Relias Media
From Relias

Vol. 41, Issue 4, January 2022
ReliasMedia.com

Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

# Mumps in Vaccinated Children

*By Philip R. Fischer, MD, DTM&H*

*Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN; Department of Pediatrics, Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates*

SYNOPSIS: Recent mumps outbreaks in the United States have involved vaccinated individuals without international travel. The genotype of the mumps virus circulating in North America and Europe is different than that of the virus used to manufacture the attenuated vaccine used in the United States.

SOURCE: Shepersky L, Marin M, Zhang J, et al. Mumps in vaccinated children and adolescents 2007-2019. *Pediatrics* 2021;148:e2021051873.

Mumps usually is a mild illness with inflammation of the parotid glands, but serious complications can result. With vaccination against mumps available since 1967 and with a two-dose series of vaccine recommended since 1989, the number of mumps cases dropped by more than 99%. Nonetheless, outbreaks continue to occur. However, the majority of pediatricians would not test for mumps in a vaccinated child with parotitis. To better understand the epidemiology of mumps and to highlight risk factors to aid in clinical diagnosis and management, Shepersky and colleagues at the Centers for Disease Control and Prevention (CDC) reviewed clinical data from reported mumps outbreaks in the United States since 2007.

Mumps is a reportable illness in the United States, and the CDC is informed of confirmed positive cases. These researchers reviewed epidemiological data from mumps-positive patients younger than 18 years of age from 2007 through 2019. They considered patients up to date with mumps vaccination if they were younger than 5 years of age with at least one dose received, and with two doses if ages 5-17 years.

There were 9,172 reported cases of mumps in children during the study period. These children represented 32% of all cases of mumps reported. Cases were reported from all 50 states and from the District of Columbia. The median number of

Financial Disclosure: None of the authors or planners of this educational activity have relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Infectious Disease [ALERT]

*Infectious Disease Alert*, **(ISSN 0739-7348), is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to** *Infectious Disease Alert*, **Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.**

GST Registration Number: R128870672.



SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

Editorial Email:
smark@relias.com

**Back issues:** Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

ACCREDITATION

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, Relias LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Relias LLC designates this enduring material for a maximum of ***3*** *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 3 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

*Infectious Disease Alert* may contain references to off-label or unapproved uses of drugs or devices. The use of these agents outside currently approved labeling is considered experimental, and participants should consult prescribing information for these products.

This CME activity is intended for the infectious disease specialist. It is in effect for 36 months from the date of the publication.

pediatric cases per year was 349, but there were peaks in 2009-2010 and 2016-2017 with much higher numbers of cases. Overall, 71% of mumps patients had their illness in association with a known outbreak of mumps.

Of patients with medical records noting vaccine status (79% had vaccine status noted), 89% had received at least one vaccine and 84% were up to date with mumps vaccination. Only 2% of mumps cases were associated with international travel. Half of pediatric patients with mumps were adolescents; interestingly, the most affected adult age group during this period was the 18- to 22-year-old group. A complication was seen in 1% of mumps-infected children, and 3% of the post-pubertal males with mumps had orchitis. (Of those with orchitis, 66% were up to date on mumps vaccination.)

The authors pointed out that the occurrence of mumps in vaccinated individuals could be because of either waning immunity over time post-vaccination or an antigenic mismatch between the circulating mumps virus strain and the vaccine strain. The ages at most risk (adolescents and young adults, at least five years after the second and final routine mumps vaccination) supports the notion of waning immunity. However, it also is true that the vaccine strain (genotype A) prompts incomplete immune responses to the commonly circulating mumps strain (genotype G). Specifically, although the A genotype vaccine provides neutralizing antibody responses against the G genotype virus, the level of those cross-reactive antibodies is less than half that of the same-genotype responses.

Unlike measles and rubella, mumps still is endemic in the United States, with cases reported each year from almost every state. International travel or exposure to a traveler is not required to get mumps.

## ■ COMMENTARY

It is true that some past mumps outbreaks, and many measles outbreaks, result from contact with someone in or from another country and occur mostly in unvaccinated individuals.[1] However, a huge take-home lesson of this new study is that the vast majority of mumps cases in the United States now are because mumps is endemic in the United States. Foreign travel is not necessary to start mumps outbreaks, and vaccination is not fully protective. Detailed virologic studies suggest that there is steady transmission of the same virus strains in the United States, mostly those with the G genotype.[2] New outbreaks do not seem to be caused by the introduction of new viral variants.[2,3]

In 1963, Maurice Hilleman was a virologist with a pharmaceutical company.[4] His 5-year-old daughter Jeryl Lynn became ill with mumps.[4] He isolated the mumps virus from her respiratory secretions, attenuated the virus, and, by 1967, produced the Jeryl Lynn strain of mumps vaccine.[4] A quick internet search reveals a 1968 photo of Jeryl Lynn holding her crying younger sister, Kristen, as Kristen received the mumps vaccine. Continued internet searching shows a 1991 photo of Jeryl Lynn with her son, Colin, as he received the vaccine. The Jeryl Lynn vaccine is an attenuated mumps virus strain with the A genotype and still is used in the United States.

Different vaccines are used in different parts of the world,[5] but side effects are more common with some of the vaccines used in other countries. Currently, though, the G genotype strain of mumps virus that is most common in the United States also is most common in Portugal[6] and Spain,[7] while genotype F, H, and I strains have emerged in Korea during the past two decades.[8]

If waning immunity was the only issue leading to mumps outbreaks continuing, adding an adolescent vaccine dose could be effective in providing longer-term protection. But, the strain difference seems relevant. The current Jeryl Lynn A genotype-based vaccine triggers less immune response to the circulating G genotype viruses, so it could be incompletely protective or subject to more serious loss of immunity as seroprotection wanes (from a lower initial starting point).

