DIAGNOSING FEVER IN RETURNING TRAVELERS

-RECOMMENDATIONS FROM THE BEDSIDE AND LABORATORY

CARLOS DEL RIO, M.D., MCAP, FIDSA
D. JANE HATA, PH.D., D(ABMM)

©2025 Mayo Foundation for Medical Education and Research

LEARNING OBJECTIVES

- Three illustrative cases of fever in travelers
- Standard of care tests
- Esoteric tests
- New diagnostic approaches
  - Syndromic NAAT panels
- Laboratory workflow

©2025 Mayo Foundation for Medical Education and Research

1 CASE DESCRIPTION

©2025 Mayo Foundation for Medical Education and Research

CASE # 1

- A 52 y/o women originally from Nigeria returned from a one-month trip in which she visited family and friends that live predominantly in the Borno State in the North-East region of the country.
- She did not take malaria prophylaxis as she grew up in Nigeria and “there was never a need to take medicines”.
- States that as she was getting on the plane to return to the U.S., she started to have chills and later had fevers.
- Since then, she notes having daily evening fevers to 39 – 40°C. She feel tired and has a bad headache.
- Went to a local clinic and was prescribed Acetaminophen which she has taken without improvement.
- On physical exam she is afebrile, her HR is 110 and her BP in 140/70. On exam she is pale, in mild distress and has a palpable spleen tip.
- Laboratory finding include mild anemia and elevated liver enzymes.

©2025 Mayo Foundation for Medical Education and Research

TRAVEL HISTORY IS KEY!

- Estimated that 8% of travelers require medical care
  - 30% require hospitalization
- When did travel occur?
  - Variable incubation periods
- Type of travel and duration
  - Urban?
  - Rural?
  - Ecotourism/Adventure tourism?
  - Other exposures (animals, plants, insects, food, water)?
- Sexual exposures
- Refugee/Migrant status
- Onset and nature of symptoms
  - Duration of fever
  - Other symptoms

Sondén K et al. Travel Med Infect Dis. 2025 May-Jun;65:102861.
Thwaites GE, Day NP. N Engl J Med. 2017 Feb 9;376(6):548-560.

©2025 Mayo Foundation for Medical Education and Research

INITIAL LABORATORY TESTING

- CBC and differential
- Liver enzymes
- Blood cultures
- Blood smear for malaria and/or rapid antigen diagnostic test (RDT)
  - RDT must be confirmed by smear

- Lumbar puncture and CSF analysis
- Other imaging
- Patient presentation and history will drive additional testing
  - Diarrhea, respiratory symptoms, rash, jaundice

Thwaites GE, Day NP. N Engl J Med. 2017 Feb 9;376(6):548-560.
Wu HM. Semin Diagn Pathol. 2019 May;36(3):197-202.

©2025 Mayo Foundation for Medical Education and Research

“THINK HORSES, NOT ZEBRAS”

-Dr. Theordore Woodward, Univ of Maryland

©2025 Mayo Foundation for Medical Education and Research

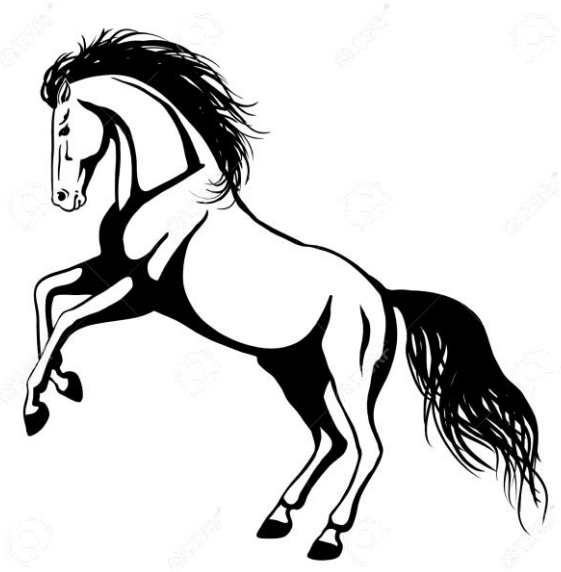
MOST LIKELY PATHOGENS; “THE HORSES”

Most Common

- Malaria
  - Species related to geography
- Dengue Fever
- EBV
  - Mononucleosis
- Rickettsial infections
  - Typhus, RMSF, ehrlichosis, *Anaplasma*
- *Salmonella enterica*
  - Serotype typhi, paratyphi
  - Enteric fever
- “Other viral infections”

Also Consider

- Influenza
- Sars CoV-2
- ETEC
- Zika
- Chikungunya
- MDR bacteria
- TB
- Regional outbreaks



