would you mind commenting on the question number one?

Dr. Ahuja: Yes, thank you. Thank you for the great presentations and some of the public comments as well.

First about 1B, I feel that based on the incidents and in the number of cases we see, 1B seems a little bit more than what we need for a safe administration of blood products. So one-time testing would be a little bit excessive in this current scenario, unless, as the previous person said, the incidence changes because of climate change, then it will have to be reconsidered. So one caveat to any recommendation that we do would be based on the current caseload, obviously, and will have to change based on changing epidemiology. I would prefer 1A selective testing based on the data that's being provided and the, you know, specificity and sensitivity of the NAT testing that was discussed before.

There was one comment that I wanted to make was 1A strategy is based off of the question of ever diagnosed with malaria question that is posed to the donors. Now, we have to remember that in a lot of countries, diagnosis of malaria is sometimes empirical based on fever patterns and there is so much of malaria that some people get just treated empirically with malaria. Now with that strategy, of course, you would probably catch more people than they may not be needed, like in instance, like they may not really have had malaria, which is fine, but it also can eliminate some people who are either not treated or based on that question alone. So, but otherwise I would prefer 1A strategy. Thank you.

Dr. Szczepiorkowski: Thank you so much. Sridhar, I think you're next.

Dr. Basavaraju: Yeah, thanks. So I had one question I was hoping that either the FDA lab experts or Susan Galel might address, and that is the comments that were made by the public speakers about the sensitivity of this test and not necessarily identifying infected donors. As I watched Susan Galel's presentation, it seemed to me that prior malaria infected donors that had resulted in transfusion-transmitted malaria would have been identified through a testing strategy, but I guess I would be interested to hear some clarification. Regarding my comments on the strategies 1A and 1B as part of our discussions here at CDC prior to this meeting when we, one thing that I learned was that there are maybe one to two countries a year that are no longer malaria endemic and that have achieved malaria elimination or eradication, I'm not sure what the term is. But it would seem difficult for a blood center to go back in time, ask a donor where they may have traveled and figure out if during that time of travel or residence that country was malaria endemic, subsequently had eliminated malaria.

So, I mean, I think that strategy 1B, I mean, I think there's definitely some credibility to the concerns that it might be overkill, but I think a one-time testing of everybody would allow for a clean slate and you sort of start over with a clean slate and then you then can risk stratify donors in more or less real time, figuring out where they went, whether that place is malaria endemic and then test them accordingly. I mean, I think that the arguments against continuing deferral versus testing to me are not that compelling. The reasons are that somewhere around 150,000 people a year are showing up to donate blood. And as was described, most of these people probably are from minority communities that might have diverse antigen profiles. They're also actually willing to donate blood and it would seem smart to try to get them to actually donate blood and use the blood because if the argument is that we have periodic shortages in certain blood groups, it's useful to actually figure out how to exit blood from those individuals

whose sole risk might be because of malaria for which there would be a viable testing alternative.

So, I think that not only I think is it that there is some benefit in allowing people to actually identifying infected donors, but also the idea of not having to unnecessarily defer people just because of malaria risk for which you have a viable test.

Dr. Szczepiorkowski: Thank you so much. I don't have many clarifying questions. So, if someone clears the 1B for the donor, so this is a person who lived in Africa and now is malaria free, is tested one time, is negative, then travels and to home country, comes back and it's six months later, not three months later, but six months later. Would you concern that this person may either have reactive diseases or actually additional malaria bringing from the country of origin?

Dr. Basavaraju: I mean, I think if they're tested, I would be comfortable with that. I mean, I guess that would be-

Dr. Szczepiorkowski: They won't be tested, yeah.

Dr. Basavaraju: I don't think they will be tested. I thought for travel, they would be, right? I mean, I guess we'd have to ask-

Dr. Szczepiorkowski: Yeah, if it's three months.

Dr. Basavaraju: Our senior colleagues to clarify. Okay. But yeah, it's above three. Yeah, right. I see what you're saying.

Dr. Szczepiorkowski: Yes. They would not be tested in that situation at six months, right? I mean, I think that that is reasonable.

Dr. Basavaraju: Okay. No, great. Thank you so much.

Dr. Szczepiorkowski: That's good. And of course, I see someone from FDA, who I think I'll say maybe Dr. Ahuja's question, or actually Dr. Ahuja's, I guess. Or yours, actually. Sorry, Sridhar, that was your question.

Dr. Kumar: Hi, Kumar. Sanjai Kumar from FDA. Would it be okay if I go ahead?

Dr. Szczepiorkowski: I don't think we can see your slides. You can just go ahead and-

Dr. Kumar: No, no, no. Just make a comment here, actually. Just wanted to make a comment about sensitivity of these NAT tests. So we need to not over-interpret the results. In regard to the copy number of RNA by 18S ribosomal RNA genes, the falciparum exist only as ring-form parasites. And the transcription increases as the ring-forms progress from invasion time to 24-hour time before they become late trophosvirus and schizogeny begins. So it depends when you determine the copy number, whether it's from the patient blood or from culture systems. So some studies have determined the copy number only to 1,000 RNA. Others claim to 10,000. And the methods will greatly vary. And I think what will matter most if this RNA determination is done from patient samples, because that will make a whole lot of difference. So that's my comment, number one. So we need to be careful about pooling data in terms of what will be captured, will not be captured based on RNA copy number coming from live samples.

