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ZOE
ZOONOSES ONLINE EDUCATION

MALARIA - PROTOCOL ON EPIDEMIOLOGICAL MONITORING AND DISEASE CONTROL IN PUBLIC HEALTH PRACTICE

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ACRONYMS

CDC = Centers for Disease Control and Prevention
DEET = N, N – diethyl-meta-toluamide
DNA = Deoxyribonucleic Acid
Hb = hemoglobin
Ht = hematocrit
NCCDSC = National Center for Communicable Diseases Surveillance and Control
NIRDMI = National Institute for Research and Development in Microbiology and Immunology
PHA = Public Health Authority
RDT = Rapid Diagnostic Test
RPHC = Regional Public Health Center
WHO = World Health Organization

1. BAKCGROUND. MALARIA IN ROMANIA

Malaria is a serious disease with endemic manifestation in the tropical regions (sub-Saharan Africa, Central and South America, India and parts of Oceania and Southeast Asia), but which may occur in some temperate areas in the form of sporadic cases (import cases). In Romania, the natural transmission of the disease has been interrupted since 1961, and after 1963 the country has been in the phase of the maintenance of malaria eradication. Over the past 10 years, there has been an upward trend in the number of cases of malaria as a consequence of the increased mobility of people globally and of lack of knowledge, or ignorance by travelers of nonspecific measures of general prevention (individual mechanical protection against mosquitoes) and of special prevention (chemoprophylaxis). During the period 2006-2016, 295 cases were reported, all of them being import cases (16 cases in 2006, 23 cases in 2007, 13 cases in 2008, 12 cases in 2009, 19 cases in 2010, 40 cases in 2011, 32 cases in 2012, 43 cases in 2013, 47 cases in 2014, 30 cases in 2015 and 20 cases in 2016). For the most cases, the infection occurred on the African continent, *Plasmodium falciparum* being the most frequently involved. The purpose of the trip in the endemic areas was a professional one, but malaria cases among tourists, people employed as military staff, or persons from endemic countries coming to study in Romania were also identified. Most patients have not taken any preventive measures before travelling.

In order to prevent deaths, to reduce the number of illnesses, to maintain the country status "territory where malaria was eradicated" and prevent the re-establishment of malaria in the region it is necessary to improve the epidemiological surveillance system at the national level with the involvement and cooperation of both preventive and clinical services as well as the intensification of pre-exposure preventive measures. In the same time, the surveillance system of vectors populations should be maintained and improved, considering the existence of some factors (the presence of the *Anopheles* mosquitos' populations, the global warming phenomenon, and the increasing of mosquitos' resistance to insecticides) which can reintroduce malaria as an endemic disease in Europe, including in Romania, without an adequate control. Refer to *CDC Malaria Risk Map* for additional information on endemic areas: www.cdc.gov/malaria/map/index.html.

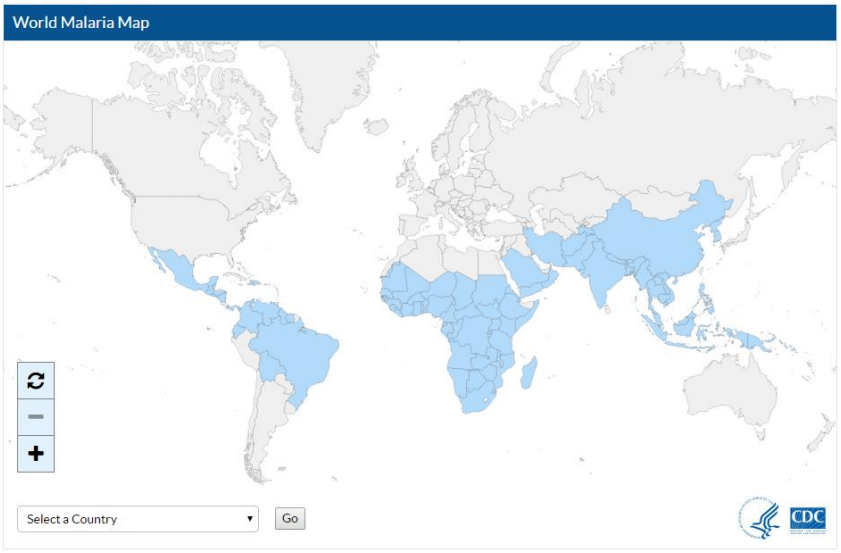

Fig. 1. World Malaria Map, 2018
Source: *CDC Malaria Maps***.** Available from: https://www.cdc.gov/malaria/travelers/about_maps.html