Mumps is endemic in the United States, and outbreaks continue to occur. Hundreds of children are ill with mumps

each year. It could be time to consider developing or using a different vaccine that provides better protection against the mumps virus strains with the G genotype.[4,5] ■


REFERENCES

1. Centers for Disease Control and Prevention. Mumps outbreak on a university campus — California, 2011. *MMWR Morb Mortal Wkly Rep* 2012;61:986-989.
2. Wohl S, Metsky HC, Schaffner SF, et al. Combining genomics and epidemiology to track mumps virus transmission in the United States. *PLoS Biol* 2020;18: e3000611.
3. Bryant P, Caldwell H, Lamson D, et al. Streamlined whole genome sequencing of mumps for high resolution outbreak analysis. *J Clin Microbiol* 2021; Nov 10;JCM0084121. [Online ahead of print].
4. Grose C. From King Nebuchadnezzar of Babylon to mumps genotyping and vaccination 26 centuries later. *Pediatrics* 2021;148:e2021052761.
5. Connell AR, Connell J, Leahy TR, Hassan J. Mumps outbreaks in vaccinated populations – is it time to re-assess the clinical efficacy of vaccines? *Front Immunol* 2020;11:2089.
6. Perez Duque M, San-Bento A, Léon L, et al. Mumps outbreak among fully vaccinated school-age children and young adults, Portugal 2019/2020. *Epidemiol Infect* 2020:149;e205.
7. Barrabeig I, Antón A, Torner N, et al. Mumps: MMR vaccination and genetic diversity of mumps virus, 2007-2011 in Catalonia, Spain. *BMC Infect Dis* 2019;19:954.
8. Won H, Kim AR, Yoo JS, et al. Cross-neutralization between vaccine and circulating wild-type mumps viruses in Korea. *Vaccine* 2021;39;1870-1876.


## ABSTRACT & COMMENTARY

# *Malassezia restricta* as a Cause of Culture-Negative Infective Endocarditis


***By Richard R. Watkins, MD, MS, FACP, FIDSA, FISAC***

*Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH*



SYNOPSIS: A retrospective study from France used deoxyribonucleic acid (DNA) detection methods to assess the microbial etiologies of 16 cases of culture-negative infective endocarditis. They identified three cases of *Malassezia restricta*, a yeast considered a member of the human skin microbiota. Notably, serologic testing cross-reacted between *M. restricta* and *Candida albicans*.

SOURCE: Houhamdi-Hammou L, Benito Y, Boibieux A, et al. *Malassezia restricta*: An underdiagnosed causative agent of blood culture-negative infective endocarditis. *Clin Infect Dis* 2021;73:1223-1230.


Despite advances in laboratory microbial detection methods during the past decade, culture-negative infective endocarditis (CNIE) still is a frequent clinical conundrum. Houhamdi-Hammou and colleagues sought to determine the etiological pathogens responsible for cases of CNIE treated at a tertiary care hospital in France using a molecular diagnostic test.

The investigators employed a highly sensitive universal microbial detection kit called the UMD-biomolecular test that uses 16S (for bacteria) and 18S (for fungi) ribosomal deoxyribonucleic acid (rDNA) gene amplification on excised cardiac samples (valves and vegetations) from patients who had undergone surgery for endocarditis, hereafter referred to as T0. Each kit contains positive and negative controls. Samples were collected between Jan. 1, 2011, and Dec. 31, 2015. Patients were considered to have CNIE when clinical and echocardiographic findings met the Duke criteria for definitive endocarditis without microbiological identification, which included 10 days of negative blood cultures, 14 days of negative cardiac tissue cultures, in house 16S-rDNA polymerase chain reaction (PCR), and negative serologies for *Coxiella burnetii*, *Bartonella*, and *Brucella*.

During the time frame for the study, there were 88 cases that met the Duke criteria for definitive endocarditis and had excised cardiac tissue. Of these, 16 were classified as CNIE. The tissues came from prosthetic mitral (n = 9) and aortic (n = 7) valves. The mean age of the patients was 58 years (range, 25-82), 10 were women, and six were men. All 16 samples were positive using the UMD-biomolecular test. Of these, 13 were positive for bacteria and three were positive for yeast. Eight of the samples for bacteria were polymicrobial and nine were positive for species of *Streptococcus*. One sample was positive for *Enterococcus cecorum*, a commensal in the intestines of mammals and birds that has been described as an emerging pathogen in the poultry industry worldwide, and one was positive for *Moraxella* spp.[1] The other three samples were 16S-rDNA PCR negative but 18S-rDNA PCR positive and all identified as *Malassezia restricta*.

Histological analysis of the three cases of *M. restricta* found single rounded or oval yeast-form cells 2 µm to

3 µm in length in two samples and short unbranched mycelial pseudohyphae with budding yeast forms in one sample. Notably, sera from two of the three patients with *M. restricta* cross-reacted with *C. albicans* antibodies in the screening and confirmation assays.

