A Rapid Review of Rapid HIV Antibody Tests

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Rapid HIV antibody tests recently approved by the Food and Drug Administration can help reduce unrecognized infections by improving access to testing in both clinical and nonclinical settings and increase the proportion of those tested who learn their results. Four rapid HIV antibody tests are now available in the United States; two are approved for use at point-of-care sites outside a traditional laboratory. All four tests are interpreted visually. Sites offering rapid HIV testing must periodically run external controls (known HIV-positive and HIV-negative specimens) and provide persons who undergo rapid testing a subject information sheet. This paper reviews the operating and performance characteristics, quality assurance and laboratory requirements, and HIV counseling implications of the currently available rapid HIV tests.

Introduction

Despite ongoing prevention and education efforts, an estimated 40,000 new HIV infections have occurred annually in the United States since the early 1990s. Of the estimated 1,039,000 to 1,185,000 persons living with HIV, approximately 252,000 to 312,000 (25%) persons are unaware they are infected [1]. Available evidence suggests that many new infections are caused by persons unaware of their HIV infection [2,3].

HIV Testing

Many persons with HIV do not get tested until late in their infection. Approximately 40% to 50% of patients with HIV infection are diagnosed with AIDS within 1 year of first testing HIV-positive [2,4–6].

Many persons who are tested do not return to learn their test results. The National Health Interview Survey found that 12.5% of persons tested in 1994 and 13.3% in 1995 did not receive their results [7], and the Centers for Disease Control and Prevention (CDC) estimates that in 2000, 31% of patients who tested HIV-positive at public-sector testing sites did not return to receive their results [8].

To reduce barriers to early diagnosis of HIV infection and increase access to treatment and prevention services, the CDC announced a new initiative, "Advancing HIV Prevention: New Strategies for a Changing Epidemic" (AHP) [8]. This multifaceted program stresses the importance of routinely offering HIV testing as part of the medical visit and expands on the 1993 recommendations for testing inpatients and outpatients in acute-care hospital settings [9]. Additionally, AHP stresses the importance of using rapid HIV tests to facilitate access to early diagnosis in high prevalence areas, for high-risk individuals, and for women during labor and delivery who have not previously been tested and in nontraditional testing settings.

Rapid HIV tests can play an important role in HIV prevention activities and expand access to testing in both clinical and nonclinical settings. They can help overcome some of the barriers to early diagnosis and improve linkage to care of infected persons. This paper will review the operating and performance characteristics, quality assurance (QA) and laboratory requirements for currently available rapid HIV tests, and counseling implications.

The Tests

Four rapid HIV tests have been approved by the US Food and Drug Administration (FDA): OraQuick® (and its newer version OraQuick® Advance) Rapid HIV-1/2 Antibody Test (OraSure Technologies, Inc., Bethlehem, PA); Reveal™ (and its newer version Reveal™ G2) Rapid HIV-1 Antibody Test (MedMira, Halifax, Nova Scotia); Uni-Gold Recombigen® HIV Test (Trinity BioTech, Bray, Ireland); and Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories, Redmond, WA). Like conventional HIV enzyme immunoassays (EIAs), rapid HIV tests are screening tests that require confirmation if reactive. Though each of these rapid HIV tests has unique characteristics, they share many common features, including how the tests work, the use of external controls, and other requirements such as the product information sheets that are provided to patients.

Table 1. US Food and Drug Administration–approved rapid HIV antibody tests for HIV-1 detection

Rapid HIV test*	Specimen type	Sensitivity†	Specificity†	CLIA category
OraQuick® Advance Rapid HIV-1/2 Antibody test	Oral fluid	99.3% (98.4–99.7)	99.8% (99.6–99.9)	Waived
	Whole blood (fingerstick or venipucture)	99.6% (98.5–99.9)	100% (99.7–100)	Waived
	Plasma	99.6% (98.9–99.8)	99.9% (99.6–99.9)	Moderate complexity
Reveal™ G-2 Rapid HIV-1 Antibody test	Serum	99.8% (99.5–100)	99.1% (98.8–99.4)	Moderate complexity
	Plasma	99.8% (99.5–100)	98.6% (98.4–98.8)	Moderate complexity
Uni-Gold Recombigen® HIV test	Whole blood (fingerstick or venipucture)	100% (99.5–100)	99.7% (99.0–100)	Waived
	Serum and plasma	100% (99.5–100)	99.8% (99.3–100)	Moderate complexity
Multispot HIV-1/HIV-2 Rapid test	Serum	100% (99.94–100)	99.93% (99.79–100)	Moderate complexity
	Plasma	100% (99.94–100)	99.91% (99.77–100)	Moderate complexity