2. RATIONALE

Malaria is a type of disease specific for the tropical areas which represents a major public health issue in the entire world. The infectious and parasitic diseases have undergone a modification in geographical distribution over the past decades as a result of changes in the conditions of the human ecosystem and by increasing the international movement of the population (due to different reasons, including the globalization of commercial actions). Knowing the dangers that threaten the population in areas that are not usually considered at risk for malaria is a priority of public health strategies. Informing the specialists, the students during the training period and the general population on epidemiological, clinical and preventive issues (through surveillance and control actions) through collaboration between human and veterinary medicine, is currently a necessity, which is in line with World Health Organization (WHO) recommendation for malaria elimination.

3. OBJECTIVES

1. To improve the level of knowledge about malaria (the epidemiological, clinical and preventive issues) among medical specialists and students through the collaboration between human and veterinary medicine.
2. To contribute to the preservation of the status of the country: territory where "malaria is eradicated" (to avoid the reestablishment of malaria).

4. DISEASE OVERVIEW

4.1 Pathogenic agent. Usually, there are 4 species of *Plasmodium* protozoa that produces malaria in humans: *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* (from humans). Also, 3 other species could be involved in the occurrence of malaria in humans: *P. knowlesi*, *P. simiovale* and *P. brasilianum* (from non-human primates via mosquito bites).

4.2 Clinical description. Typical recurrent fever (which may be periodic at 48 or 72 hours, depending on the species). The classic paroxysm begins with a period of shivering and chills lasting for around 1-2 hours and is followed by high fever. The excessive diaphoresis experienced by the patient is followed by the decrease of the body temperature to normal or below normal. Virtually all patients with malaria come with headache. Other symptoms include sweats, tiredness, malaise, nausea and vomiting, diarrhea, cough, shortness of breath, arthralgia and myalgia. Severe cases may progress to jaundice, anemia, renal failure, shock, adult respiratory distress syndrome, confusion, coma, encephalopathy, and acidosis - usually caused by *P. falciparum.*

4.3 Sources of pathogenic agents. **Humans**: when they are ill, pre-infected carriers (the future ill people during the incubation period) or chronic postinfected carriers. **Infective female *Anopheles* mosquito.**

4.4 Modes of Transmission.

Fig. 2. A lateral view of a feeding female *Anopheles stephensi* mosquito.
Source: Photo Credit: James Gathany Content Providers(s): Centers for Disease Control and Prevention's Public Health Image Library (PHIL), with identification number **#18760.**

Malaria **is almost always** transmitted by the bite of an infective female *Anopheles* mosquito.
The transmission from human to human is also possible in some conditions. *The direct mode* can be accomplished by contaminated blood transfusion or medullary transplant. Also, malaria can be transmitted from mother to foetus in the case of placental abnormalities (congenital malaria). *The indirect mode* involves, generally, contaminated needles and syringes for intravenous drug users. But all **these modes** of transmission **are rare**.

4.5 Incubation Period: Different depending on the specie: 10-12 days for *P. falciparum*, 27-42 days for *P. malariae* and 13-15 days for *P. ovale* and *P. vivax*. Inadequate or inappropriate prevention with anti-malarial drugs or partial immunity from prior exposure can lengthen the incubation period (up to 8-10 months).

4.6 Period of Communicability:

Malaria is not directly transmissible from person-to-person except for congenital transmission and through blood transfusion or through shared contaminated needles, during parasitemia. Infected human hosts may remain infectious for *Anopheles* mosquitoes for many years if they are untreated or inadequately treated: 1-2 years in untreated *P. falciparum* infections, up to 4-5 years in the case of infection with *P. vivax* and *P. ovale*, and up to 40 years or the entire life for *P. malariae* infection. The transmission by contaminated blood transfusion (or contaminated needle stick injuries) may occur as long as asexual forms remain in the circulating blood. Stored blood can remain infectious for at least one month.

4.7 Susceptibility and Resistance:

Susceptibility is general except in humans with specific genetic features. Tolerance to clinical disease is present in adults in endemic regions where exposure to infective *Anopheles* is continuous over many years.

4.8 Treatment:

The appropriate drug regimen depends upon the species of *Plasmodium* involved and the region where the infection was acquired. Consultation with an infectious disease or travel medicine specialist is strongly recommended.