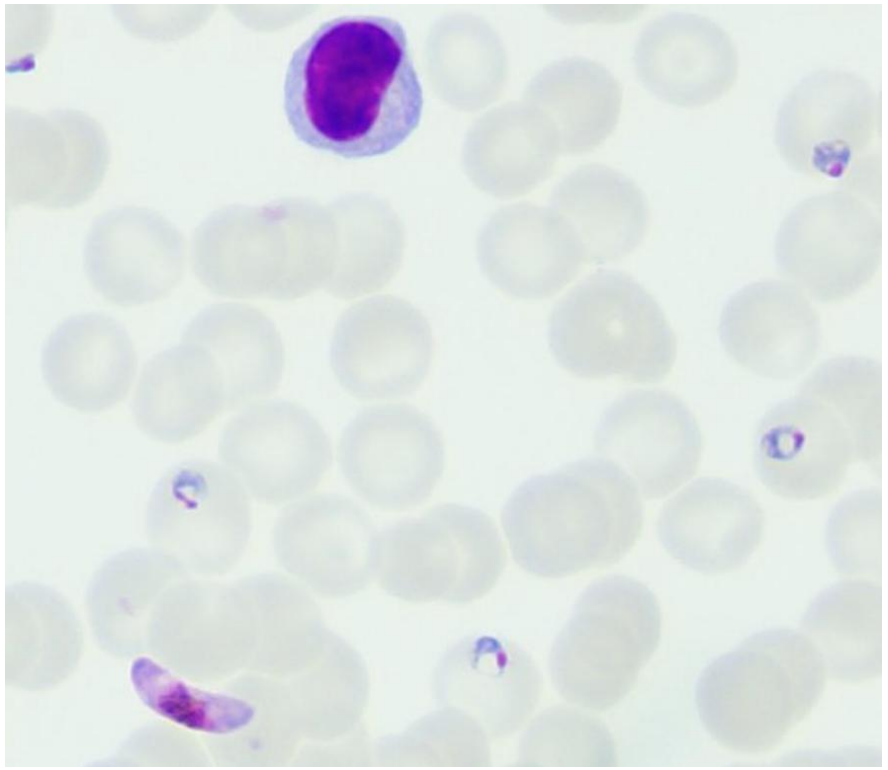
https://www.uptodate.com/contents/evaluation-of-fever-in-the-returning-traveler

Brown AB, et al. MMWR Surveill Summ. 2023 Jun 30;72(7):1-22.

©2025 Mayo Foundation for Medical Education and Research

CASE #1 - MALARIA

- Most likely cause of fever in travelers
  - *P. falciparum, P. vivax, P. ovale, P. malariae*
- Laboratory should have ability to screen STAT
  - Thick and thin smears
  - Detection of other pathogens (*Babesia, Ehrlichia*, Trypanosomes)
- Speciation from thin smears
  - Calculation of percent parasitemia
- Rapid antigen tests
  - Lateral flow immunochromographic method
    - 1 test FDA approved for use
  - Low sensitivity at ≤ 200 parasites/microliter
- NAATs
  - Not widely available, may not be STAT test