*Trade names are for identification purposes only and do not imply endorsement by the US Department of Health and Human Services or the Centers for Disease Control and Prevention.
†95% CI
CLIA—the Clinical Laboratory Improvement Amendments of 1998.
Modified from Health Research and Education Trust available at http://www.hret.org/hret/programs/hivtransmrpd.html.

All four tests are interpreted visually and require no instrumentation. HIV antigens are affixed to the test strip or membrane. If HIV antibodies are present in the specimen being tested, they bind to the affixed antigen. The test kit's colorimetric reagent binds to these immunoglobulins creating an indicator that is visually detectable.

External controls

All four rapid HIV tests require the periodic use of external controls (known HIV-positive and -negative specimens). External controls must be run 1) by each new operator prior to performing the test on patients, 2) when a new lot of test kits is used, 3) upon receipt of a new shipment of test kits, 4) when the temperature of the storage or testing area falls outside the recommended range, and 5) at periodic intervals determined by the testing facility, usually based on their volume of testing.

Subject information sheets

The FDA requires that persons who undergo rapid testing receive a subject information sheet. This sheet, provided by each manufacturer with its rapid HIV test kits, includes basic information about HIV/AIDS, HIV testing, how the test works, what the tests results mean, and specifies that reactive rapid test results need to be confirmed.

The Clinical Laboratory Improvement Amendments of 1988

All laboratory testing is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which classifies tests according to their complexity. To receive a CLIA waiver, tests must use direct, unprocessed specimens (such as whole blood or oral fluid) and be easy to perform with a negligible chance of error. Waived tests can be performed by persons without formal laboratory training outside traditional laboratories. Waived tests, suitable for use at the point-of-care, make it easier for nonclinical testing sites to offer rapid HIV tests. In order to purchase CLIA-waived rapid HIV tests, a facility must register as a laboratory with the CLIA program and adhere to the manufacturer's instructions for performing the tests.

OraQuick® and Uni-Gold are CLIA-waived; Reveal™ and Multispot are categorized as moderate complexity (Table 1). Laboratories that perform moderate complexity testing must meet more stringent standards for personnel, supervision, quality assurance, and proficiency testing than laboratories that perform waived testing.

OraQuick® Advance Rapid HIV-1/2 Antibody Test

On November 7, 2002, the FDA approved the OraQuick® Rapid HIV-1 Antibody Test for use on fingerstick blood samples. It received its CLIA waiver in January 2003. Subsequently, OraQuick® received approval for use with venipuncture whole blood and plasma (though OraQuick® used with plasma is classified as moderate complexity under CLIA). In 2004, OraQuick® Advance received FDA approval for use with oral fluid and for detection of both HIV-1 and HIV-2.

The OraQuick® test device is shown in Figure 1. The paddle-shaped device contains a nitrocellulose strip, upon which a stripe of synthetic gp41 peptides represent-

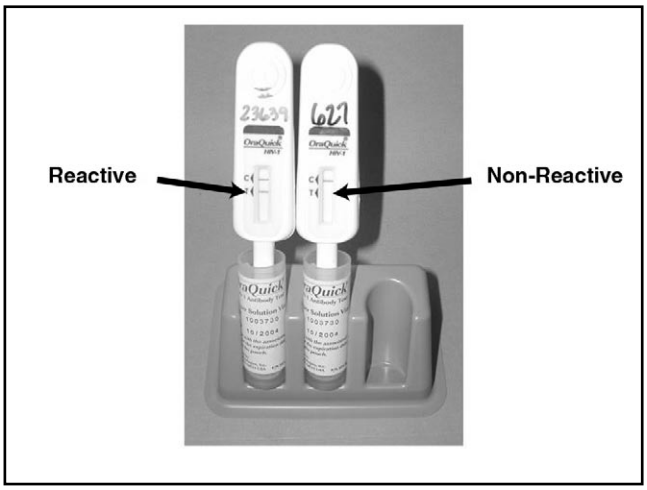

Figure 1. OraQuick® Advance Rapid HIV Antibody test.