5. MALARIA MONITORING AND SURVEILLANCE

5.1 Case definitions and classifications for import cases (used in Romania)

Case definitions

Malaria or paludism is defined mainly by associated clinical symptoms. The case definition is based on the perception of the disease in a particular country, the ways of transmission and the consequences of the disease.
Malaria is an acute infection with one of four most important *Plasmodium* species: *P. vivax*, *P. falciparum*, *P. ovale*, and *P. malariae*. Rarely three human species or simian *Plasmodium* species (*P. knowlesi*, *P. simiovale*, and *P. brasilianum*) could be responsible for the infections.

Clinical Criteria

- fever, whether or not associated with splenomegaly and anemia;
- the most common clinical symptoms associated are: headache, chills, profuse sweating, back pain, myalgia, nausea, vomiting, diarrhea, and cough;

- in the absence of treatment, *Plasmodium* infection may develop into severe or complicated malaria: coma, generalized seizures, hyperparasitemia, hypochromic anemia, hydroelectrolytic disorders, renal failure, hypoglycemia, paludic hemoglobinuria, cardiovascular collapse with shock, disseminated intravascular coagulation, pulmonary edema and death.

Laboratory Criteria:

At least one of the following:

- positive microscopic hematological examination for *Plasmodium* (thick peripheral blood drops/ smear) performed in Romania, regardless of whether the person experienced previous episodes of malaria while outside the country;
- detection of the nucleic acid (DNA) of the *Plasmodium* protozoa in a sample of peripheral blood using a validated molecular technique (polymerase chain reaction - PCR);
- detection of the *Plasmodium* protozoa specific antigen using rapid diagnostic test (RDT).

If possible, differentiation of *Plasmodium* species should be made.

Epidemiological criteria: international travel in endemic areas.

Case classification:

Possible case: not applicable

Probable case: not applicable

Confirmed case: any person meeting clinical and laboratory criteria.

By the region of origin, malaria case can be:

1. **Indigenous case** - malaria transmitted by a local mosquito within the malaria endemic territory, with no evidence of importation and no direct link to transmission from an imported case.
2. **Introduced secondary case** - malaria transmitted by a local mosquito in a territory without malaria, with strong epidemiological evidence linking the case to an imported case.
3. **Imported case -** malaria acquired outside the country. In this document, imported cases are those acquired outside Romania.
4. **Induced case -** an isolated case of malaria not associated with secondary cases, identified by epidemiological investigation, and possibly transmitted from blood donors by a blood transfusion, organ transplantation, or another parenteral route, with no evidence of a mosquito borne disease or congenital transmission.
5. **Cryptic case**: a malaria case for which epidemiologic investigations cannot identify a plausible mode of acquisition.
6. **Relapse / Chronic case** - Recurrence of the disease after it has been apparently cured: recurrence of the manifestations (clinical symptoms and / or parasitemia) of a malaria infection separated from previous manifestations of the same infection by an interval greater than any normal periodicity of the paroxysms. True relapses of malaria are caused by reactivation of dormant liver-stage parasites (hypnozoites) of *P. vivax* and *P. ovale*. Acute illness usually occurs within 45 days after the exposure; therefore, relapses of *P. vivax* and *P. ovale* are defined as occurring >45 days (up to 4 years) after travel to an malaria endemic region (the initial infection). *Plasmodium malariae* may remain subclinical for more than 30 years, with periodic recrudescence.

5.2 Laboratory analysis

- positive microscopic hematological examination for *Plasmodium* (thick peripheral blood drops/ smear) performed in Romania, regardless of whether the person experienced previous episodes of malaria while outside the country;
- detection of the nucleic acid (DNA) of the *Plasmodium* protozoa in a sample of peripheral blood using a validated molecular technique (polymerase chain reaction - PCR);
- detection of the *Plasmodium* protozoa specific antigen using rapid diagnostic test (RDT).

If possible, differentiation of *Plasmodium* species should be made.

5.3 Types of surveillance – passive

5.4 Data collection, reporting frequencies and informational flow

Peripheral level

1. Nominal reporting of confirmed cases: all healthcare providers will report immediately (by phone to the County Public Health Authority - the Department of Communicable Diseases Surveillance and Control) the minimum data of the identified case:

- name, surname
- date of birth, sex
- address
- collectivity: job place / school
- date of onset
- date of detection
- date of admission / medical unit to which the subject was oriented for admission
- clinical data
- travel to malaria endemic areas
- confirmation date with lab diagnosis.