All three of the patients had undergone cardiac valve replacement two to 15 months before T0. Patient 1 was a 66-year-old man who had a new heart valve placed at T0 and was treated with vancomycin, gentamicin, and rifampin. He never received antifungal treatment and died six years later with fever and heart failure. Patient 2 was a 72-year-old woman who underwent a second valve replacement at T0 and was treated with daptomycin, ceftriaxone, and gentamicin. Two weeks later, she became septic and was treated with caspofungin. She developed a subcutaneous nodule on her right flank that was positive for *M. restricta* by 18S-rDNA PCR. Two months later, a transesophageal echocardiogram revealed a peri-prosthetic valve abscess, and she died six months afterward. Patient 3 was a 42-year-old woman who also had another heart valve placed and was treated with daptomycin, ciprofloxacin, and imipenem. She developed a vegetation on the new heart valve three months later and was treated with amphotericin B and fluorocytosin. The vegetation cleared, and she was maintained on fluconazole thereafter. All three patients had either pruritic skin lesions or received lipid parenteral nutrition in the weeks to months prior to the onset of their symptoms.

## ■ COMMENTARY

This was an interesting study because it showed the usefulness of a commercial molecular test kit for identifying the etiologies of CNIE after traditional testing had led to a diagnostic dead end. It also was impressive that the kit was able to make the diagnosis, while the in-house 16S-rDNA assay was not. Perhaps this was because of more vigorous quality and manufacturing controls in the commercial assay. Also, there was no in-house 18S-rDNA PCR test available for fungal testing during the study time frame.

*M. restricta* is a lipophilic yeast and one of the most abundant *Malassezia* species of the human skin microbiota. It is considered an opportunistic pathogen associated with skin disorders, such as seborrheic dermatitis and dandruff.[2] Although there have been case reports of infections caused by other types of *Malassezia*, including a case of endocarditis from *M. furfur*, this is the first report of endocarditis caused by *M. restricta*. Because of their inherently low pathogenicity, *Malassezia* easily can be considered colonizers or contaminants in clinical samples. *Malassezia* are difficult to grow with routine culture methods because they are unable to synthesize medium and long chain fatty acids, therefore requiring special culture media containing added lipids. The pathophysiology for *Malassezia* endocarditis remains unknown, although an obvious hypothesis is acquisition from the human skin and contamination of vascular catheters.

The cross-reactivity between *M. restricta* and *C. albicans* serology is concerning. Often cardiac tissue is not available in cases of CNIE, so 16S rDNA and 18S rDNA testing cannot be performed. Thus, clinicians must rely on fungal serologies to diagnose fungal endocarditis when blood cultures and antigen tests are negative. *Malassezia* is intrinsically resistant to echinocandins, which is the recommended treatment of endocarditis caused by *Candida*. Of the three patients with *M. restricta* endocarditis in the present study, only one received appropriate antifungal therapy.

Diagnosing endocarditis caused by *Malassezia* is challenging. Thus, it is worth mentioning the current recommendation that histological staining and molecular testing, including for fungi, should be performed on cardiac samples when the causative pathogen is obscure. ■

### REFERENCES


1. Dolka B, Chrobak-Chmiel D, Czopowicz M, Szeleszczuk P. Characterization of pathogenic *Enterococcus cecorum* from different poultry groups: Broiler chickens, layers, turkeys, and waterfowl. *PLoS One* 2017;12:e0185199.
2. Morand SC, Bertignac M, Iltis A, et al. Complete genome sequence of *Malassezia restricta* CBS 7877, an opportunist pathogen involved in dandruff and seborrheic dermatitis. *Microbiol Resour Announc* 2019;8:e01543-18.

ABSTRACT & COMMENTARY

# Malaria in the United States

***By Stan Deresinski, MD, FACP, FIDSA***

*Clinical Professor of Medicine, Stanford University*

SYNOPSIS: The number of cases of imported malaria in the United States continues to increase, with most cases caused by *Plasmodium falciparum* and most of the infections acquired in Africa, particularly West Africa. Almost three-fourths of U.S. residents with malaria had failed to take chemoprophylaxis and the remaining one-fourth often had poor adherence with recommended medications.

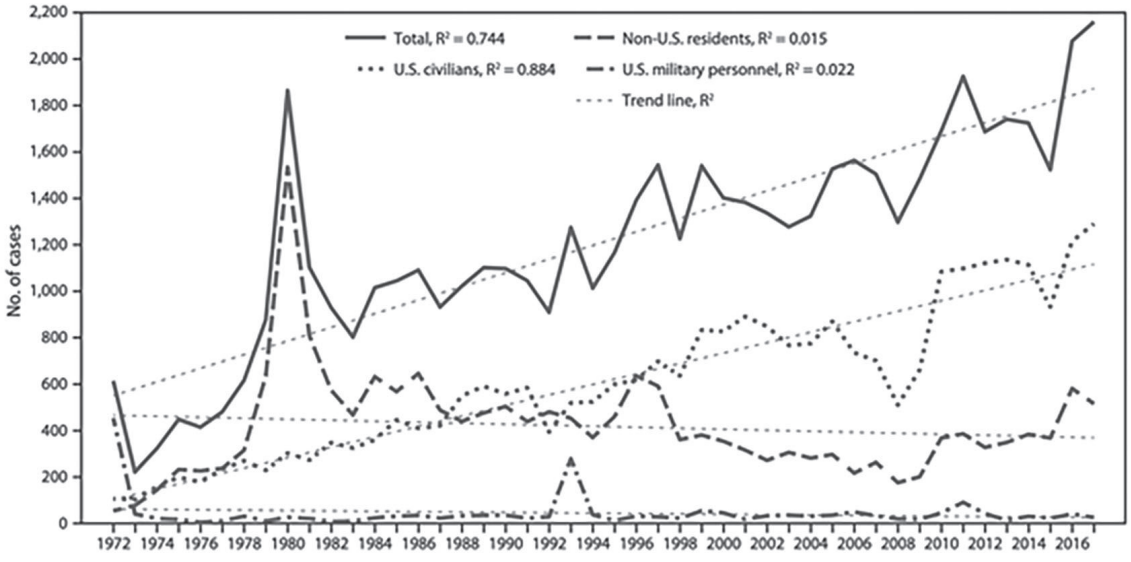
SOURCE: Mace KE, Lucchi NW, Tan KR. Malaria surveillance — United States, 2017. *MMWR Surveill Summ* 2021;70:1-35.