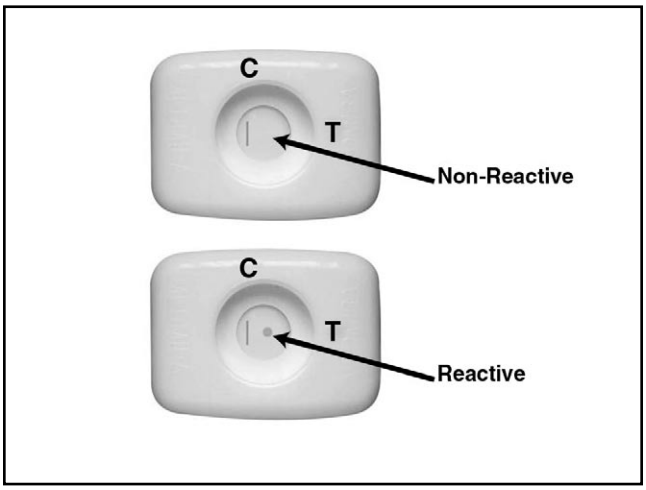

Figure 2. Reveal™ G2 Rapid HIV-1 Antibody test.

ing the HIV-1 envelope and the gp36 region of the HIV-2 envelope have been applied in the "T" (test) location, and a stripe of goat antihuman IgG in the "C" (control) location. The specimen of blood or plasma is added directly to the developer vial. For oral fluid testing, the oral fluid sample is collected by swabbing the gums with the paddle-shaped device. The test device is then added to the developer vial. If HIV antibodies are present in the specimen, they bind to the peptides causing a red line to appear in the test location. As the solution migrates further, it encounters the antihuman IgG control, and if an adequate specimen was added, a red line appears in the control location.

The test result should be read no sooner than 20 minutes and no later than 40 minutes after the test device is inserted into the developer vial. A red line at both the test and control location indicates a valid reactive test result; a red line only in the control location indicates a valid negative test result. The test is invalid and should be repeated with a new device if no line appears at the control location or if lines appear outside the areas indicated by the triangles [10].

Designed as a point-of-care HIV test, OraQuick® has been used in numerous settings including labor and delivery [11•], ambulatory clinical sites [12], emergency departments [13,14], hospital inpatient services [15] (Greenwald JL, unpublished data), correctional facilities [16], and for occupational exposures [17–19]. Additionally, OraQuick® has also been used by the military in battlefield operations [20].

Reveal™ G2 Rapid HIV-1 Antibody Test

On April 17, 2003, the FDA approved the Reveal™ Rapid HIV-1 Antibody Test to detect HIV antibodies in serum or plasma. In June 2004, it was superseded by the second generation Reveal™ G2 test, which incorporates an internal control [21]. Reveal™ G2 consists of a test cartridge and a proprietary colorimetric detection agent. Positive and negative external controls, which must also be reconstituted, are supplied with the kit.

Reveal™ is considered reactive if both the red control line and central red test dot appear, negative if only the control line appears, and invalid if the control line does not appear (Fig. 2). The Reveal™ G2 only takes 3 minutes to run [22]. However because it requires serum or plasma from centrifuged blood samples and several reagent steps, it is classified as a moderate complexity test under CLIA and is usually performed in a clinical laboratory.

Uni-Gold Recombigen® HIV Test

The Uni-Gold Recombigen® HIV Test received FDA approval in December 2003 for testing whole blood, serum, and plasma for antibodies to HIV-1. It was waived under CLIA in 2004 for use with venipuncture and fingerstick whole blood specimens [23]. The device consists of a rectangular plastic test cartridge and a dropper bottle of buffer solution (Fig. 3). Peptides from the immunodominant region of the HIV-1 envelope are immobilized on a nitrocellulose strip in the test region. Reagents are also bound at the control region to indicate whether the test is functioning correctly, but these do not detect IgG and thus appearance of the control line does not validate that adequate patient specimen has been added. One drop of specimen is added to the specimen well on the test cartridge followed by four drops of wash buffer. The specimen combines with the colorimetric reagent and migrates along the nitrocellulose strip past the test and control regions. The test is read 10 to 12 minutes after specimen is added. A line in both the test and control regions indicates a reactive test; a line in only the control region indicates a negative test. When used with whole blood, the test is valid only if the control line is present and the sample well is red, indicating that an adequate blood sample has been added [24].

