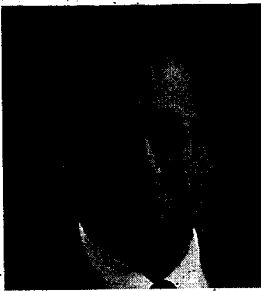




Risk in Perspective

Whose Blood Is Safer?



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We suggest modifying the definition of a "high-risk" blood donor group to include populations with a high ratio of HIV-to-AIDS incidence, even though the population may have low HIV prevalence.

Suppose you need a blood transfusion and are concerned about the risk of contracting HIV from donated blood. Suppose also that you are given a choice between receiving donated blood from a female or male donor. Whose blood would you choose? Intuition says that a female donor's blood is preferable, because both current levels of infection and rates of new infection are lower in women.

Blood banks in the U.S. have followed such logic in recruiting donors from segments of the population believed to be "low risk." However, the truth is not that simple. In 1992, researchers from the Centers for Disease Control and Prevention (CDC) noted in a study published in the *New England Journal of Medicine* that "data do not support the conjecture that HIV infection from screened blood is more likely in areas with high incidences rather than low ones; that is, the risk of HIV infection from screened blood may not be directly proportional to the prevalence of AIDS in a geographic area."

In this issue of RISK IN PERSPECTIVE, we explain this observation

and describe the role of the stage of the AIDS epidemic on the accuracy of negative test results for first-time donors.

ELISA TEST AND FALSE-NEGATIVE ERRORS

The commonly used test for blood bank screening is an antibody test, called the enzyme-linked immunoabsorbent assay (ELISA). This test does not detect HIV.

Rather, it detects the presence of antibodies to HIV, which the human body creates as a reaction to the HIV infection. However, this reaction is not immediate and may occur any time from three weeks to a few months after infection. The period between infection and seroconversion (developing antibodies to HIV) is called the seronegative window or simply "the window." ELISA tests performed on an HIV-infected person in the window will produce a negative result (commonly referred to as a "false-negative").

The rate of false-negative errors of the ELISA test is extremely low. According to a CDC report by Lackritz et al. published in the *New*

England Journal of Medicine in 1996, for first-time donors in the U.S., rates vary from 1 per 210,000 to 1 per 1,140,000.

There are two sources of false-negative errors associated with the ELISA test. The first is *random measurement error*, which occurs when someone has detectable HIV antibodies, but the ELISA test is interpreted as negative. Random measurement error can occur from several sources; including human error in recording or reporting, and errors due to instrumentation and measurement. This error — which increases with the prevalence of HIV in a given population (explaining the tendency of blood banks to solicit more donations from the low-prevalence populations), — can be reduced by repeated testing, and can be estimated easily.

The second type of error is the *window error*, which occurs when HIV antibodies are not present despite the presence of HIV. Repeated testing cannot eliminate this type of error. As the accuracy of the ELISA test has improved, the window has become the major cause of false-negative error.

We developed a model which, for any population, permits an estimation of the separate or overall effects of both of these errors.

These estimates can be used to evaluate the risks and benefits of collecting and screening blood in various population sub-segments. The parameters of the model are: sensitivity of the ELISA test, the prevalence (the proportion of infected

individuals in population) of HIV, incidence rate of HIV (the number of newly infected persons per 100,000 people), and incidence rate of AIDS (the number of new AIDS cases per 100,000 people).

SERONEGATIVE WINDOW ERROR

Consider the pool of potentially infected blood donors, persons not known to be infected with HIV at the time of the current screening (see three scenarios on diagram). An infected donor could be at one of the following two stages: 1) in the window when the infection cannot be detected (all test results will be false-negative), or 2) at the stage when his/her infectious status is detectable by ELISA (i.e., antibodies to HIV have already developed). The next period is a stage when either the individual develops overt AIDS, or leaves the pool of potential donors for other reasons (e.g., having a positive HIV test or dying from other causes) prior to developing AIDS. The average duration from infection to AIDS is conservatively estimated to be ten years. In the diagram, there are two areas in which the infected blood donor can reside: white or shaded. The probability that an infected donor is in the window is equal to the ratio of the white area to the entire area on the graph (white plus shaded).

Consider the scenarios on the diagram. The probability that an infected donor is in the window is smaller in scenario one, a hypothetical steady-state epidemic than for scenario two, an early epidemic,

and greater in scenario one than scenario three, a matured epidemic. The main determinant of the risk of being in the window for a potential donor is the ratio of the incidence of HIV to the incidence of AIDS. The greater this ratio, the higher the risk that an infected donor is in the window and cannot be detected by the ELISA test. This ratio reflects the stage of the AIDS epidemic in a specific population. Window error plays a proportionally greater role during the early stages of HIV dissemination in a population where the incidence of new HIV infection is high relative to the incidence of AIDS.

WHOSE BLOOD IS SAFER?

Measurement error is more important when the epidemic has matured, while window error is more important during an early epidemic. As the sensitivity of the ELISA test increases by virtue of technical progress or repeated tests, the window error becomes dominant, and can more than offset "prevalence selection," the (self-) referral of donors based on the prevalence of HIV in their populations.

A roughly similar situation may apply between men and women today. The combined effect of window and measurement errors can lead to mistakes in evaluating the safety of blood donations. The model that we have developed for evaluation of the blood contamination risk takes into account both these errors. For example, for first-

time U.S. donor population considered in Lackritz et al. our estimate of false-negative error was 1 per 530,000 (compare to the authors' observations: between 1 per 210,000 and 1 per 1,140,000).

These findings may explain, in part, the above-cited CDC observation that cases of transfusion of contaminated blood often take place in areas where the epidemic recently began. They also explain published reports from the onset of the HIV epidemic in Thailand, when an increase of HIV transmission by negative blood was observed.

Although new HIV testing technologies, such as the p24 antigen test, may shorten the duration of the window period, the lessons gained from this study will continue to apply in populations with very high HIV incidence and low prevalence. These principles will continue to be applicable in the developing world and to new epidemics of blood-borne diseases.

CONCLUSION

The criterion for a population to be defined as "high risk" is its high false-negative rate. A population with a high HIV prevalence is currently considered a high-risk population, since it is *likely* to have a higher false-negative rate due to measurement error.

We suggest modifying the definition of a "high-risk" blood donor group to include populations with a high ratio of HIV-to-AIDS *incidence*, even though the population may

FURTHER READING

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have low HIV prevalence. The reason is that the high false-negative rate will be due to the window error. ELISA-negative blood donated by persons in a long-standing "high risk" group may actually be safer than blood donated by persons in a "low-risk" group in which the incidence of HIV infection is rising rapidly. Only by considering the effects of the antibody-negative window can we assess how much to trust negative results in HIV screen-

ing, and what donor-selection strategies are optimal. In the U.S. the epidemic is mature now, which reduces the window error regardless of changes in the ELISA testing kit's inherent sensitivity. An extremely low false-negative rate among U.S. donors has the potential to be reduced further by more rigorous consideration of the relative risks of specific groups and soliciting donations from the safest populations.