This most recent Centers for Disease Control and Prevention (CDC) analysis of malaria diagnosed in the United States found that the 2,161 confirmed cases identified in 2017 was the highest number in 45 years. *Plasmodium falciparum* accounted for 1,523 (70.5%) of the total, while 216 (10.0%) were caused by *Plasmodium vivax*, 119 (5.5%) by *Plasmodium ovale* (119 [5.5%]), and 55 (2.6%) by *Plasmodium malariae*. In 22 cases (1.9%), the infection was caused by more than one species, while the species was not recorded in 226 cases (10.5%). Two of the cases were acquired congenitally, two were acquired by blood transfusion, and three were cryptic — i.e., no source could be identified in individuals without a history of travel.

Of the total number of cases, 1,819 (86.1%) were imported from Africa, with two-thirds of these from West Africa. Three-fourths of affected U.S. civilians who reported a reason for travel indicated they had been visiting friends and relatives. Only 28.4% of affected U.S. residents had taken chemoprophylaxis and, among these, adherence to the regimen was frequently poor, with 996 for whom the information was available either failing to adhere to the prescribed regimen or taking a regimen other than that recommended by CDC. Ten U.S. residents were among the 27 women who were pregnant and none of the 10 had taken chemoprophylaxis.

Symptoms of malaria began within 90 days after return to the United States in 94.8%. The malaria was classified as severe in 312 cases (14.4%) and seven of these patients died. Testing of 123 *P. falciparum*-positive samples failed to identify any with genetic polymorphisms associated

**Figure 1: Number of Malaria Cases* Among U.S. Civilians, U.S. Military Personnel, and Non-U.S. Residents — United States, 1972-2017**




$R^2$ = square of the Pearson product moment correlation coefficient
* 2017: N = 2,161
Source: Mace KE, Lucchi NW, Tan KR. Malaria surveillance — United States, 2017. *MMWR Surveill Summ* 2021;70:1-35.

with resistance to artemisinin. In contrast, such polymorphisms indicative of resistance to pyrimethamine were detected in 97.3%, to sulfadoxine in 69.4%, to chloroquine in 33.3%, to mefloquine in 2.7%, and to atovaquone in 2.7%.

■ COMMENTARY

The worldwide total number of cases of malaria in 2017 was approximately 219 million. Africa accounts for approximately 92% of global cases, and 99.7% of cases on that continent are caused by *P. falciparum*; 93% of all malaria deaths occur in Africa. The increased number of cases in the United States in 2017 represents a long-term continuation of an upward trend (*see Figure 1*), which, however, likely has been interrupted during the COVID-19 pandemic because of its effect on travel.

Lack of adequate (or any) prophylaxis continues to be the major cause of malaria in traveling U.S. residents. Efforts to confront this problem effectively must continue and intensify. ■

ABSTRACT & COMMENTARY

# Treatment of Severe *Plasmodium falciparum* Malaria with Intravenous Artesunate

***By Stan Deresinski, MD, FACP, FIDSA***

*Clinical Professor of Medicine, Stanford University*

SYNOPSIS: A prospective nationwide study in France found that intravenous artesunate use was rapidly adopted by clinicians and was safe and highly effective in the treatment of severe malaria due to *Plasmodium falciparum*.

SOURCE: Roussel C, Ndour PA, Kendjo E, et al; FRench Artesunate Working Group. Intravenous artesunate for the treatment of severe imported malaria: Implementation, efficacy, and safety in 1391 patients. *Clin Infect Dis* 2021;73:1795-1804.

Rousel and colleagues evaluated the results of a national French program designed to facilitate the deployment of artesunate for the treatment of imported severe malaria due to *Plasmodium falciparum*. They prospectively collected data on 1,391 patients from 110 centers from 2011-2017, the first years of the program. During that time, the proportion of patients treated with artesunate increased from 9.9% between 2011 and 2013 and went on to increase to 71.4% in 2017, while the use of intravenous quinine correspondingly decreased. Of note is that one-fourth of patients instead received first-line oral therapy during the period of study, but with a switch from atovaquone-proguanil to artemisinin-based combinations.

Parasitological failure was observed in 27 of the 318 patients with blood smears on days 3, 7, and 28. This included 13 with slow clearance (i.e., taking > 7 days), seven with clearance followed by early resurgence before day 8, and seven with late resurgence occurring between days 8 and 28. No k13 (Kelch 13 propeller) nonsynonymous mutations were detected in the seven cases in which pretreatment blood samples were available.

