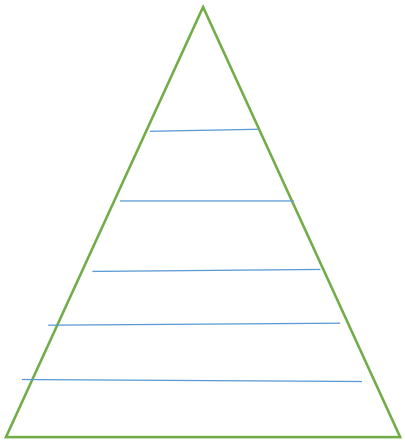
Questions for the final exam on course “Evidence-Based Medicine” for the First Grade master’s students on specialty “Medicine”

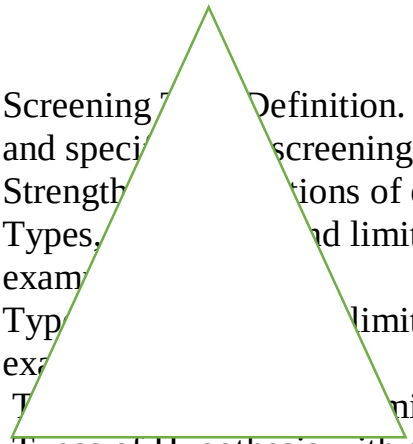
Blocks	Questions
Block 1	1. To give the definition, principles and role of “Evidence-Based Medicine” in clinical practice. 2. To describe the components of Evidence-Based Medicine. 3. To describe the 5-steps in Evidence-Based Medicine model. 4. What is study design? To describe types of epidemiologic studies and using of them in Medicine due to issues. 5. To describe meaning and using of analytical studies to solve Clinical Medicine issues. 6. To describe meaning and using diagnostic and screening tests to solve Clinical Medicine issues. 7. Randomized Controlled Trial: study designs. Definition. Objectives. Using. Outcomes. 8. To describe the Systematic Review: definition and 6 steps. 9. To describe the Meta-Analysis: definition, steps and feature from Systematic Review. 10. To describe Grading of evidence and levels of recommendation. 11. To describe step 3 of EBM – Appraising the clinical relevance and validity of the evidence in the current clinical environment. 12. To describe step 4 of EBM- Applying evidence-based interventions in the current clinical environment 13. To describe step 5 of EBM – Assessing the efficacy and utility of EBM practice. 14. To describe Clinical Practical Guidelines: definition, principles of development and using in Medicine. 15. The AGREE system and how to use it for evaluation of Clinical Practical Guideline.
Block 2	1. Background Questions versus Foreground Questions. What are the differencies? 2. To fill the PICOT Model for Clinical Questions (Diagnosis, Etiology, Therapy, Prognosis, Prevention, Ham) due to task1. Task 1. Identify background questions, create a PICOT and a focused clinical question for this case: 54 year old male patient was diagnosed with intermediate grade prostate cancer and wants to know whether to get a radical prostatectomy or radiation treatment. He is concerned about death from prostate cancer and also risks of impotence and incontinence.

PICOT Model	Clinical questions
P	
I	
C	
O	
T	

3. To draw Hierarchy of Evidence and give explanation every step.



4. To describe the best search principles and fill a list of Database. Draw the table
5. To write the steps of searching the scientific papers on problem of Prevalence of Malaria in Afghanistan.
6. To draw the Hierarchy of Evidence on levels of Evidence due to TRIP Database, Filtered Information and Unfiltered Information.



7. Screening ... Definition. Purposes. Using? What are sensitivity and speci... screening test? Sen=? Spec=?
8. Strength... tions of ecologic studies with example.
9. Types, ... nd limitations of Cross-sectional studies with exam...
10. Typ... limitations of Case-control studies with ex...
11. T... nitations of Cohort studies with example.
12. Types of Hypothesis with examples.
13. Core Elements of a Clinical Trial with examples.
14. Clinical Trial Phases in Testing of New Drugs: names of phases according to purpose, number of group participants, objectives.

