biostatistics 2

7.4.2014

Marek Čierny

Q1

A 5-year-old child, who lives with his missionary parents in a rural locality in Sierra Leone, Africa, contracts an illness that is initially characterized by vomiting and periods of moderate fever. Over the next few days, his condition dramatically worsens, he becomes markedly lethargic, and his fever intensifies to the point of delirium and convulsions. At the aid station, a blood smear reveals the infective agent (shown in the image). What is the cause of this child's illness?

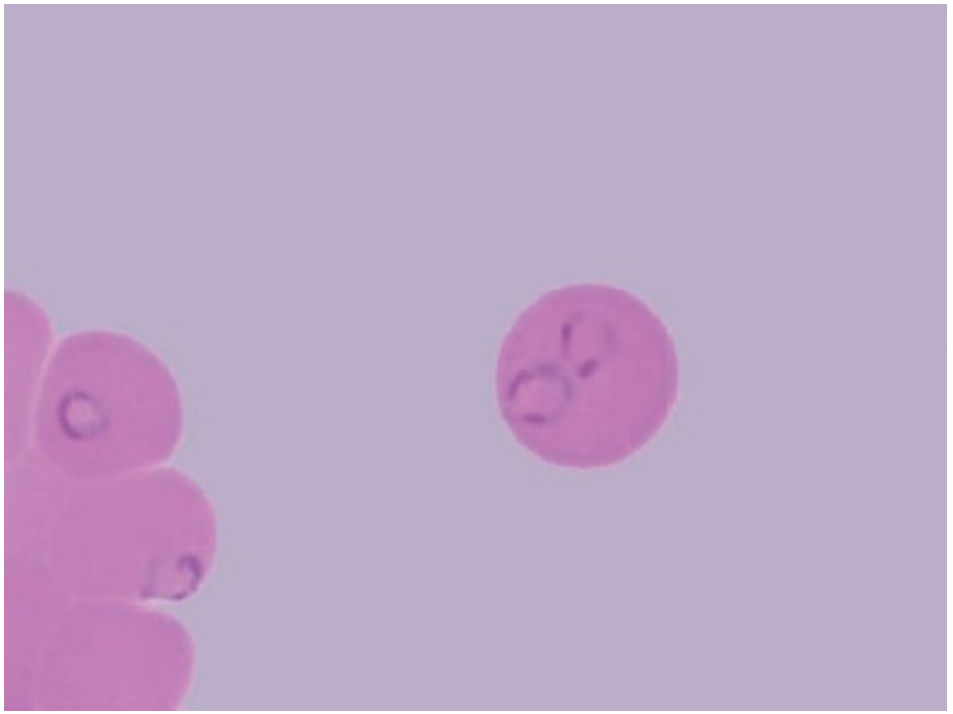
(A) Babesia microti

(B) Brugia malayi

(C) Cryptosporidium parvum

(D) Leishmania tropica

(E) Plasmodium falciparum



Q1

A 5-year-old child, who lives with his missionary parents in a rural locality in Sierra Leone, Africa, contracts an illness that is initially characterized by vomiting and periods of moderate fever. Over the next few days, his condition dramatically worsens, he becomes markedly lethargic, and his fever intensifies to the point of delirium and convulsions. At the aid station, a blood smear reveals the infective agent (shown in the image). What is the cause of this child's illness?