Forty-one (4.1%) of 1,011 patients followed for 28 days died, most (80%) within four days after diagnosis. Compared to the total group, mortality was higher in those with an initial parasitemia > 10%, as well as in patients older than 50 years of age and those of European origin, while it was lower in those of African origin. The outcome in pregnant women and in human immunodeficiency virus (HIV)-infected patients was similar to that of the entire cohort. While an initial parasitemia > 10% was associated with higher mortality, there was no mortality difference between those with levels < 4% and those with 4% to 10%.

The drug generally was well tolerated, although the only pregnant patient treated during her first trimester experienced a hemorrhagic miscarriage. Hematological adverse effects were reported in 43.3%, although their relation to treatment as opposed to the illness itself is uncertain. The exception is post-artesunate-delayed-hemolysis (PADH), which occurred in 42.8% of patients specifically followed to detect it. As previously reported, this occurred more frequently in those of European as compared to African origin — 57.9% vs. 29.2%.

■ COMMENTARY

This French nationwide prospective study demonstrates the safety and efficacy of intravenous

(IV) artesunate in the treatment of severe *P. falciparum* malaria. The U.S. Centers for Disease Control and Prevention (CDC) recommends that intravenous artesunate is the treatment of choice for patients with confirmed severe malaria as defined by the presence of at least one of the following: parasite density > 5%, impaired consciousness, seizures, circulatory collapse/shock, pulmonary edema or acute respiratory distress syndrome, acidosis, acute kidney injury, bleeding or disseminated intravascular coagulation, jaundice, or hemoglobin < 7 g/dL.[1,2] Intravenous artesunate also is recommended for patients unable to take oral medications.

Despite the overall safety of artesunate, PADH occurred in 42.8% of patients monitored for its occurrence in this study. Fortunately, most often this is a relatively benign event. Nonetheless, the CDC states: "All persons treated for severe malaria with IV artesunate should be monitored weekly for up to four weeks after treatment initiation for evidence of hemolytic anemia."[1,2] PADH also has occurred after oral treatment with artemether-lumefantrine. ■


REFERENCES

1. Centers for Disease Control and Prevention. Treatment of malaria: Guidelines for clinicians (United States). https://www.cdc.gov/malaria/diagnosis_treatment/clinicians1.html
2. Centers for Disease Control and Prevention. Intravenous artesunate for treatment of severe malaria in the United States. https://www.cdc.gov/malaria/diagnosis_treatment/artesunate.html


ABSTRACT & COMMENTARY

# Screening and Diagnosis of Chagas Disease in the United States


***By Stan Deresinski, MD, FACP, FIDSA***

*Clinical Professor of Medicine, Stanford University*



SYNOPSIS: Chagas disease is an important public health problem in the United States. An expert panel has made a series of specific recommendations for screening for and diagnosis of Chagas disease in at-risk groups.



SOURCE: Forsyth CJ, Manne-Goehler J, Bern C, et al; U.S. Chagas Diagnostic Working Group. Recommendations for screening and diagnosis of Chagas disease in the United States. *J Infect Dis* 2021; Oct 8:jiab513. [Online ahead of print].


Chagas disease affects more than 300,000 people in the United States, most with chronic infection acquired during residence in Latin America. Forsyth et al reported the recommendations of an expert group, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, for screening and diagnosis of infection with *Trypanosoma cruzi*, the etiologic agent of Chagas disease. Unless otherwise stated below, all the recommendations are considered strong with low levels of evidence.

The populations targeted for screening include at least three groups:
1. those who were born or resided for more than six months in endemic areas of Mexico, Central, or South America;
2. first-degree relatives of individuals with a previous diagnosis of Chagas disease;
3. individuals with documented exposure to triatomines ("kissing bugs") — this recommendation is graded as conditional, low;
4. travelers to endemic areas of Latin America with confirmed exposure to triatomines or with other risk factors — this recommendation is graded as conditional, low;
5. consideration of screening women of childbearing age who have lived in endemic areas — this recommendation is graded as strong, moderate.

Those from endemic areas who have any of the following clinical and/or laboratory abnormalities should undergo diagnostic testing:
- those with suggestive electrocardiographic abnormalities, such as first degree atrioventricular block, premature ventricular contractions, atrial fibrillation, right bundle branch block, left anterior fascicular block, bifascicular block, low-voltage QRS complex, bradycardia, or tachyarrhythmias;
- echocardiographic evidence of regional wall abnormalities, especially those affecting basal inferolateral sites, or apical aneurysm;
- congestive heart failure;
- thromboembolic phenomena;
- megacolon or megaesophagus;
- immunosuppressed patients, including those receiving tissue, organs, or blood components from infected donors and others with epidemiological

risks, including by repeated polymerase chain reaction (PCR) — no GRADE is indicated for this recommendation.

Congenital Chagas disease:
Neonates and infants (< 1 year of age) born to infected mothers should undergo screening as recommended by the Centers for Disease Control and Prevention (CDC) — this recommendation is strong, moderate.

Algorithmic test use:
To enhance diagnostic accuracy, serologic testing for chronic Chagas disease should use two distinct assays that use different antigens or different formats and, if discordant results are obtained, a third distinct test should be used as the tie breaker. In low prevalence contexts, public health laboratories and clinicians performing screening should use the most sensitive test available and follow the same recommendation regarding repeat testing. These recommendations are strong, moderate.

Initial evaluation of symptomatic or asymptomatic patients in whom Chagas disease has been confirmed:
This should include an electrocardiogram (strong, high) and an echocardiogram. If the latter is not available, a chest X-ray should be performed (conditional, low).