The second point I would like to make is falciparum only ring-forms appear, but other malaria don't sequester that much, viavex, malaria and all. You will have multiple forms, multiple stages, late schizons, early trophozoites, and the copy number will vary there very greatly also. So just the comment about sensitivity determination. Yeah, so the data which has been presented, we have reason to believe it will be sensitive enough. And we hear these concerns about the low number of TTM cases in recent years. So that could be more of a success story because the donors are more informed now. FDA policies are more clearly defined.

Definitions are clear now really. So I think we have to keep all these things. How much risk exists there at population level? You have to keep all that into account. Yeah, sure. So Dr. Eder.

Dr. Eder: So we wanted to comment on the public comments that were concerned about predictions about the test performance. And from the data that was presented, the arguments that they're using are flawed. And from the data that we have, as Sanjai said, we believe the test would be sensitive and has proven sensitive in the cases that Dr. Galel presented of actual transfusion and transmitted malaria cases where they called the donor back and performed less sensitive PCR tests that were still positive. So for those reasons, although admittedly it's indirect, we believe there's more evidence to support that the test will work to detect asymptomatic parasitemia than it won't work.

Dr. Szczepiorkowski: Thank you, Dr. Eder. Thank you for your comments. Okay. Ms. Cumming, I think you're next on my list. I'd like to make sure that everyone has a chance to comment on those, please.

Ms. Cumming: Sure. So my thoughts on strategy 1A and 1B, if I'm interpreting the information correctly, is that both would return or allow far more diverse donors to the donor pool, which is a positive. The difference would be that strategy 1B would potentially prevent half of the 13 or so cases that we saw over a 21 year period if it had been in place. So we're talking about potentially, based on data to this point and climate change and things such as what Sridhar suggested about what's considered an endemic area and what isn't changing over time can change this. But it appears to me that the differences for a great cost for strategy 1B, we would have potentially prevented six cases, but both have the additional benefit of adding more diverse, critically needed donors to the donor pool. And so the question for me is the extreme, what I think would be probably an extreme cost for 1B to be worth it. And so I'm a bit torn. I'm leaning toward 1A as

my preference, just because of that. I think both would potentially be an improvement. And so I think those are my thoughts on 1A and 1B, unless I'm misinterpreting information.

And then as far as strategy two goes, the concept of having a higher threshold than a single case in a zip code was raised. And I'm curious about that. And it might've been helpful to maybe see additional data on the local outbreaks in the US over time and the numbers of cases. I know with West Nile virus, a single case does trigger pooled testing in a jurisdiction. So it would be consistent with that. But I am curious about other thoughts on whether or not raising that threshold might make sense. Thank you.

Dr. Szczepiorkowski: Thank you, Ms. Cumming. We'll come back to the question number two. I'd like to focus on question number one. Thank you for the clear comment. Sridhar, I think you have a comment to your question or?

Dr. Basavaraju: Yeah, my understanding, I guess if I could be corrected if I'm wrong, all of the cases of transfusion transmitted malaria would have been identified in strategy 1B, right? Because everybody would have been tested once.

Ms. Cumming: I believe so.

Dr. Basavaraju: So that would have identified the people who had remote travel. And then the new cases, the six cases that Melissa was referring to, I think would have also been identified, right? Or maybe not. I'm not sure. I don't remember.

Ms. Cumming: In 1B, I think they would have. I'm talking to the process failure cases would not have been captured by 1A. They would have been captured by 1B with a universal one-time test.

Dr. Basavaraju: Right, you're right.

Ms. Cumming: But –

Dr. Szczepiorkowski: I think we have to look at it. Yeah, go ahead.

Ms. Cumming: I was gonna say, but to the point you made Dr. Ziggy earlier about, what about someone who's six months out and then wouldn't be tested in strategy 1B? Do you then negate the gain of those six cases by having a strict sort of three-month timeline and only testing travelers in strategy 1B? So over time, would you lose that potential benefit is a valid question, I think.

Dr. Szczepiorkowski: And I think the other valid question might be that it will happen overnight. So the strategy 1B will maybe stretch over a number of years before every single donor, if they decide to return, will actually be tested. So that's another aspect of practicality of that. So Suchitra, I guess I will give you the day's spot now. You can comment. And then we'll return to the list of my people here.

Dr. Pandey: Yes, so thank you. You know, I just, I did have one follow-up question before I can just share my overall thoughts about strategy 1B is that when you have someone who is in a setting of like a semi-immune type of persistent infection, is the parasitemia intermittent? So this was a question I didn't ask during the presentations, but where, you know, if you did a one-time testing of all donors based off, you know, so then you won't need to question them anymore about have they ever had residents in one of these countries, but could those individuals not be picked up if parasitemia is intermittent? If you just do a one-time testing, could you miss them in the future?