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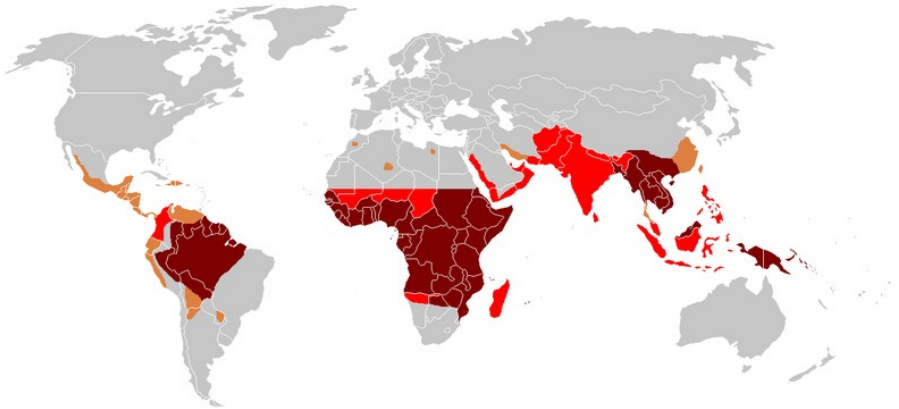
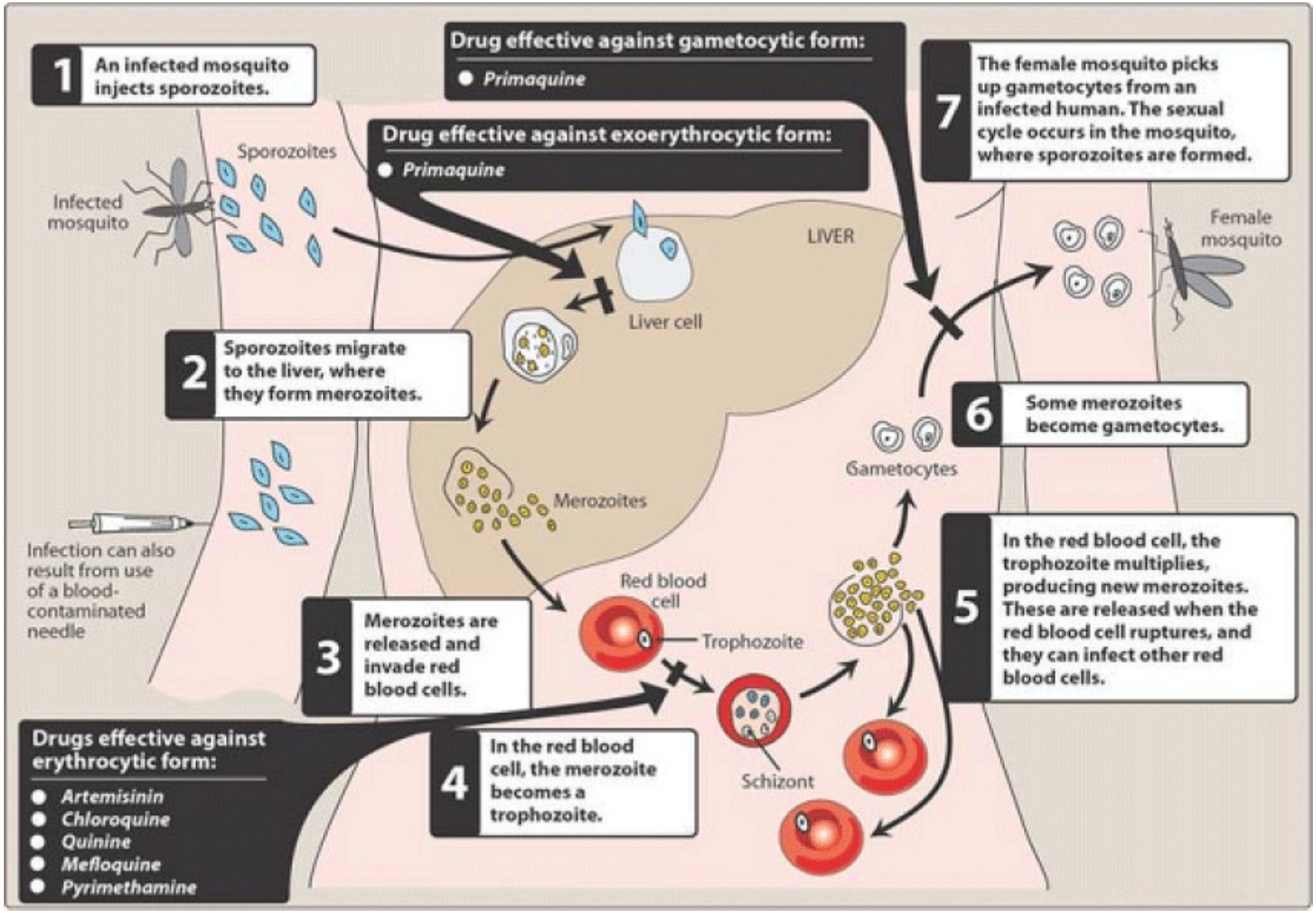
The double ring trophozoites seen in the red blood cells, and the lack of erythrocytic Schüffner's dots are consistent with P. falciparum. This is the most severe form of malaria and rapid diagnosis is critical. This type of malaria is wide spread in Africa and young children are extremely vulnerable to the disease largely because they are immunologically naive. Frequently, the manifestations of fever are experienced by children with a falciparum infection. Complications of this infection include renal failure and cerebral malaria.