■ COMMENTARY

The natural history of Chagas disease was examined recently by evaluation of a cohort of infections identified by screening of blood donors in Brazil.[1] Evaluation at the time of initial screening found that approximately one in 10 already had known diagnosis of cardiomyopathy and, on follow-up almost two decades later, approximately one-half were dead, with a mortality rate of 80.9 per 1,000 person-years. Of those first found to have cardiomyopathy at screening, the mortality rate at follow-up was 15.1/1,000 person-years, while it was only 3.7/1,000 and 3.6/1,000 person-years in seropositives without cardiomyopathy and in seronegatives, respectively. New-onset cardiomyopathy was detected during the follow-up period in 12% of seropositives, occurring at a rate of 13.8/1,000 person-years, while it occurred at a rate of only 4.6 /1,000 person-years in seronegatives.

Thus, given the estimate of > 300,000 people affected in the United States, Chagas disease is a significant public health problem that must be better addressed. The recommendations of the expert panel reviewed here are an important step in this process. ■

REFERENCE

1. Nunes MCP, Buss LF, Silva JLP, et al. Incidence and predictors of progression to Chagas cardiomyopathy: Long-term follow-up of *Trypanosoma cruzi*-seropositive individuals. *Circulation* 2021;144:1553-1566.

ABSTRACT & COMMENTARY

# Infections Before Age 20 Years Increase the Risk of Multiple Sclerosis

***By Hai H. Hoang, MD***

*Assistant Professor of Clinical Neurology, Weill Cornell Medical College*

SYNOPSIS: The relationship between childhood infections and the risk of multiple sclerosis is supported by increasing evidence. Using the Swedish Total Population Register, researchers found that patients diagnosed with infection in adolescence showed an increased risk of multiple sclerosis, even after exclusion of infectious mononucleosis, pneumonia, and central nervous system infection.

SOURCE: Xu Y, Smith KA, Hiyoshi A, et al. Hospital-diagnosed infections before age 20 and risk of a subsequent multiple sclerosis diagnosis. *Brain* 2021;144:2390-2400.

There are many theories on the etiology of multiple sclerosis. Frequently cited in increasing the risk of multiple sclerosis is the involvement of infections. Two meta-analyses found that infectious mononucleosis, a clinical manifestation of Epstein-Barr virus infection, in adolescents and young adults more than doubled the multiple sclerosis risk. Other infectious pathogens that have been linked with multiple sclerosis include human herpesvirus 6 (HHV-6) and *Chlamydia pneumoniae*.

However, the underlying mechanism between infections and an increased risk of multiple sclerosis is not known. One theory includes the molecular mimicry hypothesis, which suggests that infectious agents with homologous sequences or structures to a

host's myelin antigens could trigger cross-activation of autoreactive T cells to attack host tissue. Another theory suggests that macrophages and natural killer cells activated by infectious agents elsewhere in the body, such as the lungs, can result in pro-inflammatory cytokine production and nonspecific activation of pre-primed T cells. This allows them to cross the blood-brain barrier, causing inflammation in the central nervous system (CNS), and inducing multiple sclerosis pathogenesis by triggering autoimmune responses against myelin.

Xu et al used a large population-based cohort in Sweden to assess the risk of a multiple sclerosis diagnosis from age 20 years associated with hospital-diagnosed infection in adolescence (ages 11-19 years) and earlier childhood (between birth and age 10 years). The researchers hypothesized that during adolescence, environmental exposures are likely to be more causally associated with an increased risk of a subsequent diagnosis of multiple sclerosis and that exposures in earlier childhood are less likely to contribute to such a diagnosis.

A total of 462,157 and 338,352 individuals had hospital-diagnosed infections between birth and age 10 years and between ages 11 and 19 years, respectively. Only infections before age 20 years were considered in patients older than 25 years of age with first multiple sclerosis diagnosis, so that there was a delay of at least five years between exposure and multiple sclerosis diagnosis.

Any infection from birth to 10 years of age was not statistically significantly associated with an increased risk of a subsequent diagnosis of multiple sclerosis when compared to no infection from birth to 10 years of age. Those at greater risk of a multiple sclerosis diagnosis were individuals with any infection in adolescence, defined as at between the ages of 11 and 19 years. Infectious mononucleosis in adolescence, between ages 11 and 19 years, increased the risk of being diagnosed with multiple sclerosis after adjustment for pneumonia, sex, and parental socioeconomic position. Viral infection (excluding infectious mononucleosis in adolescence) did not statistically significantly increase the risk of being diagnosed with a subsequent case of multiple sclerosis, compared with no viral infection. However, there was an increased risk of being diagnosed with multiple sclerosis associated with bacterial infection in adolescence, which remained statistically significant when individuals with bacterial infection but without CNS infection, infectious mononucleosis, and pneumonia diagnoses were compared with those without bacterial infection.

This study concluded that any hospital-treated infection in adolescence increased the risk of a multiple sclerosis diagnosis from age 20 years, although the effect size was small (hazard ratio, 1.33).

## ■ COMMENTARY

Given that this study relied on patients hospitalized for an infection, the total number of infections in adolescence and earlier childhood was underestimated, because infections diagnosed in outpatient clinics were not included. Another limitation was the inability to analyze the risk of a multiple sclerosis diagnosis associated with specific types of CNS infection, because of small numbers of patients with multiple sclerosis and earlier CNS infections. Although this study was able to identify multiple infectious pathogens rather than a single pathogen contributing to the risk of a multiple sclerosis diagnosis, the study did not consider whether multiple infectious pathogens act independently or interact with each other in an additive or multiplier effect. Overall, this was a well-designed cohort study, which further supports the theory that infections during childhood and adolescence may play a role in the underlying cause for multiple sclerosis. ■

Infectious Disease [ALERT]

# Updates

By Carol A. Kemper, MD, FACP

## *Candida auris* Outbreak in Southern California

SOURCE: Karmarkar EN, O'Donnell K, Prestel C, et al. Rapid assessment and containment of *Candida auris* transmission in postacute care settings — Orange County, California, 2019. *Ann Intern Med* 2021;174:1554-1562.