So that was one question I wasn't sure of that answer. If the assays are sensitive enough to pick it up, if you just do that one-time testing and you don't test anymore for a resident's history, if those individuals have this semi-immune persistent infection with intermittent parasitemia, then you don't have parasitemia, though.

Dr. Szczepiorkowski: So your concern is that that level of parasitemia will be variable and therefore on occasion, those donors will be negative on the test irrespective of how sensitive the test might be, just because of the circumstances, okay.

Dr. Pandey: Yeah, that's a question which I'm not sure. And so, you know, for 1B, that was a question I had, because then could you potentially miss if you don't test the donor again for resident's history? But in general for 1B, if I'm looking at these two strategies, and, you know, I think there is also significant increased testing burden, and as others have said, with strategy 1B and, you know, so in terms of the two strategies, 1A versus 1B, I think I would lean more towards 1A, but I do wanna say, you know, my role is to be the industry representative. And we did hear from in the public hearing, the opinions of the community and the industry with blood centers through ABB and ABC, ARC. And basically, I think other than the issues and concerns that have come up about additional studies and modeling and really trying to be able to determine better the analytical sensitivity, especially in very low parasitemia, although we did see some data, I think that supports that this is a very sensitive assay.

I think the other key point to emphasize that has come up in both discussions I've had and also in these public hearings is flexibility and the ability for, when you already have a current strategy with the questioning. And albeit, I recognize the loss of donors from potentially unnecessary deferrals and the importance, and I applaud FDA for having this in their reasoning, the blood availability, the safety in addition to blood availability and diversity of blood donors. I think there's still the current strategy that is there present with these, with the questioning has been shown to be safe with only, and I think Evan shared some of this one in 10 million or one case every two years. So the current strategy is safe as well. And I think the thought is that if we go, like I said, for my personal or thought as the industry rep strategy, 1A of these two would be

the preference, but can there still be, as we heard from some of the public hearings that an alternate to the testing and still blood centers could determine to maintain the deferral strategy, I think is very important as well.

Having that flexibility has been proven to be safe. And we know that different blood centers, blood centers are very different with the current risk, even based off their donor populations. So if a donor center already has, you know, their blood donor population in general, not as many travel deferrals or residency for them to continue on using deferrals, if that's an option that would be a safe approach. So I think the general thing I have heard is essentially the FDA or can the FDA consider in addition to selective testing. So strategy 1A, let's say, still having that option of deferral based strategy as well. And one last thing I will say is strategy 1A, if you go into a little bit of the details, I think there is still some questions about, for example, the question, have you ever lived in a malaria endemic country? There are challenges. We've heard about some of that with just trying with how things have changed with what countries are endemic, not endemic. I think there's concerns about how an accurate history will be obtained.

And one last thing I will say, and then I will pass the mic, is a very important consideration is this, and we've heard this, the selective testing model based off questioning. I think it's an important strategy to think of it that way, but it's new. I think blood centers, Beck systems, many of them may not be designed to do this sort of selective testing. There probably will be some level of manual, and then that does also increase the risk of errors. So we will, it's like you solve some issues with errors being made with maybe less complex questioning, but I think there will be new errors that will be potentially seen because of some of the challenges with selective testing in this type of setting based off questioning.

Dr. Szczepiorkowski: No, thank you. I appreciate that. I think there are definitely also good thoughts. Ms. Cumming?

Ms. Cumming: Just to follow up on that, I wanted to just add the comment that I agree that the current strategy appears to be keeping the blood supply quite safe. I mean, very safe. And we're talking about a difference of potentially a few cases. And while it may not, while it seems to me our charge is to assess these strategies in terms of the safety of the blood supply, I can't help but think about, are there other harms being done by us preventing blood products from particular demographics from going into the blood supply that are very needed? And are there other harms that are happening that are not well quantified because of a lack of availability of blood products? That's all I wanted to say. Thank you.

Dr. Szczepiorkowski: Appreciate it. I think that we recognize that every strategy has a trade-off. And I think a part of that is we don't know all of them at the current stage. Great, thank you. Brenda, would you mind commenting on question number one now?

Dr. Grossman: Okay. If I understand correctly, the regulatory framework which we're working under is that there's a licensed test and therefore we have to use it. And if that's true, I am not gonna be able to pick between strategy 1A and 1B based on my experience working in a large blood center and in a small hospital collection facility where I know if I had to implement this test for my blood donors, I would do two different things. And so I think we can't ignore these cries for give us some flexibility because one size doesn't fit all. And if we have to choose one or the other, as you heard from everybody, there are limitations to both. And I think we need to decide the outcome we want, which I think is a diverse blood supply and available blood supply and a safe blood supply. And I think there are more than one ways to get to that. So I cannot choose here.

And I also want to echo what Evan said. When we look at this in the context of the other infectious diseases that we have worried about in the past, it's just not on the same magnitude. So that's my comments.

The other comment I have is I think if we are required to test, I think it's important that we ensure that we have the test and the reagents and everything available to test everybody. And that a single supplier concerns me because we've all had critical supplies that disappeared. And so we have to have some sort of plan for what to do if that were to occur. And the systems that can keep track of all this because they're complicated algorithms and it's gonna take time to implement this. And that's really all I have to say.