Babesia is a related organism that typically causes mild disease, and is transmitted by ticks in the northeastern United States. Brugia is a helminth parasite associated with elephantiasis. Cryptosporidium is an intestinal protozoan associated with severe diarrhea in the immune compromised and L. tropica is an intracellular protozoancausing skin ulcers.

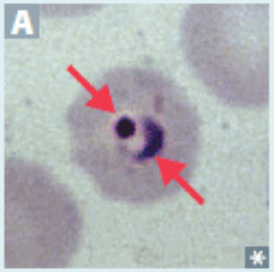
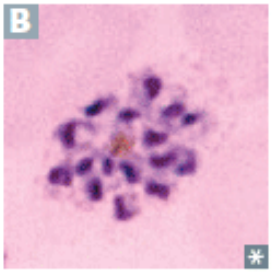


Q1


1 An infected mosquito injects sporozoites.
Drug effective against gametocytic form:
Primaquine
7 The female mosquito picks up gametocytes from an infected human. The sexual cycle occurs in the mosquito, where sporozoites are formed.
Drug effective against exoerythrocytic form:
Primaquine
Sporozoites
Infected mosquito
LIVER
Liver cell
Female mosquito
2 Sporozoites migrate to the liver, where they form merozoites.
6 Some merozoites become gametocytes.
Gametocytes
Merozoites
Infection can also result from use of a blood-contaminated needle
Red blood cell
Trophozoite
5 In the red blood cell, the trophozoite multiplies, producing new merozoites. These are released when the red blood cell ruptures, and they can infect other red blood cells.
3 Merozoites are released and invade red blood cells.
Drugs effective against erythrocytic form:
Artemisinin
Chloroquine
Quinine
Mefloquine
Pyrimethamine
4 In the red blood cell, the merozoite becomes a trophozoite.
Schizont

Q1

Protozoa—Hematologic infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Plasmodium ***P. vivax/ovale*** ***P. falciparum*** ***P. malariae*** 	Malaria: fever, headache, anemia, splenomegaly *P. vivax/ovale*—48-hr cycle (tertian; includes fever on first day and third day, thus fevers are actually 48 hr apart); dormant form (hypnozoite) in liver *P. falciparum*—severe; irregular fever patterns; parasitized RBCs occlude capillaries in brain (cerebral malaria), kidneys, lungs *P. malariae*—72-hr cycle (quartan)	Mosquito (*Anopheles*)	Blood smear, trophozoite ring form within RBC A, schizont containing merozoites B 	Begin with chloroquine, which blocks *Plasmodium* heme polymerase; if resistant, use mefloquine or atovaquone/proguanil If life-threatening, use intravenous quinidine (test for G6PD deficiency) *Vivax/ovale*—add primaquine for hypnozoite (test for G6PD deficiency)

CLINICAL AND LABORATORY PREDICTORS OF IMPORTED MALARIA IN AN OUTPATIENT SETTING

- The review included a study
  - which "investigated all patients presenting at a university outpatient clinic with a complaint of fever or malaise after returning from the tropics" "and in whom a malaria test was performed".
  - For each patient the collected data "included the patient's demographical data, travel history, preventive measures against malaria, details on symptoms and signs at admission, laboratory results, final diagnosis, treatment, and outcome."
  - "Likelihood ratios (LR) of the different clinical and laboratory parameters" were compared between two groups:
    - A: "patients with at least one of the tests positive for malaria"
    - B: "patient with negative tests for malaria on all occasions"
- What's the type of this study, which was included in the review?
- A) Cross-sectional study

  B) Case-control study

  C) Cohort study

  D) Systematic review

  E) Clinical trial

CLINICAL AND LABORATORY PREDICTORS OF IMPORTED MALARIA IN AN OUTPATIENT SETTING

- The review included a study
  - which "investigated all patients presenting at a university outpatient clinic with a complaint of fever or malaise after returning from the tropics" "and in whom a malaria test was performed". - INCLUSION CRITERIA
  - For each patient the collected data "included the patient's demographical data, travel history, preventive measures against malaria, details on symptoms and signs at admission, laboratory results, final diagnosis, treatment, and outcome." - FINDINGS
  - "Likelihood ratios (LR) of the different clinical and laboratory parameters" were compared between two groups:
    - A: "patients with at least one of the tests positive for malaria" CASES
    - B:"patient with negative tests for malaria on all occasions" CONTROLS
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CLINICAL AND LABORATORY PREDICTORS OF IMPORTED MALARIA IN AN OUTPATIENT SETTING