<table>
<tr><td></td><td>15. Types of clinical questions (domains) due to studies with examples.</td></tr>
<tr><td>Block 3</td><td>
1. Cohort study measurement.
Task. The table below summarizes the findings. A total of 479 subjects completed the questionnaire, and 124 of them indicated that they had been exposed to the kiddy pool. Of these, 16 subsequently developed Giardia infection, but 108 did not. Among the 355 subjects who denied kiddy pool exposure, 14 developed Giardia infection, and the other 341 did not.
<table>
<tr><td>Risk factor</td><td colspan="2">Disease</td><td>Total</td><td></td></tr>
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Question. Measure Relative Risk?

2. Measure Efficacy of RCT on formula in task.
Task. From the Physicians' Health Study (unadjusted result): in treated group from 54,560 patients with CVD have MI 139 patients; in placebo group – from 54, 356 – 239 patients.
a) What is Rate of MI in the treated group?
b) What is Rate of MI in the placebo group?
c) What is efficacy of CVD patients' treatment?

3. To fill studies due to strength of Evidence in the table "Levels of Evidence."
<table>
<tr><td></td><td colspan="3">Levels of Evidence</td></tr>
<tr><td></td><td>Strongest</td><td>Moderate</td><td>Limited</td></tr>
<tr><td rowspan="7">studies</td><td></td><td></td><td></td></tr>
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4. Calculate and determine the truth of Sensitivity and specificity
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Truth

		Have disease	Do not have disease		
Screening	Positive	80	100	180	
	Negative	20	800	820	
		100	900	1,000	

a) Sensitivity?
- A. 18%
- B. 20%
- C. 44%
- D. 80%

b) Specificity?
- A. 2%
- B. 11%
- C. 89%
- D. 98%

5. Calculate and interpret predictive value positive (PPV) and predictive value negative (NPV):

		+	–	Totals
Questionnaire Response	+			
	–			
Totals				

If, TP=65, FP =1, FN=35 and TN=99
Then what is PPV, NPV and Prevalence?

6. Formulate clinical questions to DEPTH model in Medicine.

D	E
P	Th

7. What is PRIZMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and how to use it in Evidence –Based Practice.
8. The task: Salivary Cotinine Test ("Gold Standard")

		+	-	Totals
Questionnaire Response	+	65	1	66
	-	35	99	134
	Totals	100	100	200

Questions: Calculate

1. Sensitivity?
2. Specificity?
3. PPV?
4. NPV?
5. Prevalence?

9. The association of smoking with coronary heart disease (CHD) is investigated by following a group of 3,000 smokers and 5,000 nonsmokers over a 25-year period. Suppose CHD develops in 84 of the smokers and in 87 of the nonsmokers.
   Task. Set up an appropriate 2 x 2 table representing these data. Calculate and interpret RR.

	SHD developed		
	Yes	No	Totals
Smoker			
Nonsmoker			
Totals			

10. Make Critically Appraising the Article.

Myocarditis associated with *Plasmodium vivax* malaria: a case report

***Ana Maria Revoredo da Silva Ventura*[1],[2], *Tânia do Socorro Souza Chaves*[1],**

ABSTRACT
Malaria remains a major public health problem in Brazil where *Plasmodium vivax* is the predominant

species, responsible for 82% of registered cases in 2013. Though benign, *P. vivax* infection may sometimes evolve with complications and a fatal outcome. Here, we report a severe case of P. *vivax* malaria in a 35-year-old Brazilian man from a malaria endemic area, who presented with reversible myocarditis. **Keywords:** Malaria. Reversible myocarditis. Severe *Plasmodium vivax* malaria.