Dr. Szczepiorkowski: Well, very nice encapsulating. Thank you so much, Brenda. I think the question about the test has to be introduced or not, it appears to me that there's some flexibility, but having said that, we were told today that because of the CFR, we need to consider the test. Ms. Lattimore, you're next I notice. Oh, sorry, I apologize. Susan Galel, do you want to comment as our speaker?

Dr. Galel: Yes, thanks, Ziggy. Yeah, a couple of people have made comments expressing concern about availability. And I just wanted to say in my discussions with our commercial team, they do not anticipate supply challenges. We were even able to adequately keep the blood supply, our supply chain going during COVID. And I also wanted to comment, I think one of the public commenters made a statement, they were somehow using data from our specificity study to predict yield. And I just wanted to say, I don't think that's an accurate way to predict yield because our specificity study was performed in donors that are currently eligible. So all of the other donors that have recently traveled and former residents that are currently deferred would not have been included in that study. So you can't use data from that study to predict yield.

Dr. Szczepiorkowski: Thank you so much. Now, Ms. Lattimore.

Ms. Lattimore: Thank you, and thanks for all of the comments thus far. They've really echoed a lot of the questions that I found from the speakers. I think one thing that I was thinking about was from a consumer perspective, is there any impact that this would have on directed donors and would they run through this same process, that process be impacted or different in any way? Because certainly when you talk about underserved individuals or individuals that have racial and ethnic diversity, some of those needs are more urgent in nature. And so I'm curious how that might be addressed.

Then I think the second piece is, from my perspective, it looks like there are shortfalls from both strategy 1A and strategy 1B. Certainly selective testing doesn't catch everything. It does appear, and maybe someone can clarify this for me, it does appear that through the current process flow of denial, all of the variables that would screen someone out from being a donor today are captured in the selective testing for strategy 1A. And if somebody can clarify that for me, that would be helpful. Would there be any other situation where there would be an automatic denial of the donor status around their exposure to malaria or travel or any other issue that we might not be picking up?

And then on the 1B side, healthcare expenses, astronomical, I would A, hate one more thing. And I know this is not our consideration, but to tax an already challenging space of blood donation, and this is certainly not my area of expertise, but I do have a lot of questions around why three months came up as the travel time. There was a lot of discussion earlier today about people who are asymptomatic and who might not have the opportunity to even know that they are infected with malaria at the time of presentation. So I'm wondering how those individuals might be captured in either of these strategies. But really at the end of the day, if there are more

people who are eligible to donate blood and we can retain them in the system and this doesn't negatively impact the safety screening, either of these strategies are better than what's happening currently.

Dr. Szczepiorkowski: Let me just ask if there's anyone on CBER who would like to answer the two questions you had. Is there anyone available? I don't want to misspeak. Anne, thank you.

Dr. Eder: Sure, so regarding your first question, if I can paraphrase it to make sure I understood it. So you're asking about patients who might have rare blood needs, needs for rare blood types. And if a sibling is more likely to be a compatible donor for that patient, would either strategy somehow make it more difficult or prevent that unit from getting to the patient who needs it? Was that your question?

Ms. Lattimore: Yeah, I'm just curious if there is any difference in directed donor screening versus-

Dr. Eder: So the short answer is no. Okay. Neither screening, let me just, the short answer is directed donors, if there's an exceptional medical need, the CFR already allows for consideration if an individual patient needs a unit of blood. And the testing will just make more donors eligible. So it shouldn't have any effect on whether a patient needs a directed donor. Okay. And then I forget your second question, I apologize.

Ms. Lattimore: My second question had to do with strategy one. So I'm sorry, I apologize. It's hard to see the slide that had the process flow map that's currently in place with the questioning that takes place from a medical history and travel screening perspective. Is there anything in strategy 1A that is not being picked up under the selective testing from a history screening perspective, specific, obviously, to exposure –

Dr. Eder: I see what you're saying. So is B missing anything that A might be picking up? Well, I think the discussion about whether three months is appropriate has been very helpful to us because I think that would be a limitation of 1B. Whereas if you're testing prior residents at every donation, that person would be tested more than once. So it is possible that three months isn't the right interval to consider testing after re-exposure to a malaria endemic area. So that discussion was very helpful. And you're right. That's the sort of thing that differs. That's the sort of thing that distinguishes 1B from 1A. But generally, 1B picks up more of what we know is causing the cases of transfusion transmitted malaria that get through. Yeah.

Ms. Lattimore: Thank you.

Dr. Eder: Great questions, thank you.

Dr. Szczepiorkowski: Thank you. Okay. Okay, Dr. Maldarelli, you are next on my list.

Dr. Maldarelli: Thanks. So this has been such a great discussion and I'm pretty sure I can't add much to it. I really think the goal of reducing transmission-associated diseases, as I think Dr. Bloch pointed out clearly, is gonna be very difficult to measure with either one of them. But the advantage to having more blood in the blood supply is a very, very compelling one. And so I think putting those things together and being very just pragmatic and have to choose, I think I would choose one. I come down on the side of 1A. It might also be useful to know we talk about how many units are not being available anymore. What's the morbidity in those populations of not having that blood? So yeah, we don't have as much blood for those populations. What does that translate into? Do they still get the blood they need, but we're always on the edge? Or there's a lot more morbidity here than we know about, and that becomes a more compelling reason. But not having any of that data, I'm for 1A.