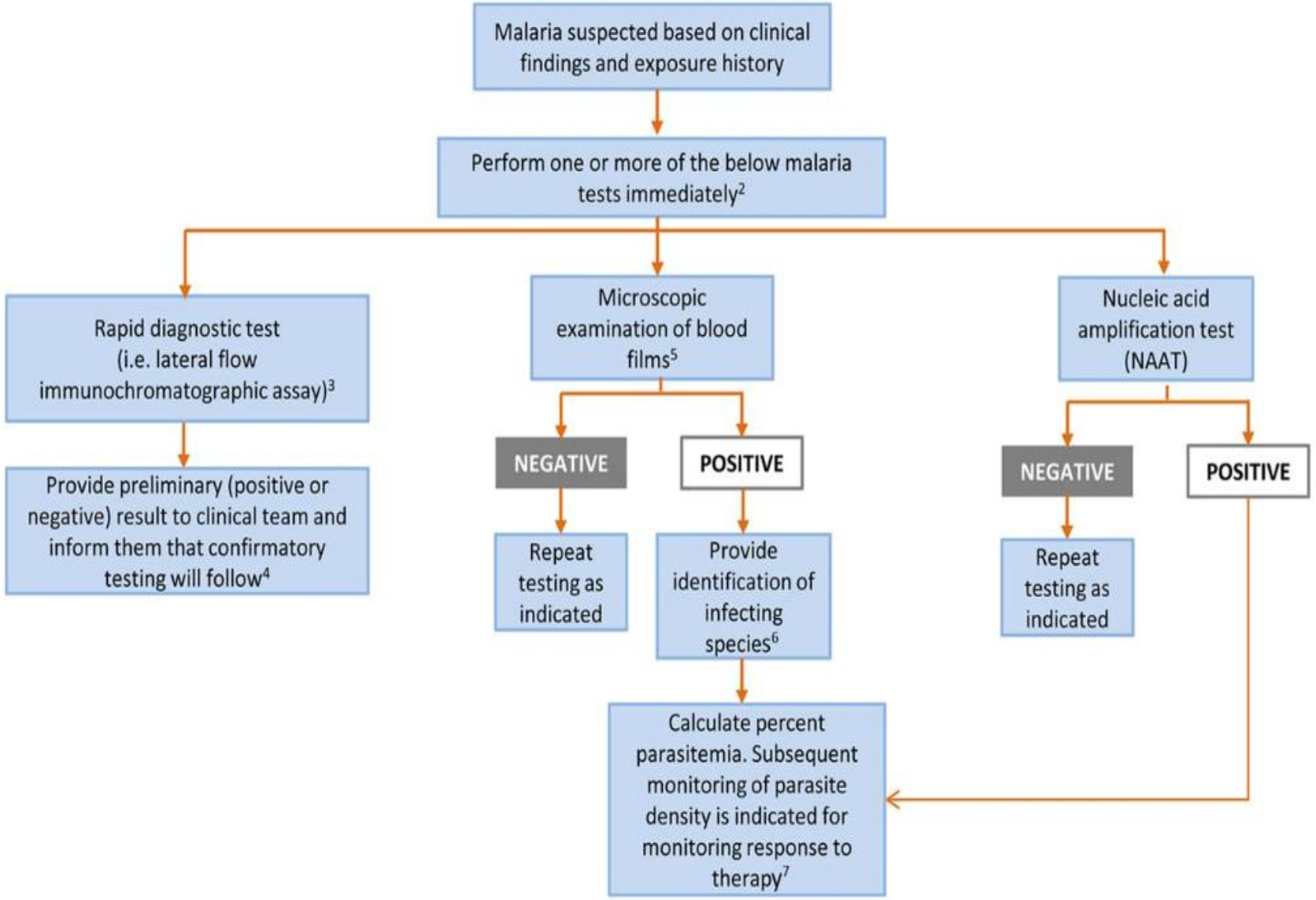
Christmas Eve 2024

Thwaites GE, Day NP. N Engl J Med. 2017 Feb 9;376(6):548-560.

©2025 Mayo Foundation for Medical Education and Research

LABORATORY ALGORITHM FOR MALARIA

- Smears still considered gold standard
  - Repeat every 6-8 hours for up to 3 days
- Speciation critical for clinical management
- Quantification
  - Severe malaria ≥ 5% parasitemia
- RDT requires smear confirmation
- NAATs require smear confirmation for % parasitemia



Mathison BA, Pritt BS. 2017. J Clin Microbiol 55:7.

©2025 Mayo Foundation for Medical Education and Research

LESS LIKELY PATHOGENS; “THE ZEBRAS”

- Viral infections
  - Measles
  - Viral hemorrhagic fevers
    - Ebola
    - Marburg
  - Rabies
  - WNV
  - Mpox
  - Oropouche
- Parasitic infections
  - Leishmaniasis
  - Various helminths
  - *Entamoeba histolytica*
- Bacterial infections
  - Brucellosis
  - Tetanus
  - Melioidosis
  - Q Fever
- US Travel
  - Plague
  - Babesiosis
  - *Coccidioides immitis/posadasii*
  - Ehrlichiosis/Anaplasmosis
  - Hantavirus
- Emerging pathogens

https://www.uptodate.com/contents/evaluation-of-fever-in-the-returning-traveler

Brown AB, et al. MMWR Surveill Summ. 2023 Jun 30;72(7):1-22.

©2025 Mayo Foundation for Medical Education and Research

TYPES OF TESTS AVAILABLE
-*WHAT CAN YOUR LAB DO?*

Culture/Microscopy

- Bacterial ID
  - Phenotypic
  - MALDI-TOF
- AST methods
- Ova and Parasite exam
- Malaria smears

Serology

- Antibody detection
- Antigen detection
- Immuno-chromatographic
  - Lateral-flow devices
- Immunoassay
  - Automation

Molecular

- NAATs
  - LDTs
- Single analyte
- Multiplex
- Syndromic panels
- NGS

©2025 Mayo Foundation for Medical Education and Research

SYNDROMIC TESTING NAAT PANELS POST-TRAVEL

-ARE THESE USEFUL?

Respiratory

- Adenovirus
- Coronavirus 229E, HKU1, NL63, OC43
- SARS-CoV-2
- HMPV
- Human Rhinovirus/Enterovirus
- Influenza A virus
- Influenza A virus A/H1
- Influenza A virus A/H3
- Influenza A virus A/H1-2009
- Influenza B virus
- RSV

- *Bordetella parapertussis*
- *Bordetella pertussis*
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*

Gastrointestinal

- Astrovirus
- Adenovirus F40/41
- Norovirus GI/GII
- Rotavirus A
- Sapovirus (I, II, IV, and V)

- *Campylobacter (C. jejuni / C. coli / C. upsaliensis)*
- *Clostridioides (Clostridium) difficile* (toxin A/B)
- *Plesiomonas shigelloides*
- *Salmonella*
- *Yersinia enterocolitica*
- *Vibrio (V. parahaemolyticus / V. vulnificus / V. cholerae)*
- EAEC, EPEC, ETEC, STEC EIEC

- *Cryptosporidium*
- *Cyclospora cayetanensis*
- *Entamoeba histolytica*
- *Giardia lamblia*

Meningitis/Encephalitis

- CMV
- Enterovirus
- HSV 1,2
- HHV-6
- Human parechovirus
- VZV

- *Escherichia coli* K1
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

- *Cryptococcus (C. neoformans/C. gattii)*

©2025 Mayo Foundation for Medical Education and Research

SYNDROMIC TESTING NAAT PANELS POST-TRAVEL

-ARE THESE USEFUL?