Also, all healthcare providers who are detecting a case will fill in the Single Report Sheet in accordance with GD 589/2007 that will be forwarded to the County Public Health Authority.

2. Case Report Form / Sheet (Appendix 1):

- will be filled in by the specialist doctor from the institution where the case is admitted;
- will be sent by the specialist doctor from the institution where the case is admitted to the local Public Health Authority (PHA) - Department of Communicable Disease Surveillance and Control, within **7 days** from the date of admission.

Local Level: Public Health Authority

1. Nominal reporting of confirmed cases within **24 h** since the identification, by phone / by fax / by email at the Regional Public Health Center (RPHC), the minimum data of the identified case.

2. Case Report Form / Sheet (Appendix 1):

- will be validated by the epidemiologist from the PHA - Department of Communicable Disease Surveillance and Control;
- the Case Report Form also includes a 14-day check-up from the beginning of the treatment, for the notification of relapses in the case of therapeutic failure;

- the Report Forms are sent **monthly** to the RPHC, in **the first 5 days** of the month, for the previous month, and from here to the National Center for Communicable Diseases Surveillance and Control (NCCDSC).

3. PHAs will send the slides for **confirmation to the National Reference Laboratory** at the Cantacuzino National Institute of Research and Development for Microbiology and Immunology (NIRDMI), accompanied by the Specimen Submission Form presented in **Appendix 2.**

As soon as the results of the laboratory investigations carried out by Cantacuzino NIRDMI will be available, they will be transmitted by the County PHA to RPHC.

Regional level: RPHC

1. **Immediate nominal reporting of the confirmed case** at the NCCDSC, by phone.

2. Case Report Form / Sheet (Appendix 1):

- it is sent **monthly** by fax or mail to the NCCDSC
- **monthly** (in **the first 10 days** of the following month) the database is sent, in the unique electronic template, or by fax to NCCDSC.

National level: NCCDSC

1. **Nominal phone / fax reporting of the epidemiological risk situations** (exceeding the alert threshold according to the provisions of Ministry of Health Order No. 883/2005) to Ministry of Heath - Department of Public Health: within **24 hours** of notification.

The National Reference Laboratory at Cantacuzino NIRDMI will inform the PHA about the results within **7 days** of the of the specimens receipt. The diagnostic algorithm recommended by the Reference Laboratory at Cantacuzino NIRDMI is presented in Appendix 2.

5.5. Data processing and analysis

Public Health Authority - at the local level

- the general and specific incidence, by age group
- the general and specific mortality, by age group
- the general and specific fatality rate, by age group.

Regional Public Health Center - at the regional level

- the general and specific incidence, by age group, in the counties from the ascribed territory
- the general and specific mortality, by age group, in the counties from the ascribed territory
- the general and specific fatality rate, by age group, in the counties from the ascribed territory
- % of cases who received chemoprophylaxis, in the counties from the ascribed territory.

NCCDSC - at the national level

- the general and specific incidence, by age group, at the national level
- the general and specific mortality, by age group, at the national level
- the general and specific fatality rate by age group, at the national level
- % of cases who received chemoprophylaxis, at the national level
- the geographical origin of infection for the detected cases
- % of cases to whom Plasmodium specie was identified.

5.6. Feedback and dissemination of information

The feedback will be done **quarterly** and the dissemination will be done **annually**, by each of the structures involved in malaria epidemiological monitoring and surveillance, towards the data sources.

5.7. Evaluation indicators

- the timely reporting rate
- the rate of timing transmission of the Case Report Form
- the rate of the correct fill in of the Case Report Form
- the percentage of the confirmed cases that corresponded to the case definition.

6. STANDARD MALARIA CASE INVESTIGATION AND CONTROL MEASURES

6.1 Case investigation (the epidemiological investigation/inquire)

1. Contact the medical provider who ordered testing of the case and obtain the following information (including medical records for hospitalized patients):

- confirm the diagnosis using the case definition
- collect the demographic data of the patient (address, birth date, gender, race/ethnicity, primary language, and phone number)
- record height and weight of the patient
- record the date of onset (approximate if exact date is not known)
- record the hospitalizations: location and duration of stay
- record the outcomes: survived or date of death
- record pregnancy status for women
- record any history of malaria 12 months prior to this report
- record clinical complications from the recent attack: cerebral malaria, renal failure, Acute Respiratory Distress Syndrome, anemia (Hb<11, Hct<33), or other
- blood transfusion or blood products transfusion ≤ 2 years prior to the onset (dates, places, lot numbers, and manufacturer)
- record the therapy received ("treatment given") for this attack including date started and stopped.