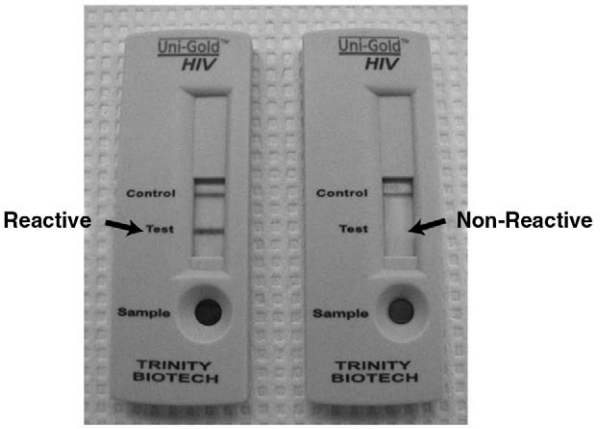

Figure 3. Uni-Gold Recombigen® HIV test.

Multispot HIV-1/HIV-2 Rapid Test

The Multispot HIV-1/HIV-2 Rapid Test received FDA approval in November, 2004 [25]. Multispot is classified as a moderate complexity under CLIA, approved for use on fresh or frozen serum and plasma to both detect and distinguish HIV-1 from HIV-2.

Multispot consists of a test cartridge and five reagents: specimen diluent, wash solution, conjugate, development reagent, and stop solution. The cartridge contains a membrane on which microparticles have been immobilized in four spots. Two of the spots consist of recombinant and synthetic gp41 peptides to detect HIV-1 antibodies; one consists of synthetic gp36 peptides to detect antibodies to HIV-2; and the fourth spot consists of goat antihuman IgG as the internal control.

The test is considered positive for HIV-1 if the control spot and either or both of the HIV-1 spots turn purple, and positive for HIV-2 if the control and HIV-2 spots appear (Fig. 4). If purple appears in the control spot, the HIV-2 spot, and one or both of the HIV-1 spots, the test is considered HIV reactive (undifferentiated). In this case, the specimen may be tested by additional methods which allow differentiation between HIV-1 and HIV-2. The test is negative when only the control spot appears. The absence of the control spot indicates an invalid result, regardless of any other spot pattern.

Rapid HIV Antibody Test Performance and Interpretation of Test Results

Like conventional EIAs, rapid HIV tests are screening tests. If performed correctly, they detect HIV antibodies with sensitivities similar to currently available EIAs [10,22,24–29] (Table 1). A negative rapid HIV test result requires no further confirmatory testing. False negative results, though rare, may occur in a person who has been acutely infected but who has not yet developed HIV antibodies. Therefore, any patient testing negative who has had known or suspected exposure to HIV within 3 months should be instructed to retest 3 months after the exposure date [30]. Additionally, false-negative rapid HIV test results have been observed in some patients receiving highly active antiretroviral therapy with undetectable virus in whom levels of HIV antibody have waned below the level of detection by the rapid HIV test [31].

A reactive result from any of the four rapid HIV tests is interpreted as a "preliminary positive" and requires confirmation by a more specific assay, typically a Western Blot (WB) or immunofluorescent assay (IFA) [10,22,24,25]. Performing a standard EIA screening prior to confirmatory testing is not required. However, if an EIA is performed, the specimen must still proceed to WB or IFA testing regardless of the EIA result. A positive WB or IFA confirms the diagnosis of HIV infection. If the confirmatory test yields negative or indeterminate results, follow-up HIV testing should be performed on a blood specimen collected 4 weeks after the initial reactive rapid HIV test result [32•] as some patients newly infected with HIV may not have developed antibody levels sufficient to produce a positive WB or IFA [33].

Table 1 presents the test performances of US FDA-approved rapid HIV tests. It is important to note that because the test specificities are less than 100%, false positive rapid test results are an expected but rare event. When testing low seroprevalence areas, a higher proportion of reactive tests will be false positives because there are few true positives in low-prevalence populations. The causes of falsely positive rapid HIV tests (ie, a reactive rapid HIV test with a negative or indeterminate confirmatory test) are poorly understood. Certain medical conditions may be associated with a slightly increased risk for false-positive OraQuick® rapid HIV tests (eg, hepatitis A and B viruses, Epstein-Barr virus, multiparity, and the serologic presence of rheumatoid factor) [10].