Respiratory

- Adenovirus
- Coronavirus 229E, HKU1, NL63, OC43
- SARS-CoV-2
- HMPV
- Human Rhinovirus/Enterovirus
- Influenza A virus
- Influenza A virus A/H1
- Influenza A virus A/H3
- Influenza A virus A/H1-2009
- Influenza B virus
- RSV

- *Bordetella parapertussis*
- *Bordetella pertussis*
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*

Gastrointestinal

- Astrovirus
- Adenovirus F40/41
- Norovirus GI/GII
- Rotavirus A
- Sapovirus (I, II, IV, and V)

- *Campylobacter (C. jejuni / C. coli / C. upsaliensis)*
- *Clostridioides (Clostridium) difficile* (toxin A/B)
- *Plesiomonas shigelloides*
- *Salmonella*
- *Yersinia enterocolitica*
- *Vibrio (V. parahaemolyticus / V. vulnificus / V. cholerae)*
- EAEC, EPEC, ETEC, STEC EIEC

- *Cryptosporidium*
- *Cyclospora cayetanensis*
- *Entamoeba histolytica*
- *Giardia lamblia*

Meningitis/Encephalitis

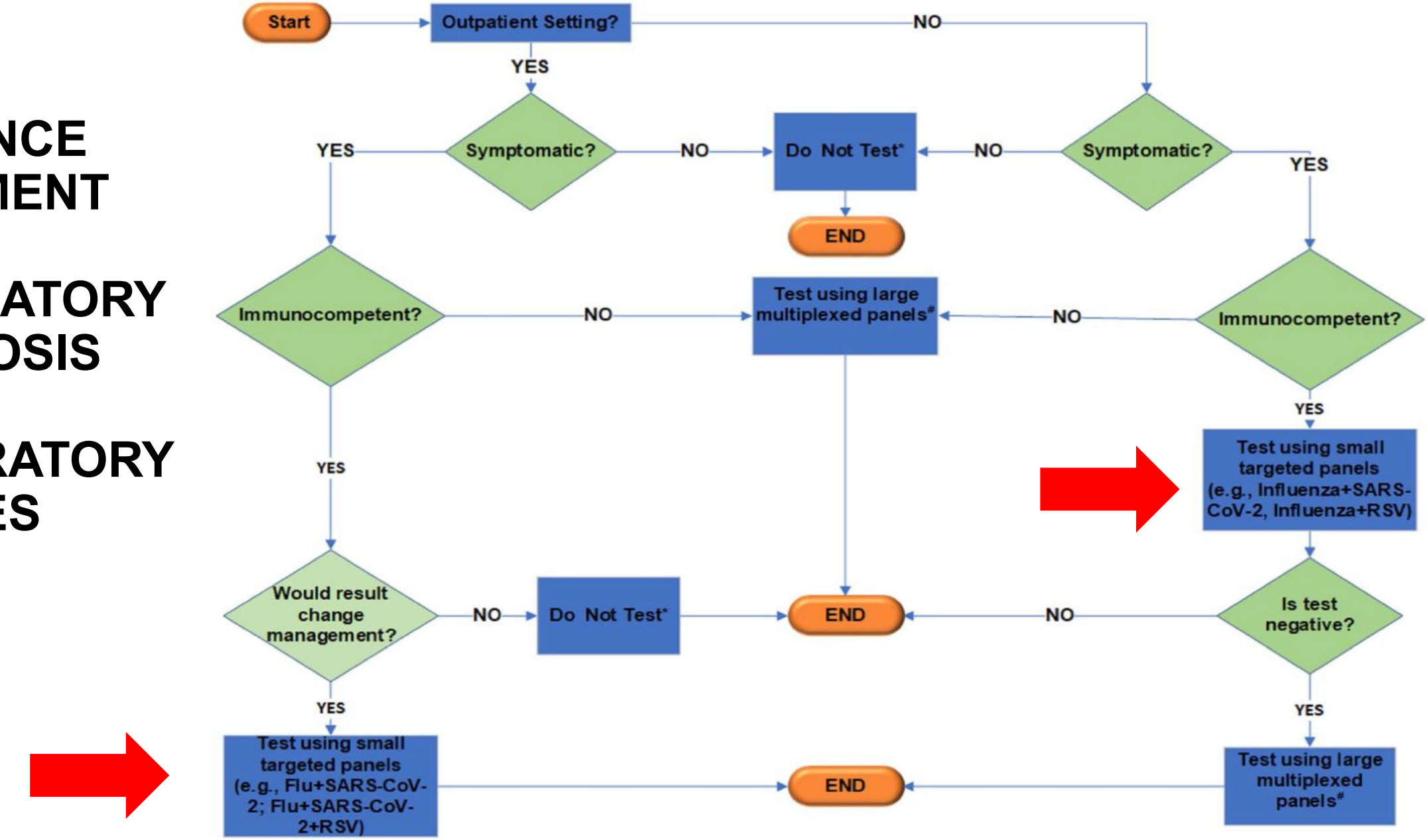
- Targets not among most likely pathogens
- Use based on clinical presentation