Quietly, in 2018-2019, *Candida auris* was introduced and quickly spread among southern California long-term acute care facilities (LTAC) and ventilatory-capable skilled nursing facilities (vSNF). Before long, an outbreak was in full swing, involving 182 cases at nine different facilities.

Previous to this, only two cases of *C. auris*, both urinary isolates, had been detected in California. But beginning in October 2018, laboratory surveillance began to detect *C. auris* in random urine specimens in southern California. By February 2019, *C. auris* was detected in a patient in a vSNF in Orange County.

Within a month, point prevalence surveillance was begun in 17 facilities in the area, initially identifying 44 additional patients in three LTAC and six vSNF. Surveillance was expanded, patients were tested at discharge from a facility, and clinical specimens were examined for suspicious yeast. Point prevalence surveillance continued every two weeks at any facility with an identified case, and then monthly for those with negative surveillance for two consecutive testings two weeks apart.

By October 2019, 182 cases of *C. auris* had been identified, confirming ongoing transmission within and between facilities. The median age was 72 years (range, 29 to 93 years). A majority of the patients were non-ambulatory (73%), and many were dependent on tracheostomies and gastrostomy tubes. Fourteen (8%) patients developed clinical infection, including infections of the blood stream (43%), urine (21%), and wounds, abdominal abscesses, drains, and respiratory specimens (14% each). By January 2020, 22 of 182 patients (12%) died within 30 days of identification of *C. auris*, and 47 (26%) died within 90 days, although only one of these deaths was directly attributed to *C. auris*.

At the same time, investigation revealed critical gaps in infection prevention, environmental cleaning and disinfection, respiratory therapy practices, and hand hygiene, which were rectified. Follow-up assessments demonstrated improvement in cleaning practices, better signage, chart labeling, and improved hand hygiene rates. Improved infection prevention practices and ongoing surveillance were able to limit the outbreak to just two facilities.

Whole genomic sequencing of 81 available isolations revealed they were all highly related within clade III, indicating the outbreak likely began with a single unrecognized case, with fairly recent transmission between the nine facilities. Susceptibility studies of 137 isolates showed them all to be azole resistant (fluconazole minimum inhibitory concentration (MIC) ≥ 32 mcg/mL) and echinocandin susceptible. Ten (7%) were amphotericin resistant (MIC ≥ 2 mcg/mL, confirmed by Etest), confirming multidrug resistance.

There is an urgent need for enhanced surveillance for *C. auris* in acute care and long-term care facilities throughout the United States. State and local governments should work to improve infection control and environmental cleaning in LTACs (and provide sufficient educational resources, guidance, and funding). Further, there is a need for proactive national interfacility communication and notification for patients colonized and infected with multidrug-resistant/extremely drug-resistant organisms. ■

## Healthcare Worker Vaccine Mandates

SOURCE: Emanuel EJ, Skorton DJ. Mandating COVID-19 vaccination for health care workers. *Ann Intern Med* 2021;174:1308-1310.

"The mutual dependence and reciprocal interest which man has upon man, and all the parts of civilised community upon each other, create that great chain of connection which holds it together." — Thomas Paine, *Rights of Man*, 1791.

Twenty months into the COVID-19 pandemic, and the United States is still wallowing in arguments about vaccine mandates, including those specifically directed at healthcare workers (HCWs). As of October 2021, only 21 of 50 states (42%) require either vaccination or routine testing of HCWs. Only six states mandate "vaccination or termination" for HCWs, barring an acceptable medical or religious exclusion. Nine states have laws actively banning employers from mandating vaccination.

It was not until August 2021 that the federal Department of Health and Human Services (HHS) mandated vaccination for 25,000 members of its own workforce, and as of Nov. 3, 2021, the White House announced that the Centers for Medicare and Medicaid Services (CMS) would require HCWs working in any facility providing care to such patients to be fully vaccinated — covering 17 million workers and 76,000 acute care facilities. Within a week, 10 states filed a lawsuit in the U.S. District Court for the Eastern District of Missouri, alleging that CMS does not have the authority to regulate vaccination, and the court granted a preliminary injunction Nov. 29, 2021.

Although all acute care health facilities, rehabilitation centers, and long-term acute care facilities are required to report HCW influenza vaccination rates to the National Health and Safety Network (NHSN), no specific requirement for influenza vaccination, or for any other vaccine (e.g., hepatitis B virus), for HCWs exists. So why mandate this vaccine and not others, such as influenza? For years, the healthcare community has tacitly recognized a low level risk of nosocomial transmission of influenza and other respiratory viruses from HCWs to patients. However,

the frequency of nosocomial exposure was low, the risk of mortality from influenza is low (~0.02% to 0.03% for H1N1 influenza in 2009), and antiviral treatments are available. In contrast, COVID-19 appears to be more transmissible than influenza, nosocomial exposures are frequent, the mortality rate is higher (~1% to 1.4% in the United States), and effective treatments are lacking.