Dr. Szczepiorkowski: Oh, great, thank you very much. Yes, I think we all recognize that there is definitely limitations with a lot of blood types, and sometimes it's quite struggling to get those to our patients. But there might be more modeling to be done to figure out how to approach that the most efficient way. Okay, Traci Mondoro, actually, she must have left by now. She left me with her comments, so I will briefly go where was her comments. I'll find it. So let me move to the next person and then we'll find the comments. So the next person on my list is Dr. Pandey. I understand, anything you would like to add to the previous presentation?

Dr. Pandey: No, I think the only thing is if maybe Dr. Galel can, if she has any information about, or just her thoughts on that scenario of intermittent parasitemia and the sensitivity of the assay and being able to pick that up if you have someone with a semi-immune persistent type of infection, could it potentially miss in that scenario?

Dr. Galel: So I don't have any direct evidence of the existence of intermittent parasitemia in these individuals with sustained chronic infection. I guess for me, the data that the follow-up samples were, positive in all the donors suggested that you draw a sample and it would be detected with the exception of one donor who had that, as I said, sort of a very late CT value on the follow-up sample and was positive on the retained sample. Whether that represents intermittent parasitemia or just the limitations of the DNA-based PCR assay, I think is an argument. And again, our assay is a lot more sensitive, but to my knowledge, there have not been longitudinal studies of people, these people with chronic sustained infection.

Dr. Pandey: Thanks.

Dr. Szczepiorkowski: Susan, just wanted to confirm with you, neither Dr. Perez nor Dr. Perkins are here.

Dr. Galel: Say that again?

Dr. Szczepiorkowski: Neither Dr. Perez and Dr. Perkins are here.

D. Galel: Correct, correct.

Dr. Szczepiorkowski: Okay, great, thank you. So I would move to Dr. Scanlan, if you can share your comments.

Dr. Scanlan: Yes, I also support the selective testing model 1A. I think that there are obviously problems with disclosure in the donor history section, and those would be picked up by 1B, but only, and someone had said that 1B was like starting with a clean slate that you would detect people, but then malarial travel will happen after that, and it just didn't make a lot of sense to me. So I think the selective testing 1A would be my preference as well. Mostly for the benefits to the blood supply, not so much to safety, because it's such a low incidence disease and treatable.

Dr. Szczepiorkowski: Thank you very much, Dr. Scanlan. And I don't see, okay, Dr. Wahed, sorry.

Dr. Wahed: Yeah, my comments are actually more or less like Mark's. I do not have, sort of like I have, I don't think 1B, because of the expense, I wouldn't prefer that, because it's not going to add much more benefit to what we will get using a strategy 1A. So my preference would be 1A.

Dr. Szczepiorkowski: Can I ask you, because you recognize it's biostatistics, so am I correct to state that?

Dr. Wahed: Yes, that's correct.

Dr. Szczepiorkowski: So we've heard today a couple of statements, which I wonder if you'd like to comment on those. One, of course, is that 2023, and we're going to call it question number two, but actually maybe that's good, because make a U-turn now.

For 15 years, we had none local to local malaria infections. We have all of a sudden three, four different states, different places, clearly different organisms, what it looks like. Is that a

beginning of a trend? Is that just a fluke? Is that something you, how would you approach from a biostatistics perspective?

Dr. Wahed: The problem is without the data, as a biostatistician, I cannot tell much, right? But the figure that was being shown, that is actually amazing, because during the travel bans, there weren't much of the cases that you could, right? But after the ban is lifted, now the COVID is there, but we have started traveling extensively again. And the cases of malaria that is being back to the increasing, same increasing trend as pre-COVID, right? So I think we should be concerned about that, but I cannot tell much without that, you know.

Dr. Szczepiorkowski: Right, well, thank you very much. I think there's, I think more to learn, I guess that's the definition. That's fantastic. Did I miss anybody from the list except for myself? So what it seems to be so far, looking at lots of very complex data, which was put into the data committee on that question, I think we all struggled a little bit with fully appreciating the impact of either of those strategies. I think it's what Dr. Eder has mentioned is that our current deferral may or may not be actually the ideal scenario, but be optimal. I think also we need to define what is our goal. If our goal is zero malaria transmission, that's a reasonable plan, that's a good goal, but maybe more focused selective testing may achieve this goal better than having. But also impressed by the pro-clinic study, which was shown that there was one person who was actually positive out of 826 or so, which by itself means that in the group, which was identified there as people who were already on the deferral list for the three years, there might be some individuals who were, who had transmitted malaria, and I pray that 1B is not going to solve that problem.

So I think from my impression, what we've learned today, I think that it's really a very diverse situation where we have not only different organisms, five different different malaria types, but also a geography format where they come from and who are being introduced in this

country. And I think that's very important to take into consideration. I feel that, as mentioned by others, Babesia is not a good example because I do believe Babesia being an endemic disease is quite a different story than malaria.