*Bacterial culture still needed for AST, submission to PH

- Consider use of smaller, targeted panels or single NAAT assays

©2025 Mayo Foundation for Medical Education and Research

ADLM GUIDANCE DOCUMENT ON LABORATORY DIAGNOSIS OF RESPIRATORY VIRUSES

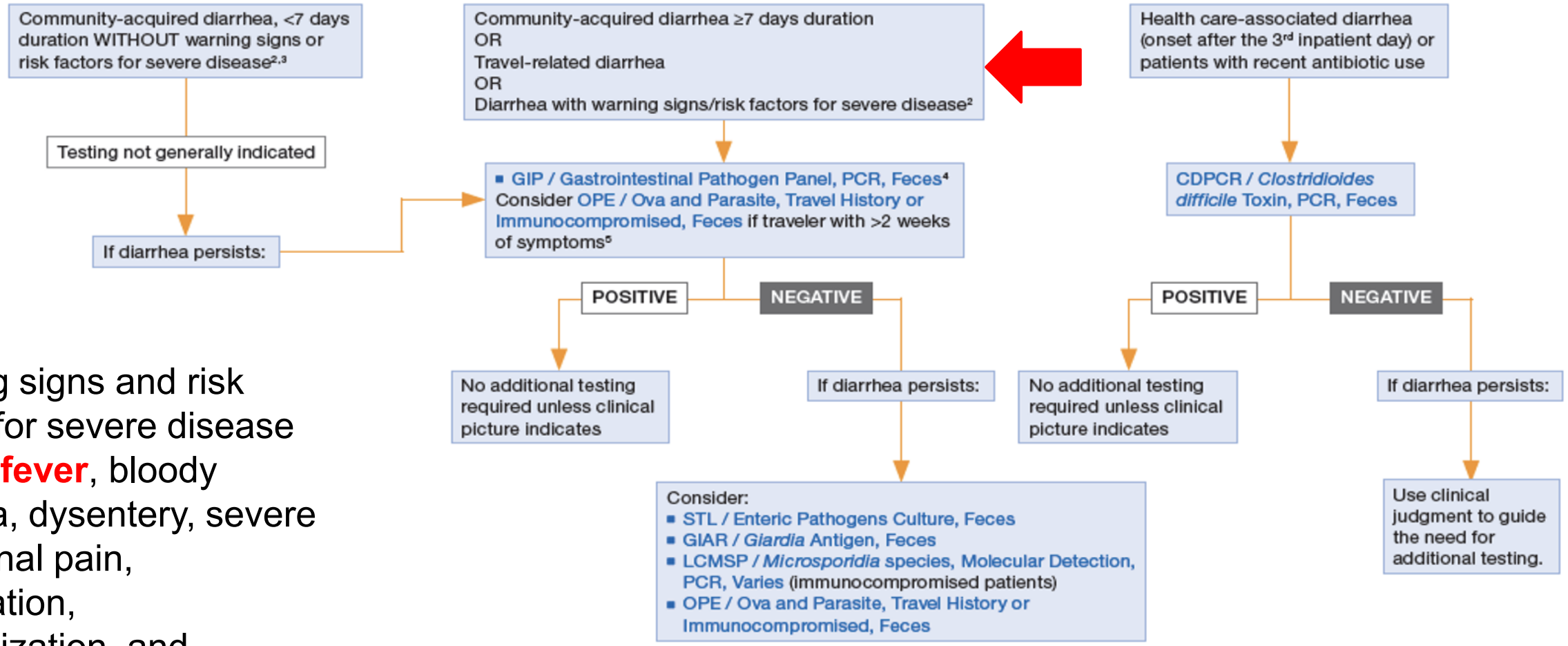


Berry G. et al. J Appl Lab Med. 2024 May 2;9(3):599-628

©2025 Mayo Foundation for Medical Education and Research

LABORATORY TESTING FOR INFECTIOUS CAUSES OF DIARRHEA

MAYO CLINIC LABORATORIES



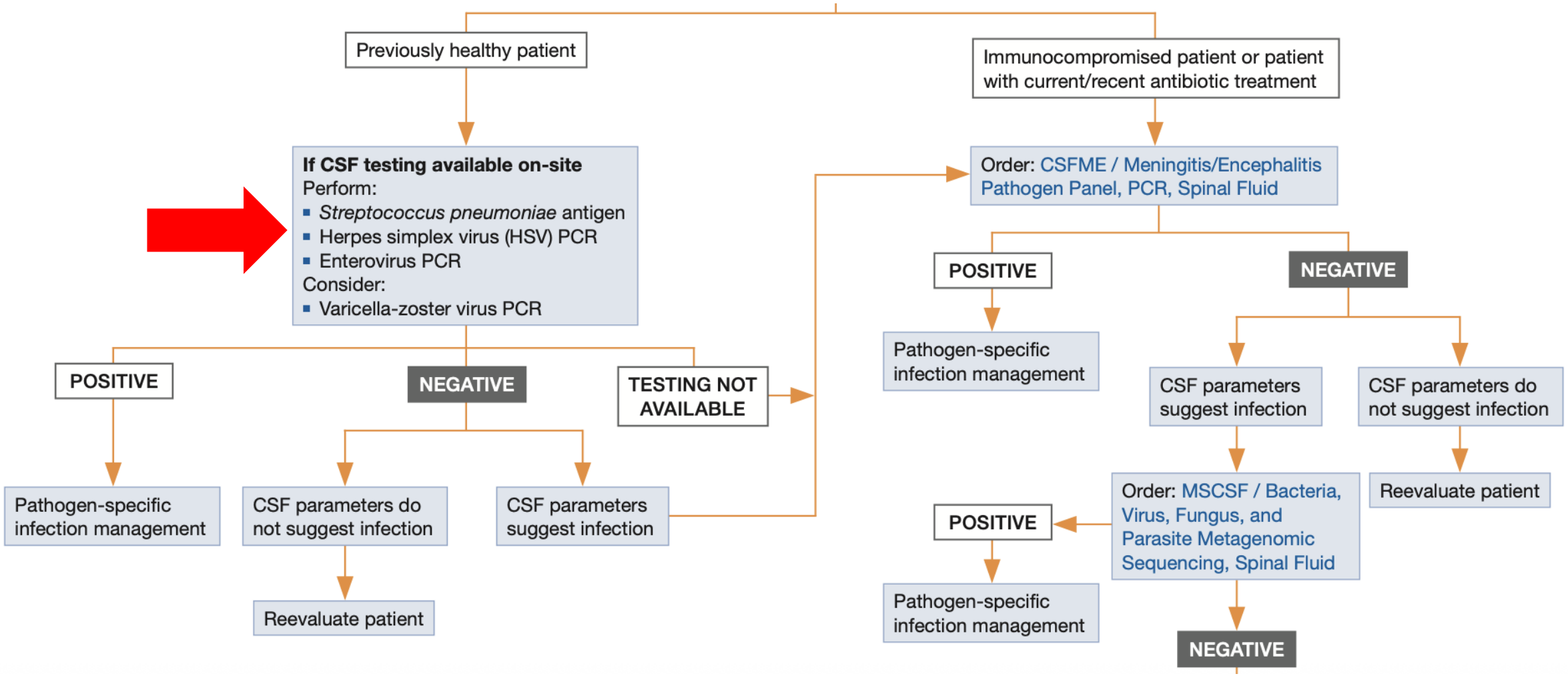
Warning signs and risk factors for severe disease include **fever**, bloody diarrhea, dysentery, severe abdominal pain, dehydration, hospitalization, and immunocompromise

https://www.mayocliniclabs.com

©2025 Mayo Foundation for Medical Education and Research