2. Interview the case or proxy to help identify the source of pathogenic agent, focus the investigation within the incubation period of the specific infectious agent and on the following potential risks of the disease transmission:

- To identify the residence in or the travel to malaria endemic areas, ask about the following:
  - ✓ Was there travel outside of Romania 30 days before the illness onset?
    - Did the patient travel in Romania? (If yes, City and dates)
    - Did the patient travel internationally? (If yes, City/Country and dates)
  - ✓ Was there travel/residence outside of Romania during the past 2 years?
    - If yes, and not recorded previously, record all countries, date returned to Romania, duration of stay in the foreign country
  - ✓ For travel from Romania, record:
    - Reason for travel of the most recent trip.
- Record YES or NO if the patient received chemoprophylaxis prior to and during the travel to prevent malaria.

- Other risks to consider: use of parenteral drugs and exposure to mosquitoes during the incubation period.
- With no travel to endemic areas, see **Managing Special Situations**.

3. Investigate epidemiological links between cases (clusters, household, co-workers, etc).
    - Ask on the presence of other cases (record the names).

Investigator responsibilities

1. Report all confirmed and suspected cases to the local Public Health Authority.
2. Contact medical provider to collect additional information and confirm diagnosis using current case definition:
    - collect all the information requested in Step 1 of the case investigation.
    - ensure that the case/proxy is aware of the diagnosis.
3. Continue a case investigation to identify the potential source of pathogenic agent - start the case investigation within **7 days** of the report.
    - fill in an interview with the Malaria Case Report Form.
    - finish the case investigation in 14 days of the report.
4. Conduct contact investigation to identify additional cases.
5. Identify whether the source of pathogenic agent is a major public health concern.
    - ***Was there no travel to a malaria endemic area?***
6. Conduct Case or Contact Management as needed.
7. Record data collected during the investigation.
8. As appropriate, use the Case report Form to notify the case, contacts and other individuals or groups.

6.2 Contact Investigation

Contacts are defined as those exposed to a potential source of pathogenic agent, the *Anopheles* mosquito vector, or to the blood of a malaria case. Consider:

- travel companions are investigated as contacts
- persons who shared intravenous drug paraphernalia with a malaria case are at risk.

6.3 Isolation, Work and Daycare Restrictions

No specific restrictions. Use standard universal precautions with patients (use adequate, complete and correct protective equipment; handwashing; prevention of accidents and other types of occupational exposure).

6.4 Case Management

Advise no blood donation for exclusion period (e.g., years after treatment or risk travel) and record the following:

1. Before the start of the treatment for the patient with malaria, record all the prescription and over-the-counter medicines the patient had taken during the 2 weeks before starting the treatment.
2. Seven days after the treatment was started, record whether or not all signs or symptoms of malaria were resolved without additional malaria treatment.
3. Four weeks after the patient started the treatment, follow-up with case to assure compliance with treatment:

- list all prescriptions and over-the-counter medicines the patient took during the 4 weeks after starting therapy
- record if the medicine for malaria was taken as prescribed
- record any adverse events the patient experienced within the 4 weeks after receiving malaria treatment.

4. Report any changes in patient status (i.e., death, dismissal from hospital, completion date of treatment).

6.5 Contact Management

1. If a history of needle sharing is obtained from the case, investigate and treat all persons who shared the equipment.
2. In transfusion-acquired malaria, all donors must be located and their blood examined for malaria parasites and for anti-malarial antibodies; parasite-positive donors should receive treatment.
3. Consider testing asymptomatic travel companions as well.

6.6 Environmental Measures

None

6.7 Education

1. Information on malaria risk, prevention, and treatment for travelers:
   - ZOE Malaria Guide on ZOE web site: http://zoeproject.eu
   - Informative materials for general public on ZOE web site: http://zoeproject.eu

2. Personal Protective Measures for travelers to endemic areas (tropical areas of South America, Africa and Asia):
   - follow a professional-recommended prophylaxis regimen (CDC, WHO, NCCDSC)
   - use insecticide-impregnated mosquito nets while sleeping;
   - remain in well-screened areas;
   - wear protective clothing;
   - use mosquito repellents containing DEET (N,N-diethyl-meta-toluamide) and reapplying as needed.

