LAB: SCREENING

FOR ANTIBODIES TO THE HUMAN IMMUNODEFICIENCY VIRUS

Source Centers for Disease Control. *1992 EIS Course.*

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Objectives

After completing this case study, the student should be able to:

1. Define and perform calculations of sensitivity, specificity, predictive value positive, and predictive value negative.
2. Describe the relationship between prevalence and predictive value.
3. Discuss the trade-offs between sensitivity and specificity.
4. List the principles of a good screening program.

Part I

In December 1982, a report in the *Morbidity and Mortality Weekly Report* (MMWR) described three persons who had developed acquired immunodeficiency syndrome (AIDS) but who had neither of the previously known risk factors for the disease: homosexual/bisexual activity with numerous partners and intravenous drug use. These three persons had previously received whole-blood transfusions. By 1983, widespread recognition of the problem of transfusion-related AIDS led to controversial recommendations that persons in known high-risk groups voluntarily defer from donating blood. In June 1984, after the discovery of the human immunodeficiency virus (HIV), five companies were licensed to produce enzyme-linked immunosorbent assay (EIA, then called ELISA) test kits for detecting HIV antibody. A Food and Drug Administration spokesperson stated that "getting this test out to the blood banks is our No. 1 priority." Blood bank directors were anxiously waiting to start screening blood with the new test until March 2, 1985, the date the first test kit was approved by the FDA.

In the prelicensure evaluation, sensitivity and specificity of the test kits were estimated using blood samples from four groups: those with AIDS by CDC criteria, those with other symptoms and signs of HIV infection, those with various autoimmune disorders and neoplastic diseases that could give a false-positive test results, and presumably healthy blood and plasma donors.

Numerous complex issues were discussed even before licensure. Among them were agreeing on the significance of a negative blood test, determining the percentage of antibody-positive persons who were capable of transmitting the virus, understanding the magnitude of the problem of false-positive test results, and determining whether test-positive blood donors should be notified.

It is now March 2, 1985, and you are the State Epidemiologist of State Y. The first HIV antibody test kits will arrive in blood banks in your state in a few hours. Meeting with you to discuss the appropriate use of this test are the Commissioner of Health, the medical director of the regional blood bank, and the chief of the State Y Drug Abuse Commission.

To help in your discussions, you turn to prelicensure information regarding the sensitivity and specificity of test kit A. The information indicates that the sensitivity of test kit A is 95.0% (.95) and the specificity is 98.0% (.98).

Question 1 With this information, by constructing a two-by-two table, calculate the predictive value positive and predictive value negative of the EIA in a hypothetical population of 1,000,000 blood donors. Using a separate two-by-two table, calculate *PVP* and *PVN* for a population of 1000 drug users. Assume that the actual prevalence of HIV antibody among blood donors is 0.04% (.0004) and that of intravenous drug users is 10.0% (.10).

The blood bank director wants your assistance in evaluating the EIA as a test for screening donor blood in State Y. In particular, she is concerned about the possibility that some antibody-positive units will be missed by the test, and she wonders about false-positive test results since she is under pressure to develop a notification procedure for EIA-positive donors.

Question 2 Do you think that the EIA is a good screening test for the blood bank? What would you recommend to the blood bank director about notification of EIA-positive blood donors?

The chief of the State Y Drug Abuse Commission has noticed a dramatic increase in AIDS among clients of his intravenous-drug-abuse treatment programs. He wants to do a voluntary HIV antibody seroprevalence survey of intravenous-drug-abuse clients for planning purposes and would like to assess the feasibility of using the test as part of behavior modification counseling.

Question 3 Do you think that the EIA performs well enough to justify informing test-positive clients in the drug-abuse clinics that they are positive for HIV?

Question 4 If sensitivity and specificity remain constant, what is the relationship of prevalence to predictive value positive and predictive value negative?

Part II

EIA results are recorded as optical density ratios (ODRs). The ODR is a ratio of absorbance of the tested sample to the absorbance of a control sample. The greater the ODR, the more "positive" is the test result. The EIA, as with most other screening tests, is not perfect; there is some overlap of optical density ratios of samples that are actually antibody positive and those that are actually antibody negative.This is illustrated in Figure 4.4 (p. 67).

Establishing the cutoff value to define a positive test result from a negative one is somewhat arbitrary. You initially decide that optimal density ratios greater than "B" on Figure 4.4 are positive.

Question 5a In terms of sensitivity and specificity, what happens if you raise the cutoff from "B" to "C"?

Question 5b In terms of sensitivity and specificity, what happens if you lower the cutoff from "B" to "A"?

Question 6 From what you know now, what is the relationship between sensitivity and specificity of a screening test?

Question 7 What would the blood bank director and the head of drug treatment consider in deciding where the cutoff point should be for each program? Who would probably want a lower cutoff value?

Part III

You are concerned that because of the low predictive value of the EIA in the blood donor population, the blood bank personnel cannot properly inform those who are EIA positive of their actual antibody status. For this reason, you wish to evaluate the Western blot test as a confirmatory test for HIV antibody.

The Western blot test identifies antibodies to specific proteins associated with the human immunodeficiency virus. The Western blot is the most widely used secondary test to detect HIV antibody because its specificity exceeds 99.99%; however, it is not used as a primary screening test because it is expensive and technically difficult to perform. Its sensitivity is thought to be lower than that of the EIA.

Because the Western blot test is not generally available, the blood bank director is wondering whether the initial EIA-positive results can be confirmed by repeating the EIA and by considering persons to have the antibody only if results of both tests are positive.

You decide that you want to compare the performance of the repeat EIA and the Western blot as confirmatory tests. To do this, use your earlier hypothetical sample of 1,000,000 blood donors. Assume that serum specimens that are initially positive by EIA are then split into two aliquots; a repeat EIA is performed on one portion and a Western blot on the other portion.

Question 8 What is the actual antibody prevalence in the population of persons whose blood samples will receive confirmatory testing?

Question 9 Calculate the predictive value positive of the two sequences of tests: EIA–EIA and EIA–Western blot. Assume that the sensitivity and specificity of the EIA are 95.0% and 98.0%, respectively. Assume that the sensitivity and specificity of the Western blot are 80.0% and 99.99%, respectively.

Question 10 Why does the predictive value positive increase so dramatically with the addition of a second test? Why is the predictive value positive higher for the EIA–WB sequences than for the EIA–EIA sequence?

Part IV

It is now July 1987 and the Governor has asked you to evaluate a proposed premarital HIV-antibody-screening program. A bill to establish the program is to be presented to the

Additional Information

The following 10 principles of good mass screening programs were proposed by Wilson and Jungner of the World Health Organization in 1968:

1. The condition being sought is an important health problem for the individual and the community.
2. There is an acceptable form of treatment for patients with recognizable disease.
3. The natural history of the condition, including its development from latent to declared disease, is adequately understood.
4. There is a recognizable latent or early symptomatic stage.
5. There is a suitable screening test or examination for detecting the disease at the latent or early symptomatic state, and this test is acceptable to the population.
6. The facilities required for diagnosis and treatment of patients revealed by the screening program are available.
7. There is an agreed policy on which to base treatment of patients.
8. Treatment at the presymptomatic, borderline stage of a disease favorably influences its course and prognosis.
9. The cost of the screening program (which would include the cost of diagnosis and treatment) is economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding is a continuing process, not a "once and for all" project.

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