MENINGITIS/ENCEPHALITIS ALGORITHM

MAYO CLINIC LABORATORIES



https://www.mayocliniclabs.com

©2025 Mayo Foundation for Medical Education and Research

2 CASE DESCRIPTION

©2025 Mayo Foundation for Medical Education and Research

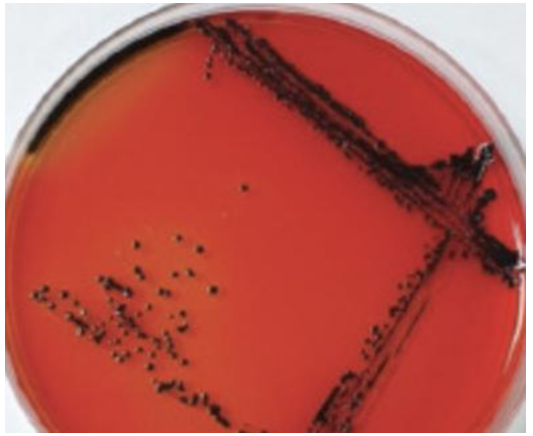
CASE # 2

- A 37 y/o male returned from a 2-week trip to Colombia where he went hiking and backpacking in the jungle.
- He states that during the trip he had a short episode of loose stools.
- Two days after retuning home to the U.S. he developed fever, headache and malaise.
- He has no appetite and feels unwell.
- On physical exam he is febrile to 39^{o} C, his HR is 60 and his BP in 100/60. His exam is otherwise normal with no hepatosplenomegaly.
- Laboratory finding include pancytopenia and elevated liver enzymes.