INTRODUCTION. Brazil, where malaria is endemic in the Amazon region[1], is one of the few countries around the world with *Plasmodium vivax* predominance. We report a case of *P. vivax* malaria in a 35-year-old patient from Anajás, a province in the Island of Marajó, State of Pará (00º98'S, 49º93'W), which is considered a high-risk area for malaria. Severe malaria is caused mainly by *Plasmodium falciparum.* Severe cases similar to those that have been described for *P. falciparum* malaria have been reported with *P. vivax* malaria, but few cases have been reported with cardiac involvement[2,3].

CASE REPORT. The 35-year-old male patient was an electrician and 5-year resident of Anajás, State of Pará, Brazil. He had no previous history of malaria or cardiovascular system disorders. After discharge from the hospital following spinal cord injury due to an occupational accident, the patient presented with a 5-day history of fever, chills, headache, and asthenia,and was again hospitalized. In the hospital, a thick blood smear was positive to *P. vivax* (30,000 asexual parasite forms/mm^3), and he was treated with 150mg chloroquine (4 tablets on the first day and 3 tablets on the second and third days) plus 15mg primaquine (2 tablets/day for 7 days) according to the treatment regime proposed by the Health Ministry of Brazil[4]. In the third day of hospitalization, primaquine was discontinued and the patient transferred to the intensive care unit due to worsening respiratory distress concomitant with signs of heart failure and petechial hemorrhagic suffusion on the thorax, abdomen and lower limbs. Normal white blood cell count observed at admission evolved to leukopenia (3,000/µL/mm^3), and hemoglobin decreased from 12.8g/dL to 8.9g/dL. Thrombocytopenia was present both at admission (20,000 platelets/mm^3) and in day 3 (15,000 platelets/mm^3). Chest radiography revealed pulmonary edema and cardiomegaly), Ecocardiography revealed left ventricular dilatation during systole (5mm, normal = 4mm) and diastole (73mm, normal = 56mm), decreased left ventricular ejection fraction (LVEF) (47%, normal > 58%), diffuse hypokinesia and mild mitral regurgitation. Blood and urine cultures were negative. Results of serological tests for dengue, yellow fever, infectious mononucleosis, Chagas disease, enterovirus (Coxsackie and Echovirus), human immunodeficiency virus (HIV) and human T-lymphotropic virus (HTLV) were also negative. Polymerase chain reaction (PCR) to confirm *P. vivax* infection was not performed.

The patient gradually improved with antibiotic therapy (oxacillin and ceftriaxone), administered with antimalarials due to the clinical severe condition. He was also administered diuretics (furosemide and spironolactone), digoxin and carvedilol and was maintained in negative fluid balance. A thick blood smear was negative to *Plasmodium* sp to day 5, and after 12 days of treatment, he was discharged (February, 11^{th}, 2009) in regular health and administered carvedilol (1 tablet, 2 times/day). Thereafter, he did not return to Anajás and was monitored on a monthly basis in the Laboratory of Clinical Malaria Essay at the Evandro Chagas Institute, in Ananindeua, State of Pará, Brazil, relapsing on the 46^{th} day post-treatment, with 3,500 asexual *P. vivax* parasite forms/mm^3. At this time, the standard treatment was reintroduced. A negative blood smear was observed on day 4, which persisted for up to 90 days with monthly controls. In May - 2009, radiography showed normal lung transparency and normal cardiac area; electrocardiography showed normal sinus rhythm; and echocardiography showed a 34-mm ventricular diameter in systole, 50-mm left ventricular diameter in diastole, LVEF of 60%, and heart valves without morphologic or dynamic abnormalities.