7. MANAGING SPECIAL SITUATIONS

7.1 Outbreaks

1. Outbreak definition: one or more cases for which a known risk factor (i.e., recent travel to an endemic area) cannot be identified should be considered a potential outbreak and adequate resources applied to the investigation.
2. Notify the local Public Health Authority immediately.
3. Active case finding will be an important part of any investigation.

7.2 No Recent Travel to Endemic Areas

Consult with local Public Health Authority about any case that does not have a history of recent travel to an area endemic for or experiencing a recent outbreak of malaria.

7.3 *Plasmodium falciparum* Case

The high prevalence of chloroquine resistance among *P. falciparum* parasites, as well as the potential for severe illness, makes chloroquine alone usually a poor choice for therapy.

- Chloroquine does have some anti-parasitic properties, so depending on the level of resistance, it may reduce the parasite levels sufficiently and make the patient feel better while setting the stage for potential treatment failure.
- If a *P. falciparum* case is only treated with chloroquine, verify the treatment information and discuss treatment options with the case physician.
- Additional treatment information can be found at:
  - ZOE Malaria Guide on ZOE web site: http://zoeproject.eu
  - ZOE Handbook of main zoonotic diseases: http://zoeproject.eu/documents/state_of_arts/IO2_Handbook%20of%20Main%20Zoonotic%20Diseases.pdf
  - National Center for Communicable Disease Surveillance and Control (https://cnscbt.ro/index.php/metodologii/malarie)

8. MALARIA DIAGNOSIS

8.1 Clinical diagnosis

The prompt and accurate diagnosis of malaria has the advantage of introducing specific treatment as soon as possible in order to save the patient's life and reduces the cost of hospitalization that unnecessary antimalaric administration would entail.

Signs and symptoms of malaria are nonspecific.

Clinically, malaria is diagnosed in most cases on the basis of fever episodes or the caractheristics of fever.

In the case of Romania where the risk of malaria transmission is very low, the clinical diagnosis of malaria will be based on time and place of exposure (travel in malaria endemic areas) and on fever within the last 3 days preceding the symptoms.

Particular attention will be paid to pregnant women who have traveled to endemic areas.

8.2 Laboratory diagnosis

The most common laboratory methods used are to highlight the parasite in the thick blood drops test and the rapid diagnostic test.

8.2.1. Light microscopy

The identification of the parasite on the smear or the thick blood drops has the advantage of low cost and great sensitivity and specificity, with the condition to be performed by well-trained

staff. Other advantages of the direct test are the identification of the parasite type and its cellular load.

8.2.2. Rapid diagnostic tests

The rapid test for detecting *P. falciparum* antigen has a slightly higher cost, variable sensitivity and specificity depending on the temperature and humidity. This test can accompany the direct test to strengthen the diagnosis confirmation.

The laboratory test to confirm the diagnosis of malaria should be performed within 2 hours since the presentation of the patient with the suspicion of malaria based on anamnesis, symptomatology and clinical examination.

If for various reasons the laboratory diagnosis is not possible within the mentioned interval, the treatment should be chosen based on the anamnesis (the history of travel in the endemic area being very important) and the clinical examination.

8.2.3. Molecular diagnostic tools

The molecular identification of malaria parasite represents the diagnostic certainty method, but the Polymerase Chain Reaction (PCR) results are not always available fast enough in order to be of great value in establishing the diagnosis of infection with *Plasmodium*. The PCR is most useful for the confirmation of the parasite species after the diagnosis was made either by microscopy of thick drops, or by RDT.

9. ROUTINE PREVENTION

A. Immunization Recommendations

None, although malaria vaccines are under development.

B. Prevention Recommendations

Current information to prevent malaria is available from the ZOE Malaria Guide (http://zoeproject.eu); National Center for Communicable Disease Surveillance and Control (https://cnscbt.ro/index.php/metodologii/malarie) and CDC Malaria Risk Map for further information on endemic areas (https://www.cdc.gov/malaria/map/), including country-specific recommendations. Factors such as geography, climate, season, mosquito species, and mosquito control efforts vary the risk for malaria, as does a person's travel style. Prevention had three parts: avoid mosquito bites, chemoprophylaxis, and prevent later recurrence of the symptoms.