©2025 Mayo Foundation for Medical Education and Research

CASE #2 LABORATORY WORKUP

- Broad differential
- Stool plated to BA, MAC, XLD
- Gastrointestinal NAAT panel performed
  - *Salmonella* sp.
- Gram-negative bacilli on XLD after 2 days of incubation at 37^{o} C.
  - XLD Red colonies with black center (H_2S)
  - MAC no color
- *Salmonella* sp. identified by MALDI-TOF
- Reported to public health laboratory
  - Isolate submitted for serotyping



Salman HA et al. PMCID: PMC8404135

©2025 Mayo Foundation for Medical Education and Research

CASE #2

WHAT'S A LAB TO DO?

Culture

- Selective or chromogenic media
  - MAC, S/S, HE, XLD, bismuth sulfate, enrichment broth
- TSI: K/A; H_2S
- Consider turnaround time

Serotyping

- Capsular antigen (Vi)
- Somatic antigen (O)
  - Serogroup D
- > 2500 serotypes
- Generally performed at PH laboratories

Antimicrobial Susceptibility Testing

- Only for invasive and typhoidal isolates
- See CLSI M-100
- AM, CIP, LVX, SXT, CRO, CTX, AZM
- XDR emerging (Middle East, SE Asia)

CMPH 5th ed. Ch. 3.7.1.

©2025 Mayo Foundation for Medical Education and Research

CASE #2

WHAT'S A LAB TO DO?

MALDI-TOF

- Need pure culture isolate
- ID as *Salmonella* sp. (genus level)
- Database dependent

Molecular

- Multiplex GI NAAT performed direct from specimen
- *Salmonella* sp. (*enterica* and *bongori*)
- Subtypes Typhi and Paratyphi included
- NGS for strain typing

Reporting

- Reportable to Public Health
  - PulseNet
- Organism needed for PH submittal

CMPH 5th ed. Ch. 3.7.1.

©2025 Mayo Foundation for Medical Education and Research

CASE RESOLUTION

- Identified by public health laboratory by WGS as
  - *Salmonella enterica* subsp. *enterica* serotype Typhi
  - O antigen Serogroup D
- *Salmonella enterica*
  - Six subtypes (I – VI)
- AST results (primary agents): All susceptible
  - Ampicillin
  - Ciprofloxacin/Levofloxacin
  - TMP/SFX
  - Cefotaxime/ceftriaxone
- Emergence of XDR strains with resistance to all first-line agents
  - Pakistan/Iraq; consider carbapenem or azithromycin

https://stacks.cdc.gov/view/cdc/102640.Feb 12, 2021

©2025 Mayo Foundation for Medical Education and Research

3 CASE DESCRIPTION

©2025 Mayo Foundation for Medical Education and Research

CASE # 3

- A 5 y/o boy travelled to Italy with his parents to visit friends that live near Milan. They stayed for 5 days.
- Three days after returning the parents noticed that he had a runny nose and a cough. He developed high fever the next day as well as bilateral conjunctivitis.
- He felt unwell and had no appetite.
- Approximately two days later the mother noticed a rash that was mostly in the hairline and behind the ears.
- On physical exam he is febrile to 38.8^{o} C and tachycardic. He has bilateral conjunctivitis and a maculopapular rash in the face and upper body.
- Laboratory finding include leukopenia with lymphopenia and elevated liver enzymes.
- Mother states that she has her family do not believe in vaccines.

©2025 Mayo Foundation for Medical Education and Research

CASE #3

-*WHAT'S A LAB TO DO?*

- Infectious differential (just a few)

Viruses causing rash	Bacteria causing rash
EBV, VZV	*Neisseria meningitidis*
Primary HIV	Staphylococcal toxic shock
Parvovirus B19	Rickettsial infections
Enterovirus	Typhoid fever

- NP swab submitted for culture and NAAT
  - All analytes negative by respiratory panel
  - Inoculate blood and respiratory cultures
- Clinical presentation can aid diagnosis and guide isolation

Wu HM.Semin Diagn Pathol. 2019 May;36(3):197-202.

©2025 Mayo Foundation for Medical Education and Research

MORE INFORMATION COMES TO THE LAB….