DISCUSSION. The worldwide prevalence of severe *P. vivax* malaria cases is not well known, probably because there are no defined severity criteria for malaria caused by *P. vivax*. However, the World Health Organization (WHO) criteria for severe *P. falciparum* malaria seem to apply to the broad spectrum of the most severe *P.vivax* malaria cases described[3,5]. A *Plasmodium vivax* malaria case complicated with myocardial failure and hemorrhagic diathesis in an adult man from a malaria endemic area (Anajás) in the Amazon region (Brazil) without a previous history of malaria, was reported in addition to the first *P. vivax* malaria episode in six patients who presented with cardiac involvement (from a series of 22 malaria cases admitted in a German hospital)[2]. Similarly a case of myocarditis associated with primary *P. vivax*

malaria has been reported in a woman from South Korea[3]. Though these primary cases were related to the absence of specific immunity to the parasite, severe cases, including cardiac damage, may occur in patients with previous malaria who have some degree of immunity, making this relationship between myocarditis and malaria unclear[2]. Our patient presented with high parasitemia (30,000 asexual parasite forms/mm^3), which might have influenced the severity, although additional studies are necessary to determine to what extent high parasite density may be considered a marker of severity in *P. vivax* infections, as indicated by Lacerda et al.[6]. In a recent review of cardiac involvement in parasitic infection, Hidron et al. reported that *Trypanosoma cruzi* is the main parasite to compromise the heart; however the authors did not mention malaria[7]. Myocardial involvement in malaria seems uncommon, with unclear physiopathology in the majority of cases associated with *P. falciparum*. Autopsy findings have shown parasites and parasitized red blood cells blocking myocardial capillaries, leading to ischemic cardiomyopathy, and a dilated heart has also been observed. In addition, the toxic effects of high levels of tumor necrosis factor (TNF) may play a role in the inflammatory process in the heart, with migration of lymphocytes and plasma cells, among others[3,8].

11. To give and explain the Classification of Evidence Levels.
12. To fill a table of Levels of Evidence and Grades of Recommendations. Draw the table with answer
13. What is difference between Systematic Review and Narrative Review? To fill the table.

Feature	Systematic Review	Narrative Review
Question		
Sources and		
Selection		
Appraisal		
synthesis		
Inferences		

14. The rates of Myocardial Infarction (MI) were obtained from the Physicians'Health Study in RCT. In the study are used Aspirin.
    - Rate of MI in the treated group = 254.8 per 100,000 per year
    - Rate of MI in the placebo group = 439.7 per 100,000 per year

    Task. Calculate Efficacy of treatment by Aspirin.

15. Read the scientific paper and evaluate – type, purpose, subjects, methods and results of the study.

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Safety and Immunogenicity of DNA Vaccines Encoding Ebolavirus and Marburgvirus Wild-Type Glycoproteins in a Phase I Clinical Trial

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Abstract . Outbreaks of *Ebolavirus* and *Marburgvirus* have occurred in Africa and have intermittently reemerged, with varying case fatality rates. A 2014 outbreak of *Ebolavirus* disease (species *Zaire ebolavirus*) in West Africa, including Guinea, Sierra Leone, Liberia, and Nigeria, has been the worst outbreak to date and the first to be localized primarily in urban areas [6]. A case fatality rate ranging from 60% to 87% was reported in the first few months of the outbreak. This outbreak affected community members as well as healthcare workers and seems to have spread person to person through regional and international travel. *Marburgvirus* disease has primarily occurred in travelers [4, 5] and, has case fatality rates of 23%–90% [7], the potential to spread internationally with increasing global travel, and the potential threat to be used as a biological weapon. In 2006, we reported the first clinical trial evaluating a multigene DNA vaccine encoding transmembrane-deleted GP from EBOV and SUDV and nucleoprotein from EBOV [12]. The vaccine was well tolerated, with no significant adverse events. The vaccine elicited GP-specific antibody and T-cell responses that were not cross-reactive, but after further preclinical evaluation of GP antigens, we found that a transmembrane-deleted GP did not provide optimal protection and that the nucleoprotein antigen was not required for protection. The subsequent clinical trial evaluated an rAd5 vector vaccine expressing an EBOV GP with a single amino acid point mutation (point mutation GP). The product was found to be safe and well tolerated.AA Nonhuman primate studies have further shown that transmembrane-deleted and point mutation GP antigens are partially protective but WT GP constructs are safe and provide the highest level of protection [14]. Here we report the results of a phase I clinical trial evaluating 2 DNA vaccines, one that encodes for MARV Angola GP and the second for EBOV and SUDV WT GP.