1. Avoid Mosquito Bites

- Travelers should wear adequate clothing (long pants, long-sleeved shirt, hat) and use insect repellent when mosquito exposure can be anticipated. Repellents containing DEET as the active ingredient are the most effective. Travelers should identify times of day with the most risk of mosquito bites and minimize outdoor activities during those times.
- Use pesticide-treated mosquito bed nets when exposure to mosquitoes may occur at night. Bed nets are considered unnecessary if the traveler stays in air-conditioned hotels, with the windows closed at night (when most *Anopheles* mosquitoes feed).

2. Chemoprophylaxis

The main issue for most travelers is determining appropriate chemoprophylaxis. Chloroquine was the main methode of malaria prophylaxis for decades, but widespread resistance among *P. falciparum* parasites makes this regimen inappropriate in Africa, South Asia, and most of the Americas. Because prophylaxis guidelines change, refer to current resources (e.g., ZOE Malaria Guide (http://zoeproject.eu) and CDC (https://www.cdc.gov/malaria/travelers/index.html).

3. Prevent Recurrences

Dormant forms of *P. ovale* and *P. vivax* (hyponozoites) can persist in the liver and emerge weeks or months later as a relapse. Drugs to treat symptomatic disease (i.e., red blood cell infection) do not act against hypnozoites. To prevent a possible relapse, primaquine is generally given for attack of *P. ovale* or *P. vivax* malaria. However, there are some contraindications to primaquine use (e.g., G6PD deficiency, during pregnancy).

10. TREATMENT OF MALARIA CASES

- Simple or uncomplicated malaria may be treated with oral medications. Artemisinins in combination with other additional antimalarials (including: amodiaquine, lumefantrine, mefloquine or sulfadoxine/pyrimethamine), known as artemisinin-combination therapy (ACT), is the most effective treatment for *P. falciparum* infection that decreases the resistance to any single drug component.
- Another recommended combination is dihydroartemisinin and piperaquine. ACT is about 90% effective when used to treat uncomplicated malaria.
- To treat uncomplicated malaria during pregnancy, WHO recommends the use of quinine plus clindamycin early in the pregnancy (1st trimester), and ACT in later stages (2nd and 3r^{d} trimesters).
- Infections with *P. vivax*, *P. ovale* or *P. malariae* usually do not require hospitalization. Treatment of *P. vivax* should include both treatment of blood stages (with chloroquine or ACT) and clearance of liver forms with primaquine. Treatment with tafenoquine prevents relapses after confirmed *P. vivax* malaria.
- In the areas with low transmission, one single small dose of primaquine should be used in the antimalarial treatment, with the purpose of reducing the transmission of the infection. The G6PD testing is not necessary because one single small dose of primaquine is efficient in blocking the transmission and it is less likely to cause severe toxicity for subjects with G6PD deficit.
- Recommended treatment for severe malaria is the intravenous use of antimalarial drugs. For severe malaria, parenteral artesunate was superior to quinine in both children and adults. Other studies show that artemisinin derivatives (artemether and arteether) were as efficacious as quinine in the treatment of cerebral malaria in children.
- The most used drugs in malaria treatment are active against the parasite forms in the blood (the form responsible for the occurrence of the disease) and include: chloroquine; atovaquone-proguanil (Malarone®); artemether-lumefantrine (Coartem®); mefloquine (Lariam®); quinine; quinidine; doxycycline (used in combination with quinine); clindamycin (used in combination with quinine), and artesunate.

GLOSSARY

Active case detection: The detection by health workers of malaria infections at community and household level in population groups that are considered to be at high risk. Active case detection can be conducted as fever screening followed by parasitological examination of all febrile patients or as parasitological examination of the target population without prior fever screening.

Case-based surveillance: Every case is reported and investigated immediately (and also included in the weekly reporting system).

Case definition (control programmes)
Confirmed malaria: Suspected malaria case in which malaria parasites have been demonstrated in a patient's blood by microscopy or a rapid diagnostic test.
Presumed malaria: Suspected malaria case without a diagnostic test to confirm malaria but nevertheless treated presumptively as malaria.
Suspected malaria: Patient illness suspected by a health worker to be due to malaria. The criteria usually include fever. All patients with suspected malaria should receive a diagnostic test for malaria, by microscopy or a rapid diagnostic test.