Quality Assurance for CLIA-waived Rapid HIV Antibody Tests

Although CLIA-waived rapid HIV test devices are easy to use and can provide reliable results when the manufacturer's directions are followed, mistakes can occur at any point in the testing process, including storage and testing area temperature, test kit shelf-life, specimen collection, test performance and results interpretation, referring specimens for confirmatory testing, managing confirmatory test results, etc. To reduce mistakes and to ensure that the FDA restrictions for sale of the test are followed, a site that performs rapid HIV tests must have a QA program in place before offering these tests. In January 2003, the CDC convened a panel of experts including laboratory scientists and individuals from the FDA and the Centers for Medicare and Medicaid Services to develop guidelines that outline the basic parts of a rapid HIV test QA program [32•]. The *Quality*

Assurance Guidelines for Testing Using the OraQuick® Rapid HIV-1 Antibody Test are intended to assist a range of providers in developing policies, processes and procedures to ensure high quality HIV testing services. These guidelines include 1) the basics of a QA program for testing using OraQuick®, 2) an overview of government rules that apply to using this test, and 3) examples of forms/checklists that can be used to keep track of QA outcomes.

Counseling with Rapid HIV Antibody Tests

Counseling for patients choosing rapid HIV testing involves some differences compared with conventional testing, including assessing preparedness for clients to receive test results in the same session and explaining the meaning of preliminary positive results. Information can be provided either face-to-face or in a pamphlet, brochure, or video [34].

Patients with reactive rapid test results must be counseled in simple terms about the meaning of a reactive test. The provider must emphasize the need for a confirmatory test and schedule a return visit for results. Providers offering rapid HIV testing should be able to collect blood or oral fluid specimens on-site for confirmatory testing. All patients with reactive tests should be counseled on risk-reduction behaviors while awaiting the results of confirmatory testing. A simple message to convey this information could be "Your preliminary test result is positive, but we won't know for sure if you are infected with HIV until we get the results from your confirmatory test. In the meantime, you should take precautions to avoid transmitting the virus" [34]. The New York State Department of Health AIDS Institute has also created guidelines for how to discuss reactive results stratifying the language based on the patient's level of risk for HIV infection. For clients at high risk, the guidelines suggest saying "Based on your risk factors, it is *highly likely* that the preliminary test result is correct and that you have HIV" (emphasis added). For those at low risk, the phrase "quite likely" is recommended, and for those with no admitted risk factors, they advise informing them "There is a chance that this result could be a false positive" [35].

Physicians and counseling staff may be apprehensive about rapid testing specifically with regards to the ability to handle preliminary positive test results at any time. Data from RESPECT-2, a large, randomized, controlled trial that compared different forms of HIV testing and risk-reduction counseling in clients at sexually transmitted disease (STD) clinics in the United States, found that after gaining experience in the field, the majority of counselors preferred rapid testing, felt that rapid HIV testing sessions resulted in enhanced counseling, and felt that it was more convenient for both clients and counseling staff [36]. Although some have expressed concern about how counselors and clients will deal with discussing and understanding reactive results [37], others have noted that providers have extensive experience managing preliminary positive test results (eg, abnormal mammograms that require biopsies and abnormal pap smears that require colposcopy) [38] and studies of rapid testing have demonstrated good client understanding of results [39].

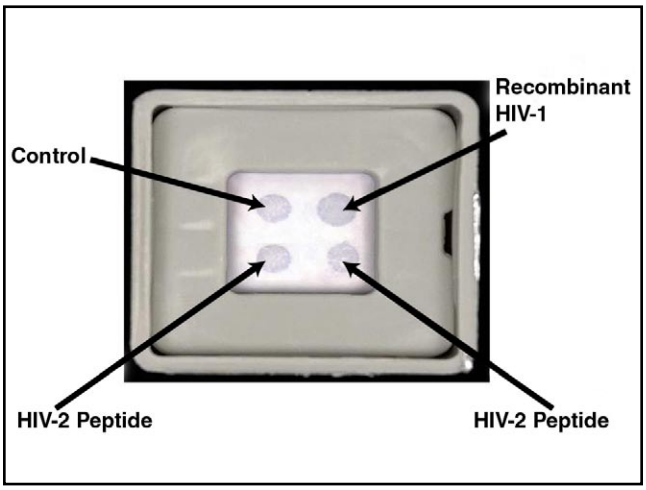

Figure 4. Multispot HIV-1/HIV-2 Rapid test.