I think fortunately for us, since 1950s, we don't have endemic malaria, but I very much hope that we tailor the approach such a way that the testing would be useful and most productive in certain groups of individuals. However, it had to be done, which in a sense, I support the idea of more modeling and being sure that we achieve the most beneficial outcome for all involved parties.

As was mentioned before, the diversity of our donor pool, individuals who present a great value to us, we don't want to defer them, obviously. And at the same time, we want to minimize the number of transfusion-related malaria, but that might be a problem because we are so low to start with. I don't think any study will be able to show the difference between any of the approaches we can take. So I think that's the challenge we'll all be facing in coming months and years.

So that reminds me of a little summary. I think that I'm hoping, and I ask maybe Anne, and if there's any other questions for the question number one, you would like the committee to let, or you got enough from the discussion at this point?

Dr. Eder: I'd like to just thank the committee for the discussion and we can go on to question two, thanks.

Dr. Szczepiorkowski: Thank you so very much. So question number two, hopefully it'll be a bit easier because that one has so many diverse changes. So here we just heard about 2023 events. I think FDA rightly wants to be prepared for this either to continue or disappear. So we heard a couple of things so far, along with that maybe one single case does not define cluster. I think

that's a reasonable statement, but I would like to again open to the same situation. If you can comment, you have any comments, any suggestions about question number two, either because of a number of classes or how to follow up with what the cluster might be. I start again with person on my list. And the first person I will have will be Dr. Ahuja. Oh, sorry. Okay, I apologize. Realizing that Dr. Bloch thought that he was first. Okay, Dr. Bloch, you go first. I apologize.

Dr. Bloch: Thank you. So the challenge is that's, I don't think you can look at this independently of question one, because if you don't have background testing, selective testing, then one can't really scale up rapidly NAS. So the analogy is West Nile virus, which has been extraordinarily effective, but with West Nile virus, there's already ongoing testing throughout the year. And then they're kind of doing this time limiting kind of the reflex individual donor NAS during times of increased incidence. So this really is contingence on first having NAS in there. I think, again, it was mentioned that we can't consider costs, but I think that's a little unfair because I think that's been applied selectively. So I think that there is, this would obviously take a lot of resources, a lot of complexity to undertake. There's always value in kind of doing public health surveillance, but I think from in terms of protecting the blood supply of malaria is just, I think is currently is fairly low risk. So I don't see a huge amounts of utility.

Dr. Szczepiorkowski: We appreciate Dr. Bloch. I think, although I, obviously that's where we operate. We cannot consider the cost, but as we all know, if you do too many things, it doesn't matter how much money you have, somewhere would be unintended consequences. And I think unintended consequences is something at least we need to identify what possible things may happen and may go wrong in respect of the cost of that intervention we're thinking about. So I feel quite comfortable with saying that there might be some intended consequences which will be

considered not necessarily to malaria, but other things we do. So that's maybe important to keep on the table. Okay, Dr. Ahuja, you're next.

Dr. Ahuja: Yes, thank you. Yeah, this is a difficult one, obviously. I didn't know much about public health surveillance. That's why I asked that question earlier about what kind of mosquito level surveillance is maintained by CDC. I mean, this assumes that, first of all, as I understand this correctly, this is a local transmission of malaria, right? So that's proven local transmission that has happened, not gotten by somewhere, somebody traveled from outside, right? Correct? Am I correct?

Dr. Szczepiorkowski: I think that's what Dr. Kumar mentioned, was basically that you have those areas where somehow, somewhere the mosquito got transported to this area and was infected with malaria and infect individuals in that area.

Dr. Ahuja: Yeah, and then this also doesn't specify whether travel to an area. So for example, there's so much travel that happens or short limited stay that happens. So what if I travel to, say, for example, there's a outbreak in Florida and I travel, I stay there for a week and I come back and I want to donate blood, does that eliminate me from, or does that make me eligible for the NAT testing because I traveled to that location within the US? I mean, there's so many nuances to this. And I know that this question is specifically limited to a single case that is detected. So then you trigger the NAT testing. I think it might be a little bit much in my opinion, but I don't know whether more evidence of local transmission should be in place before we say yes to this. That's where I would sort of lean on, not just a single case.

Dr. Szczepiorkowski: Okay, well, thank you very much. Dr. Ballow?

Dr. Ballow: Yeah, I think this question really is apropos to my comments that I made with the first question in that a number of cases were identified in Florida. And all throughout the year,

but even the summertime, there are a large gathering of individuals at different venues, whether they're outdoor concerts or parks or whatever. So, we have evidence that they actually did find the parasite in mosquitoes. That's why I asked that question originally. So I think this is important. The caveat here is time limited and selective as far as a region where cases arise. So I think this is an important part of the proposal. And I think as with climate change, we may see more malaria and transmission to different individuals, even those individuals who may be asymptomatic for one reason or another. And since we're dealing with even an elderly population in some of the Southern states like Florida, they may be partially immune compromised. So they may be at even greater risk since they will receive blood transfusions or even infected by the parasite. So I am certainly in favor of question number two.

Dr. Szczepiorkowski: In terms of that, even of the single case, although you don't know how many cases you'd have to be to trigger something.