Study Design and Procedures. VRC 206 was a single-site, phase 1, open label study examining the safety, tolerability, and immunogenicity of 2 investigational DNA vaccines, one (MAR) expressing GP from MARV Angola strain (GP [AN]) and the other (EBO) expressing WT GP from EBOV (GP [Z]) and SUDV (GP [S]) in healthy adults aged 18–60 years. The study was conducted at the NIH Clinical Center by the VRC, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, Maryland (clinicaltrials.gov NCT00605514). The study was reviewed and approved by the NIAID Institutional Review Board. The US Department of Health and Human Services human experimental guidelines for conducting clinical research were followed. All subjects gave written informed consent before participation. The study groups were not randomized because approval to proceed with the MAR DNA vaccine was received before approval to proceed with the EBO WT DNA vaccine owing to a delay in receiving preclinical data with the EBO WT DNA vaccine. Thus, group 1 was fully enrolled first to receive the MAR DNA vaccine. Later, group 2 enrolled to receive the EBO WT DNA vaccine. No more than 1 subject per day was administered vaccine for the first 3 injections in each group, and safety data through 2 weeks after these injections were reviewed by a protocol safety review team before continuing enrollment of that group. A 4-mg dose of vaccine was administered as 1 mL by intramuscular injection in the deltoid muscle, using the Biojector 2000 Needle-Free Injection Management System (Bioject). In both groups, the immunization series was a 3-dose priming regimen with an optional single-dose homologous booster. The schedule for the 3-dose priming series was targeted to study days 0, 28, and 56, within permitted windows. Based on results from preclinical immunogenicity data available after the VRC 206 study began, an optional homologous booster dose at week 32 or later was offered to subjects who had completed all 3 injections and remained in clinical follow-up. Laboratory and clinical evaluations were completed at scheduled study visits. Local and systemic reactogenicity was self-reported by subjects using 5-day diary cards after each vaccination. Clinical assessment and laboratory evaluations for creatinine, AATf, complete blood cell count, prothrombin and partial thromboplastin time were completed at scheduled study visits. Adverse events were reported for the entire duration of the study, coded using the *Medical Dictionary for Regulatory Activities*. Subjects were followed up for safety and immunogenicity for 32 weeks or for 12 weeks after receipt of the optional fourth study injection.

DISCUSSION. This is the first clinical trial report of an *Ebolavirus* WT GP construct and the first report of a *Marburgvirus* vaccine clinical trial. We have shown elsewhere that earlier-generation gene-based constructs were safe and immunogenic, including a DNA vaccine with an EBO transmembrane-deleted GP and an rAd5 vector encoding EBO GP containing a point mutation.In this phase I study (VRC 206), both the EBO and MAR WT GP vaccines were well tolerated. The WT GP constructs evaluated in the current study were immunogenic and induced both humoral and T-cell responses to all 3 GP immunogen

	inserts. The administration of a fourth dose of DNA as a homologous boost improved the otherwise waning antibody titers and T-cell responses. This report is unique in that homologous DNA vaccine induced a demonstrable boost of preexisting memory B cells and antibody responses dominated the immune response, and $CD4^+$ T-cell responses were more frequent than $CD8^+$ responses. The induction of T-cell responses by the vaccine is significant because recent nonhuman primate studies suggest that $CD8^+$ T-cell responses play an important role in protection induced by an EBO GP construct vaccine and are known to be important for efficient viral clearance [25, 26].This study (VRC 206) demonstrated that WT GP DNA vaccines were safe and immunogenic in humans. The results from this study paved the way for further evaluation of these 2 candidate vaccines in the first clinical trial of candidate *Ebolavirus* and *Marburgvirus* vaccines in Africa. A phase Ib clinical trial evaluating these vaccines opened to accrual in Kampala, Uganda, after interim safety analysis of the VRC 206 study.