Providing HIV counseling and testing may be challenging in some health care settings. Because the average primary care office visit in the United States is less than 18 minutes long [40], even the "brief" counseling protocol of RESPECT-2 could take up an entire office visit. In these situations, alternative procedures for HIV counseling with rapid testing should be considered, eg, providing information either in a face-to-face meeting with a counselor or in a pamphlet, brochure, or video [34].

Outcomes of Rapid HIV Testing—Receipt of Test Results

Compared with the standard two-session counseling and testing protocol, single-session, rapid HIV testing has the potential advantages of decreasing costs and increasing the number of patients who receive their results [41]. In anonymous testing and STD clinics in Dallas, the use of rapid testing with the Single Use Diagnostic System (SUDS) HIV-1 test (Murex, Norcross, GA) was associated with an increase in the number of patients learning their serostatus, lower costs, and improved patient satisfaction [39]. A randomized, controlled trial at a needle exchange and two bathhouses compared SUDS HIV-1 testing to other conventional HIV testing. This study found that more clients received their test results after rapid testing than with traditional testing: at the needle exchange, 66 (83%) of 80 versus 27 (56%) of 48 (odds ratio [OR] = 3.7; $P = 0.002$), and at the bathhouses, 102 (99%) of 103 versus 82 (74%) of 111 (OR = 36.1; $P < 0.001$) [38].

Patients failing to return for their confirmatory HIV test results remain a challenge [42]. Patients who do not return for confirmatory test results may choose to seek care at other

locations, already know their status, or seek retesting elsewhere. However, with rapid HIV testing, patients with reactive test results leave the initial testing visit with information that there is a high likelihood that they are seropositive compared with receiving no test result information at the end of a visit where a conventional HIV test specimen was collected. Because rapid HIV testing is likely to increase in the coming years, validation of an algorithm using a combination of point-of-care rapid HIV tests would enhance opportunities for individuals to get a confirmed HIV status.

Patient Satisfaction

Overwhelmingly, both patients and providers prefer rapid HIV tests to conventional EIAs [36,43–45]. Ninety percent (1038/1148) of persons seeking HIV testing at 24 clinical and nonclinical settings that offered the OraQuick® HIV test and an oral or serum EIA in New York, Utah, and Wisconsin preferred the rapid test; 13% of the clients in New York and Utah said they would not have tested that day if the rapid test had not been available [43].

Financial Considerations

The price for the FDA-approved rapid HIV test kits, as of July 2005, range from $14 to $25. Costs for multidose external control vials range from $20 to $26.25 [29]. According to the Centers for Medicare and Medicaid Services 2005 Clinical Laboratory Fee Schedule, average reimbursement for a CLIA-waived rapid HIV-1 antibody test (Current Procedural Terminology [CPT] code 86701QW) is $12.41/test and for a CLIA-waived rapid HIV-1/2 antibody test (CPT code 86703QW) is $19.17 [46–48]. Providers offering point-of-care, rapid HIV testing may be challenged by reimbursement not keeping pace with the list prices of the tests. In addition, comparable with counseling for other health issues, HIV counseling by a nonphysician is not reimbursable. Physicians performing HIV counseling may attempt to collect reimbursement for it by billing for prolonged services.

Conclusions

Rapid testing overcomes major barriers to individuals with HIV infection knowing their status: 1) HIV testing opportunities can be expanded to both medical and nonmedical settings and 2) rapid testing facilitates patients receiving their test results the same day, usually at the encounter where the test specimen was collected. Providing greater access to testing, prevention, and care services for persons living with HIV can reduce the number of new infections and lead to reductions in HIV-associated morbidity and mortality [49,50].

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Use of trade names and commercial sources is for identification only and does not imply endorsement by the US Department of Health and Human Services.

References to non-CDC sites on the Internet are provided as a service to this manuscript's readers and do not constitute or imply endorsement of these organizations or their programs by CDC or the US Department of Health and Human Services. CDC is not responsible for the content of these sites. URL addresses listed in this manuscript were current as of the date of publication.

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