Dr. Ballow: Well, I mean, what do you do? Do you make it one case? Do you make it two cases? Do you make it three cases? I mean, that's tough to judge. I mean, I don't know. You want to put a number on that? You want to make it two cases instead of one case?

Dr. Szczepiorkowski: No, I don't want to put a number on it. I just, I think the public comments were, I think they were highlighting the fact that one single case might be too trigger happy, so to speak, and maybe two or three. Well, they actually didn't give a number. They just said that we have five cases.

Dr. Ballow: But I figure what's going to happen if there's one case that's triggered that what's going to be done is that they're going to investigate looking at actually recovering mosquitoes and trying to see if their collection or cohort of mosquitoes carries the parasite, right?

Dr. Szczepiorkowski: Yeah, absolutely.

Dr. Ballow: Well, I think that's going to trigger, you know, trigger further investigation. So, and I think that'll be important component of this question number two is to go beyond just a question, but also to go to epidemiology. And I don't know what you call it when you look at the insect surveillance, I guess.

Dr. Szczepiorkowski: So I think that the dramatic part of that whole discussion of question two, and I just want to mention it right now, we were told that about 2000 malaria infections in the country every year identified. And of course, the actual shot tells us that our healthcare system is quite capable of identifying and treating malaria, which is great. But also what it means is that someone has to make a decision in the context of 300 cases per Florida. I don't know how many, there were a number of cases of 100. How many, which of those 300 cases or 200 cases is actually the one which had no history of trouble? And basically that would become the kind of a local transmission. So I think we are stepping on a situation where we may have hundreds of malaria cases, which were all trouble related, the majority of them, as we're told by CDC and CBER, yet we'll be looking for that one or two, which are actually not trouble related. So I don't know how that logistically is feasible. And I was thinking about asking Ms. Cumming, who has a number of cases in Massachusetts, I can imagine how difficult or how easy is it to identify locally acquired malaria versus trouble acquired malaria.

Dr. Ballow: But also remember the vulnerable patient population in some regions.

Dr. Szczepiorkowski: Of course, absolutely, absolutely. I just wanted to figure out, from a public health perspective, someone who is in trenches in Massachusetts, how would you differentiate between malaria transmitted by travel and malaria transmitted locally?

Ms. Cumming: Well, in Massachusetts, I think, in our experience, if you're able to speak with the individual, you can usually determine pretty easily if it is trouble associated. I can also

comment on the questions around, what types of vector-borne surveillance testing is happening. For example, in Massachusetts, we've been significantly impacted in the recent decade by Triple E, West Nile virus. And so those are the pathogens that we're usually doing vector-borne surveillance for. We're not doing routine vector-borne surveillance for plasmodium, I can say, looking for Triple E, West Nile virus, Jamestown Canyon virus. And so I would say that. I also, I appreciate the comments around, if we were to interview a malaria case and identify, they had no travel at all, none, but they had local, likely mosquito exposure. There would be a pretty intensive response to that, right?

For vector-borne surveillance and testing and sampling, as well as raising clinical awareness and things of that nature. So a lot would happen to immediately potentially mitigate risk. The vector-borne surveillance we do also looks at speciation and the vectors that are present and prevalent in the area. So I do think that the identification of even a single case would result in a pretty intense response that could potentially impact subsequent transmission. That's pie in the sky, we're finding out about the first case, which may not happen. But it does strike me as odd that with strategy 1A and 1B, when we screen individuals, we're only testing them if they have traveled to or have resided in an endemic area. So an area with a lot of malaria.

Whereas with strategy B, with the identification of even a single case and no evidence of sustained transmission, we're going to trigger universal testing. And it just strikes me as odd that they are so different. So I wish that there was a way to clearly, maybe we can clearly define sustained malaria transmission locally as a trigger, as opposed to a single case. I'm quite uncomfortable with a single case as being a trigger or strategy too.

Dr. Szczepiorkowski: Thank you so much, Ms. Cunningham. I apologize to pick on you, but you're out of luck. Thank you so much. Okay, Sridhar, Sridhar, you are next.

Dr. Basavaraju: Yeah, thanks. So I think that there's a lot of challenges in identifying a single case of malaria. The investigation can be very time consuming. Confirmation of testing can be lengthy. And by the time everything all gets sorted out and reported, it's possible that the risk may have passed. So, I mean, I think it's not really that a single case would be identified necessarily in real time, reported in real time, and testing gets off the ground immediately. And I also think that I don't know how much of a risk one single case in a jurisdiction necessarily poses to blood safety. So, I mean, I would advocate that there'd be no specific trigger. This isn't like West Nile virus, where there's endemic activity in the United States. I would support there being no specific trigger, threshold trigger. And instead, when a local outbreak is identified, FDA has the discretion to make a decision on that. A decision on local screening, based on consultation with CDC and local health jurisdictions. And that would allow for there to be some better understanding of the outbreak, better understanding of the surveillance methods, and also the burden and extent of the outbreak.

Dr. Szczepiorkowski: You'd be pleased to know that you got a thumb up from Ms. Cumming. You public health people, you always want to find the right solution, which is great. Okay, thank you so much. Brenda, you're next on my list. Comments about question two.