- In the study:
  - the prevalence of malaria in included population was 30%
  - Inadequate prophylaxis had 84% sensitivity and 47% specificity for diagnosis of malaria

- A 40y/o patient visits outpatient clinic in Lausanne because he had malaise and fever (38C) for 4 days. Two weeks ago he returned from trip to Kongo. He did not take mefloquine for prophylaxis.
- Using the data from the study, what is the **probability that this patient have malaria** before performing a physical exam?
- 23% 30% 40% 47% 50% 60% 84% cannot say

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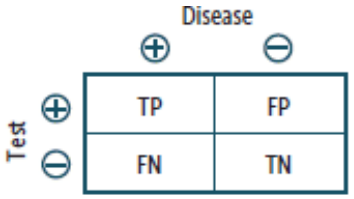
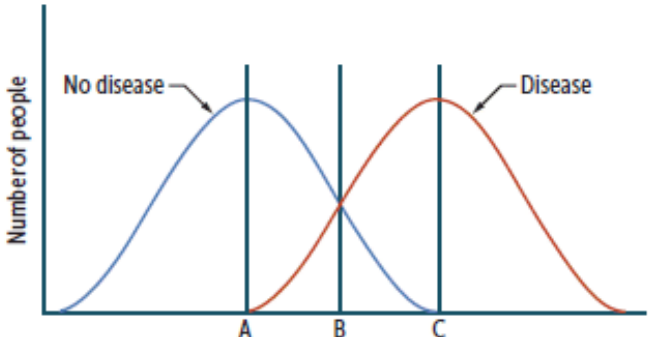
		D+		D-	
		n	%	n	%
	T+				
	T-				

Evaluation of diagnostic tests	Uses 2 × 2 table comparing test results with the actual presence of disease. TP = true positive; FP = false positive; TN = true negative; FN = false negative. Sensitivity and specificity are fixed properties of a test (vs. PPV and NPV).	
Sensitivity (true-positive rate)	Proportion of all people with disease who test positive, or the probability that a test detects disease when disease is present. Value approaching 100% is desirable for **ruling out** disease and indicates a **low false-negative rate**. High sensitivity test used for screening in diseases with low prevalence.	= TP / (TP + FN) = 1 – false-negative rate SN-N-OUT = highly SeNsitive test, when Negative, rules OUT disease If sensitivity is 100%, TP / (TP + FN) = 1, FN = 0, and all negatives must be TNs
Specificity (true-negative rate)	Proportion of all people without disease who test negative, or the probability that a test indicates non-disease when disease is absent. Value approaching 100% is desirable for **ruling in** disease and indicates a **low false-positive rate**. High specificity test used for confirmation after a positive screening test.	= TN / (TN + FP) = 1 – false-positive rate SP-P-IN = highly SPecific test, when Positive, rules IN disease If specificity is 100%, TN / (TN + FP) = 1, FP = 0, and all positives must be TPs
Positive predictive value (PPV)	Proportion of positive test results that are true positive. Probability that person actually has the disease given a positive test result.	= TP / (TP + FP) PPV varies directly with prevalence or pretest probability: high pretest probability → high PPV
Negative predictive value (NPV)	Proportion of negative test results that are true negative. Probability that person actually is disease free given a negative test result.	= TN / (FN + TN) NPV varies inversely with prevalence or pretest probability: high pretest probability → low NPV



POSSIBLE CUTOFF VALUES
A = 100% sensitivity cutoff value
B = practical compromise between specificity and sensitivity
C = 100% specificity cutoff value

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		D+		D-	
		n	%	n	%
	T+		84		53
	T-		16		47

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		n	%	n	%
	T+		84		53
	T-		16		47
		30		70	

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		D+		D-	
		n	%	n	%
	T+	25	84	37	53
	T-	5	16	33	47
		30		70	

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- PPV= TP/(DN + DN)

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- PPV= TP/(DN + DN) = 25/(25+37)= 40%