- Patient presentation:
  - Had conjunctivitis, cough, and coryza for 7 days
  - Maculopapular rash on the upper body
  - Unable to confirm vaccination history

- Clinical presentation and history suggests……

Measles

©2025 Mayo Foundation for Medical Education and Research

OPTIONS FOR MEASLES (RUBEOLA) TESTING

- Reportable disease – communicate with your PH lab first for assistance
  - 90% infection rate in susceptible populations
- Identify – Isolate – Inform
  - Handle specimens carefully!
- RT-PCR
  - NP swab, throat swab within 5 days of rash onset
  - Urine within 6-14 days of rash onset
  - Available from public health laboratories, some commercial reference laboratories
  - Laboratory-developed tests could be an option
  - No commercial FDA-approved test available
  - Measles not included on syndromic NAAT panels
- Serologic detection of measles IgM
  - Useful for confirmation
  - Negative in early disease
  - Available from public health laboratories, some commercial reference laboratories

https://www.cdc.gov/measles/hcp/clinical-overview/index.html

©2025 Mayo Foundation for Medical Education and Research

ESOTERIC TESTING FOR TRAVEL ASSOCIATED PATHOGENS

©2025 Mayo Foundation for Medical Education and Research

“TROPICAL FEVER” SYNDROMIC PANELS

BIOFIRE® FILMARRAY® TROPICAL FEVER (TF) PANEL

- *Leptospira* sp. (Group 1)
- Chikungunya
- Dengue
  - Serotypes 1,2,3,4 grouped together
- *Plasmodium* sp.
  - *P. falciparum, P. vivax, P. ovale, P. malariae*, and *P. knowlesi*
- *Plasmodium falciparum*
- *Plasmodium vivax/ovale*
- Specimen: 200 microliters whole blood (EDTA)

Manabe YC et al. Lancet Infect Dis. 2022 Sep;22(9):1356-1364.

©2025 Mayo Foundation for Medical Education and Research

TF ASSAY PERFORMANCE

- From IFU: “Evaluation for more common causes of febrile illness should be considered prior to evaluation with this panel”
- Qualitative results only
  - Quantitation of *Plasmodium* sp. requires smear
- PCR may over diagnose disease in patients from endemic areas

Target	N (pos/neg)	PPA%	NPA%
Leptospira sp.	16/1859	93.8	99.8
Chikungunya	25/1850	100	99.9
Dengue (1-4)	283/1592	94.0	100
Plasmodium sp.	345/1530	98.3	99.2
P. falciparum	248/1627	92.7	99.8
P. vivax/ovale	124/1751	92.7	99.8

Manabe YC, et al. Lancet Infect Dis. 2022 Sep;22(9):1356-1364.

©2025 Mayo Foundation for Medical Education and Research

OTHER ESOTERIC TESTS

HOW TO GET THESE DONE?

- Consider turnaround time and need for clinical intervention
- Serology
  - State PH labs/CDC – check test availability
  - Commercial reference labs
- Other NAAT testing
  - State PH labs/CDC – check test availability
  - Commercial reference labs
- Role of NGS
  - Availability
  - Turnaround time
- Viral culture
  - Few performing laboratories; potentially hazardous
- Develop an LDT?

Consider what you will do before it happens

©2025 Mayo Foundation for Medical Education and Research

LABORATORY COMMITMENT IF ESOTERIC TESTING PERFORMED

Purchase of test platform

Test verification/ validation

Training and competency of staff

Proficiency testing

Quality control/quality assurance

Reagent inventory management

Laboratory workflow

- Random access?
- Once per day?
- Once per week?
- What shift?

©2025 Mayo Foundation for Medical Education and Research

GENERAL TESTING COMMENTS

©2025 Mayo Foundation for Medical Education and Research

LABORATORY BIOSAFETY

- May evolve based on identification of pathogen
- Standard PPE
  - Impermeable gown/lab coat
  - Gloves
  - Additional respiratory protection depending on pathogen
- Use of BSC for specimen manipulation
  - Inoculation of culture plates
  - Creating smears
  - NAAT inoculation
- Use of automated test systems
  - Follow manufacturer recommendations for cleaning and disinfection
- Biohazardous waste disposal

©2025 Mayo Foundation for Medical Education and Research

LABORATORY WORKFLOW

- Consider scenarios ahead of time
  - *What might you be likely to see?*
  - Institution and laboratory drills
- Develop plans through collaboration
  - Infectious Disease
  - Infection Control
  - Clinical services (ED, outpatient)
- Consider what testing is feasible for your laboratory practice
  - Academic or referral center?
  - Small hospital or community hospital?
  - Nature of patient population

HCID Drill June 2025

©2025 Mayo Foundation for Medical Education and Research

COMMUNICATION OF FINDINGS

- Critical/alert value?
- Infection control considerations
- Notification of Public Health
- Key Groups
  - Infectious Disease
  - Infection Prevention
  - Who are your contacts?
- High Consequence Infectious Disease plan?
- Plan for laboratory handling of biological agents?

©2025 Mayo Foundation for Medical Education and Research

RESOURCES

- State PH laboratories and CDC
- CDC Yellow Book
  - https://www.cdc.gov/yellow-book/index.html
- WHO
  - https://www.who.int/emergencies/disease-outbreak-news
- GeoSentinel
  - https://geosentinel.org/alerts/?post_type=alert&s=2025
  - Membership required
- ProMED
  - https://www.promedmail.org
  - Membership required

©2025 Mayo Foundation for Medical Education and Research

THANK YOU AND SAFE TRAVELS!

©2025 Mayo Foundation for Medical Education and Research