Dr. Grossman: I'll just give a thumbs up to that too and make this go rapidly. One will not work, one case will not work, but I really agree with what was just said.

Dr. Szczepiorkowski: I appreciate it, Brenda, thank you. Ms. Lattimore?

Ms. Lattimore: Yeah, I also agree with the previous comments. It's really hard to take a single case and not understanding the time around when the local mosquito-borne malaria is actually reported, and then not having true definition around the time limited, not screening. It seems like

a lot of that needs to get sussed out before a single case is what's triggering the crescendo of work from there. So I agree with the previous comments.

Dr. Szczepiorkowski: Thank you so much. Dr. Maldarelli?

Dr. Maldarelli: Yes, I don't think I have anything more to add. I agree with that. It's between one case and two cases compelling, but with things that are Poisson distributed, when you have no cases, you have an equal probability of having one case if there's even a possibility of one. So I completely agree with what's been said so far.

Dr. Szczepiorkowski: Thank you very much. So I just have to update the committee about Traci Mondoro's position. So for the question number one, she was hedging towards 1B, which would mean. However, she had a number of questions related to it, which I'm not going to go through right now. And for the question number two, she thought that was a relatively prudent given the data which was presented by Dr. Eder. So that's the summary for Dr. Mondoro. Okay, Andy? Suchitra?

Dr. Pandey: I agree with everything that's already been said about the single case really not being enough. And I think someone had talked about, is it sustaining, is it sustained transmission? And I think we would need to, it's difficult to define what that would be. So I think working with epidemiologists, the CDC to determine when a certain region has reached that threshold to be considered as transmission. So I think I agree, single case is too low of a threshold, but we definitely need guidance in terms of how we would define what that threshold would be.

And the other thing I do want to talk, it's not on this slide per se, but the three months, like how long is the time limited NAT going to continue on? So I think right now it's three months is what's stated. And I think I was reading when the 2023 CDC update, they do like eight

weeks of surveillance following a local transmission. So that there's that data point to eight weeks versus three months and, or whatever. I think also that delay in the reporting is important, or just someone might be asymptomatic or in an incubation period for seven to 30 days. We saw that. And so by the time they're diagnosed and by the time it's reported, and by the time you trigger on, there will be a delay. So I think that also has to be considered when you're thinking about what that time limited period is going to be.

Dr. Szczepiorkowski: Thank you. I appreciate that. Dr. Scanlan.

Dr. Scanlan: Yeah. I support the comments that we'll use the little gray cells instead of a rule of one.

Dr. Szczepiorkowski: Okay. I appreciate that. Whatever you have left. Thank you. And Dr. Wahed, please.

Dr. Wahed: Did you call my name?

Dr. Szczepiorkowski: I'm sorry. Sorry, yes, I apologize. Yeah, yeah.

Dr. Wahed: Okay. So I am with the same comment with Mark. I think zero case, one case, I think these are very close probability in terms of person distribution. So I have intended to leave it to the local health officials, like whether they would make it like a time limited entity screening for all donations mandatory or something when such cases occur, like maybe one, two, or three. I would let the local health officials decide about that. I'm not sure. That's my opinion.

Dr. Szczepiorkowski: I really, really appreciate that. I think that was maybe the gesture if I could be more flexible and having resources to address such an event and then come up with the right solution, I guess.

So I think that actually ends our discussion, our deliberations. I believe Dr. Peter Marks is here and I would welcome any comments from him or from Dr. Eder at this point before we adjourn the meeting.

Dr. Marks: Whoops. Thanks, sorry. It took me a minute, too. Thanks. Thank you so much.

First of all, I really want to thank everyone for a very, very thoughtful discussion. This is a challenging area to have to think through and really appreciate the very thoughtful comments. Also want to thank the presenters at the open public hearing because I thought it was all of the presenters were very constructive in their comments and that was very much appreciated. So just want to say thank you so much. I think I want to thank all the members of the advisory committee, thank our open public hearing presenters, thank the FDA staff who did a tremendous amount of work preparing for this. There was a lot of thought that went into this and we'll obviously go back and take to heart what's been said today. And then also need to thank the advisory committee staff who have made this happen so seamlessly. So just thank you all so much and really appreciate everyone's efforts here. Anne, did you have anything else you wanted to add?

Dr. Eder: Thank you, Dr. Marks. No, I just add my thanks to the committee, the staff at FDA, Dr. Ziggy Szczepiorkowski, thank you for chairing the discussion. And we will take back what we heard and discuss it amongst ourselves. So thank you.

Dr. Szczepiorkowski: Thank you so much. And thank you very much for FDA being so open to our comments and especially listening again, echo what Dr. Marks said, thank you to all those who participated today. So Christina, I would like to turn to you to adjourn the meeting. We can't hear you.

Ms. Vert: There it goes. Can you hear me now?

Dr. Szczepiorkowski: Yes, we can.

Adjournment

Ms. Vert: Okay. Thank you all for closing comments. I wanted to thank the committee, speakers and CBER staff for working so hard to make this meeting a successful meeting. And I now call the meeting officially adjourned. Thank you.