Case definition (elimination programmes)
Autochthonous: A case locally acquired by mosquito-borne transmission, i.e. an indigenous or introduced case (also called 'locally transmitted').
Imported: A case the origin of which can be traced to a known malarious area outside the country in which the case was diagnosed.
Indigenous: Any case contracted locally (i.e. within national boundaries), without strong evidence of a direct link to an imported case. These include delayed first attacks of P. vivax malaria due to locally acquired parasites with a long incubation period.
Induced: A case the origin of which can be traced to a blood transfusion or other form of parenteral inoculation but not to normal transmission by a mosquito.
Introduced: A case contracted locally, with strong epidemiological evidence linking it directly to a known imported case (first generation from an imported case, i.e. the mosquito was infected from a case classified as imported).
Locally transmitted: A case locally-acquired by mosquito-borne transmission, i.e. an indigenous or introduced case (also called 'autochthonous').

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Definition	- Acute infection with one of four most important *Plasmodium* species: *P. vivax*, *P. falciparum*, *P. ovale*, and *P. malariae*. Rarely three human species or simian *Plasmodium* species (*P. knowlesi*, *P. simiovale*, and *P. brasilianum*) could be responsible for the infections. Typically, malaria is acquired by mosquito bite in an area where the disease is common (tropical areas of South America, Africa, and Asia) and imported into Romania with travelers. - Relapse can occur in the case of incomplete treatment, particularly with *P. vivax* and *P. ovale* due to extended dormant states in liver.
Signs and Symptoms	- Typical recurrent fever (which may be periodic at 48 or 72 hours, depending on the species). The classic paroxysm begins with a period of shivering and chills lasting for around 1-2 hours and is followed by high fever. The excessive diaphoresis experienced by the patient is followed by the decrease of the body temperature to normal or below normal - Virtually all patients with malaria come with headache - Sweats - Other symptoms: tiredness, malaise, nausea and vomiting, diarrhea, cough, shortness of breath, arthralgia and myalgia - Severe cases: jaundice, anemia, renal failure, shock, adult respiratory distress syndrome, confusion, coma, encephalopathy, and acidosis - usually caused by *P. falciparum*
Incubation	- 10-12 days for *P. falciparum* - 27-42 days for *P. malariae* - 13-15 days for *P. ovale* and *P. vivax* - Inadequate or inappropriate prevention with anti-malarial drugs or partial immunity from prior exposure can lengthen the incubation period (up to 8-10 months).
Diagnostics / Laboratory	**Lab (must be diagnosed in Romania per national case definition):** - Detection of *Plasmodium* parasites at the microscopic hematological examination (thick peripheral blood drops / smear), whether or not the person has clinical symptoms and previously had malaria in the history record. OR - Detection of the nucleic acid (DNA) of the *Plasmodium* protozoa in a sample of peripheral blood using a validated molecular technique (polymerase chain reaction - PCR). OR - Detection of circulating *Plasmodium* protozoa specific antigens using rapid diagnostic test (RDT) Differentiation of *Plasmodium* species should be made, if possible.
Differential diagnosis (guidance)	Multitude of viral and bacterial infections depending on geographic location including African trypanosomiasis, amebiasis, cholera, typhus, foodborne or waterborne gastroenteritis, meningitis, rickettsiosis, polio, schistosomiasis, HIV/AIDS, viral hemorrhagic fever, yellow fever, heat stroke

Prevention	• Refer to the ZOE Malaria Guide: http://zoeproject.eu • Malaria prevention for travel: - National Center for Communicable Disease Surveillance and Control (https://cnscbt.ro/index.php/metodologii/malarie) - Communicable Disease Surveillance and Control Departments within the local Public Health Authorities - Medicover Offices around the country, and other Authorized International Vaccination Offices (https://cnscbt.ro/index.php/sfaturi-pentru-calatori/535-cabinete-vaccinari-internationale/file). • Refer to the CDC Malaria Risk Map for further information on endemic areas: https://www.cdc.gov/malaria/map/ • CDC prevention for travel: https://www.cdc.gov/malaria/travelers/country_table/a.html
Treatment	Base on *Plasmodium* species, country of exposure (drug resistance) and illness severity.
Response	**Public health** - Document diagnosis was make in Romania (national case definition) - Obtain information to determine if case without travel exposures is: ***Introduced***: mosquito transmission from an imported human case in an area ***Induced***: acquired through artificial means (eg. blood transfusion) ***Cryptic***: isolated case that without epidemiological link **Laboratory** -Encourage submission of thick peripheral blood drops and smear to local Public Health Authority, particularly for cases with only rapid testing done without full speciation. **Infection control** - Case should not donate blood or tissues for exclusion period (may extend to 3 years).