CLINICAL AND LABORATORY PREDICTORS OF IMPORTED MALARIA IN AN OUTPATIENT SETTING

- What type of bias might be introduced in interpreting these results?
  - selection bias
  - recall bias
  - observer-expectancy bias
  - confounding
  - small sample

Bias and study errors

TYPE	DEFINITION	EXAMPLES	STRATEGY TO REDUCE BIAS
Recruiting participants			
Selection bias	Nonrandom assignment to participate in a study group. Most commonly a sampling bias. Examples include:		Randomization Ensure the choice of the right comparison/reference group
	▪ Berkson bias	A study looking only at inpatients	
	▪ Loss to follow-up	Studying a disease with early mortality	
	▪ Healthy worker and volunteer biases	Study populations are healthier than the general population	
Performing study			
Recall bias	Awareness of disorder alters recall by subjects; common in retrospective studies.	Patients with disease recall exposure after learning of similar cases	Decrease time from exposure to follow-up
Measurement bias	Information is gathered in a way that distorts it.	Hawthorne effect — groups who know they're being studied behave differently than they would otherwise	Use of placebo control groups with blinding to reduce influence of participants and researchers on experimental procedures and interpretation of outcomes
Procedure bias	Subjects in different groups are not treated the same.	Patients in treatment group spend more time in highly specialized hospital units	
Observer-expectancy bias	Researcher's belief in the efficacy of a treatment changes the outcome of that treatment (aka Pygmalion effect; self-fulfilling prophecy).	If observer expects treatment group to show signs of recovery, then he is more likely to document positive outcomes	

CLINICAL AND LABORATORY PREDICTORS OF IMPORTED MALARIA IN AN OUTPATIENT SETTING

- When implementing the study findings into practise, what are the clinitians at risk of?
  - Type I error
  - Type II error

CLINICAL AND LABORATORY PREDICTORS OF IMPORTED MALARIA IN AN OUTPATIENT SETTING

Incorrect result		
Type I error (α)	Stating that there is an effect or difference when none exists (null hypothesis incorrectly rejected in favor of alternative hypothesis). α is the probability of making a type I error. p is judged against a preset α level of significance (usually < .05). If $p < 0.05$, then there is less than a 5% chance that the data will show something that is not really there.	Also known as false-positive error. α = you saw a difference that did not exist (e.g., convicting an innocent man).
Type II error (β)	Stating that there is not an effect or difference when one exists (null hypothesis is not rejected when it is in fact false). β is the probability of making a type II error. β is related to statistical power (1 – β), which is the probability of rejecting the null hypothesis when it is false. ↑ power and ↓ β by: ▪ ↑ sample size ▪ ↑ expected effect size ▪ ↑ precision of measurement	Also known as false-negative error. β = you were blind to a difference that did exist (e.g., setting a guilty man free). If you ↑ sample size, you ↑ power. There is power in numbers.

CLINICAL AND LABORATORY PREDICTORS OF IMPORTED MALARIA IN AN OUTPATIENT SETTING

TABLE 5

Test performance of the predictors of malaria*

Condition	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Likelihood ratio for positive test (95% CI)	Likelihood ratio for negative test (95% CI)
Inadequate prophylaxis	84 (74–90)	47 (41–54)	1.6 (1.4–1.8)	0.35 (0.22–0.54)
Sweating	68 (58–77)	54 (47–60)	1.5 (1.2–1.8)	0.60 (0.43–0.80)
No abdominal pain	81 (72–88)	32 (26–39)	1.2 (1.0–1.4)	0.58 (0.36–0.89)
Temperature ≥ 38°C	57 (46–67)	75 (69–81)	2.3 (1.7–3.0)	0.58 (0.45–0.72)
Poor general health	30 (21–40)	92 (87–95)	3.6 (2.1–6.0)	0.77 (0.66–0.86)
Enlarged spleen	**23 (15–33)**	**98 (96–99.5)**	**13.6 (5.0–36.8)**	**0.79 (0.69–0.86)**
Hemoglobin < 12 g/dL	**16 (9–25)**	**97 (93–98)**	**4.6 (2.1–10.3)**	**0.88 (0.79–0.94)**
Leucocytes ≤ $10 \times 10^3/\mu L$	97 (91–99)	27 (22–33)	1.3 (1.2–1.5)	0.11 (0.04–0.33)
Platelets < $150 \times 10^3/\mu L$	**60 (49–70)**	**95 (91–97)**	**11.0 (6.4–19.1)**	**0.43 (0.33–0.53)**
Eosinophils < 5%	95 (88–98)	12 (8–17)	1.1 (1.0–1.2)	0.43 (0.17–1.02)

* 95% CI = 95% confidence interval.