What are the arguments in favor of mandatory COVID-19 vaccination for HCWs?

1. These authors argue that first and foremost, HCWs have an ethical obligation to "do no harm" and to protect their patients and their patients' families. This includes everyone working in a healthcare capacity, from the administrators to the janitors. Masking HCWs is helpful at reducing risk, but masks are designed to protect the wearer — and provide lesser protection when exhaling/talking near another person. So, while personal protective equipment (PPE) is helpful for protecting the HCW, it does not adequately prevent transmission to patients (who are unmasked).

2. Secondly, HCWs have an obligation to set an example and promote healthy behaviors. Much has been made about the real and imagined risks of the various COVID-19 vaccines. But if 17 million HCWs stand together in their willingness and acceptance of the real but tiny risk of COVID-19 vaccination, it can only serve to make others in the community more accepting. HCWs understand and can interpret the data about vaccine efficacy and risk far better than anyone else in the workforce and can serve as examples to their families and communities.

3. Mandates increase vaccine rates.

I would like to add the following to these arguments:

• We, as a society, and HCWs in particular, have an obligation to protect those who cannot protect themselves, including the developmentally disabled, the elderly, and the infirm. The very patients at greatest risk from COVID-19 infection are the least likely to have an adequate immune system response to vaccination. We place elderly patients in nursing homes, ostensibly for their safety. And yet, *The New York Times* reported on Oct. 21, 2021, a 69% vaccination rate among nursing home workers, and a rate of less than 60% in 10 states. In our county, mortality from COVID-19 infection for people 70-79 years of age is 21.8%, and for the very elderly (85 years and older) it is 35.2%. Although many individual nursing homes have mandated vaccination for their staff, some are waiting for a federal mandate.

• Available therapies for COVID-19 are often ineffective. When nosocomial exposure occurs, even the best supportive care may not be sufficient to guarantee survival. After 20 months of COVID-19, we know that nosocomial outbreaks often are not started by infected patients, but by employees with community-acquired infection. This risk can be decreased with HCW vaccination.

• HCWs don't just have an obligation to protect our patients, but to protect each other.

• HCWs have an obligation to be first in line for vaccination — and to be willing to possibly accept more risk — not only because we are at greater risk for exposure, but because we should be the first on that field. That is our job. There is a shared and proud history of HCWs being the first in line.

• Mandates and deadlines can help HCWs who procrastinate, dawdle, or who are sitting on the fence. I heard one HCW say, "I was glad someone made the decision for me." For those who may see grief at home for the decision, it takes the decision out of their hands.

• Vaccination preserves the workforce. With our first COVID-19 patient, 82 HCWs were exposed, and 70 were furloughed for 14 days. Within a day — and a single unrecognized patient — half of our intensive care unit nurses, three critical care physicians, and half of our respiratory therapists were sent home. It quickly became apparent to everyone that hospitals were going to run out of staff. Vaccination not only reduces the risk of acquired HCW infection, but vaccinated employees exposed to COVID-19 are followed and offered testing — and they can continue to work. Unvaccinated employees with exposure still are furloughed. Facilities cannot function if essential staff are unable to work.

• Vaccination reduces the workload on Employee Health and Infection Prevention. In our facility, both departments have spent hundreds of man hours following up on patient and HCW exposures — requiring individual assessment of risk, exposure, PPE, vaccination, and counseling. Despite SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) screening before all procedures and for all admissions, exposures continue to occur. It is a huge amount of work. But much of that work is reduced if the workforce is vaccinated.

• Vaccination promotes camaraderie and well-being among the staff. If you know a colleague has chosen not to be vaccinated, how does that make you feel? In a very real way, their choice affects others working on the unit. ■

## CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Log onto ReliasMedia.com and click on My Account. *First-time users must register on the site.*
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%. Tests are taken with each issue.
4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be emailed to you.

## CME QUESTIONS

**1. In the United States, most mumps illness:**

a. occurs in children.

b. occurs in unvaccinated individuals.

c. occurs in international travelers and contacts of international travelers.

d. occurs despite having up-to-date vaccination coverage.

**2. Which of the following is correct regarding *Malassezia restricta*?**

a. It is a monomorphic yeast.

b. It can be detected on affected excised cardiac valves using 18S rDNA polymerase chain reaction amplification and sequencing.

c. It is highly susceptible to echinocandins.

d. In contrast to *Malassezia furfur*, it is not associated with skin infection.

**3. Which of the following is correct regarding malaria in the United States in 2017?**

a. Most cases were caused by *Plasmodium vivax*.

b. Most cases were imported from India.

c. Less than 30% of U.S. residents with malaria had taken chemoprophylaxis during their travel to endemic areas.

d. Molecular studies indicated that resistance to artesunate is common among *Plasmodium falciparum* in the U.S. cases.

**4. Which of the following is correct regarding the use of artesunate in the treatment of *Plasmodium falciparum* infection in France between 2011 and 2017?**

a. Parasitological failure occurred in < 10% of patients who were followed with repeated blood smears.

b. The mortality rate was 41%.

c. The mortality rate was higher in patients with parasitemia levels of 4% to 10% than in those with lower levels of parasitemia.

d. Post-artesunate-delayed-hemolyis occurs more frequently in patients of African origin compared to those of European origin.

**5. Which of the following is a routine indication for serologic screening for Chagas disease in the United States?**

a. A history of myocardial infarction

b. Unstable angina

c. Pulmonary hypertension

d. Congestive heart failure in patients from endemic areas

## CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.