- A 40y/o patient visits outpatient clinic in Lausanne because he had malaise and fever (38C) for 4 days. His PHM reveals an appendectomy 10 years ago. Two weeks ago he returned from trip to Kongo. He did take mefloquine for prophylaxis.
- Using the data from the study, what is the probability that this patient have malaria before performing physical exam?
- 5% 23% 50% 60% 79% 88% 96% 98%

Does This Patient Have Malaria?

- **Context** Malaria commonly infects residents of and travelers to tropical regions. The clinical features of infection are notoriously nonspecific but have not been comprehensively evaluated.
- **Objective** To systematically review and synthesize data related to the predictive value of clinical findings for the diagnosis of malaria in endemic areas and in travelers returning from endemic areas.
- **Data Sources, Study Selection, and Data Extraction** The databases of MEDLINE and EMBASE (1950-July 2010) were searched to identify studies published in the English language of endemic and “imported” (acquired during travel) malaria. Additional studies were identified from reference lists. Studies were included that had patients suspected of having acute malaria (usually because of fever) and compared the presence or absence of clinical findings with blood smear confirmation. Two authors independently identified studies, appraised study quality, and extracted data on the patient population, outcome assessment, and clinical findings. Differences between reviewers were resolved by consensus.

- Paaladinesh Thavendiranathan, MD; Akshay Bagai, MD; Clarence Khoo, MD; Paul Dorian, MD; Niteesh K. Choudhry, MD, PhD

- JAMA. 2009;302(19):2135-2143. doi:10.1001/jama.2009.1673.

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- What is the **type of this study**?

  A) Cross-sectional study

  B) Case-control study

  C) Cohort study

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Does This Patient Have Malaria?

- **Data Synthesis** Fourteen studies for endemic malaria were identified that met review criteria. Individual symptoms are of limited diagnostic utility but presence of splenomegaly (summary likelihood ratio [LR], 3.3; 95% confidence interval [CI], 2.0-4.7) or hepatomegaly (summary LR, 2.4; 95% CI, 1.6-3.6) make malaria more likely. Combinations of findings can affect the likelihood of malaria, but their performance varies by setting. Seven studies of imported malaria were identified. The presence of fever (LR, 5.1; 95% CI, 4.9-5.3), splenomegaly (summary LR, 6.5; 95% CI, 3.9-11.0), hyperbilirubinemia (LR, 7.3; 95% CI, 5.5-9.6), or thrombocytopenia (summary LR, 5.6; 95% CI, 4.1-7.5) make malaria more likely.
- **Conclusions** In endemic areas, the likelihood of malaria is increased by the presence of splenomegaly and hepatomegaly but individual findings are of limited utility and cannot reliably exclude malaria; combinations of findings may be useful to stratify risk in patients. In returning travelers, the clinical assessment can provide substantial diagnostic benefit, although all patients still require laboratory testing because malaria can be rapidly fatal.

Take home vocabulary

- Sensitivity, Specificity
- PPV, NPV, impact of prevalence
- Case-control
- selection bias
- Malaria should be suspected in "any patient with fevers and recent travel"
  - more specific findings: splenomegaly, jaudance, anemia, thrombocytopenia
  - tropical areas

Thank you

- Zdroje:
  - VALÉRIE D'ACREMONT: CLINICAL AND LABORATORY PREDICTORS OF IMPORTED MALARIA IN AN OUTPATIENT SETTING: AN AID TO MEDICAL DECISION MAKING IN RETURNING TRAVELERS WITH FEVER, Am. J. Trop. Med. Hyg., 66(5), 2002, pp. 481–486 (http://www.ajtmh.org/content/66/5/481.long)
  - Steve M. Taylor et al: Does This Patient Have Malaria?, JAMA. 2010;304(18):2048-2056. doi:10.1001/jama.2010.1578 (http://jama.jamanetwork.com/article.aspx?articleid=186881)
  - First Aid for the USMLE step 1 2014
  - Lippincott's illustrated pharmacology
  - Lippincott's illustrated Q&A microbiology, immunology