

Diagnostic Infectious Diseases Testing Outside Clinics: A Global Systematic Review and Meta-analysis

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Background. Most people around the world do not have access to facility-based diagnostic testing, and the gap in availability of diagnostic tests is a major public health challenge. Self-testing, self-sampling, and institutional testing outside conventional clinical settings are transforming infectious disease diagnostic testing in a wide range of low- and middle-income countries (LMICs). We examined the delivery models of infectious disease diagnostic testing outside clinics to assess the impact on test uptake and linkage to care.

Methods. We conducted a systematic review and meta-analysis, searching 6 databases and including original research manuscripts comparing testing outside clinics with conventional testing. The main outcomes were test uptake and linkage to care, delivery models, and adverse outcomes. Data from studies with similar interventions and outcomes within thematic areas of interest were pooled, and the quality of evidence was assessed using GRADE. This study was registered in PROSPERO (CRD42019140828).

We identified 10 386 de-duplicated citations, and 76 studies were included. Data from 18 studies were pooled in meta-analyses. Studies focused on HIV (48 studies), chlamydia (8 studies), and multiple diseases (20 studies). HIV self-testing increased test uptake compared with facility-based testing (9 studies: pooled odds ratio [OR], 2.59; 95% CI, 1.06–6.29; moderate quality). Self-sampling for sexually transmitted infections increased test uptake compared with facility-based testing (7 studies: pooled OR, 1.74; 95% CI, 0.97–3.12; moderate quality).

Conclusions. Testing outside of clinics increased test uptake without significant adverse outcomes. These testing approaches provide an opportunity to expand access and empower patients. Further implementation research, scale-up of effective service delivery models, and policies in LMIC settings are needed.

Keywords. decentralized, HIV, infectious diseases, self-collection, self-testing, STD

Infectious disease diagnostics are not available to large numbers of people around the world, especially in low- and middle-income countries (LMICs) [1]. Diagnostic and screening tests are often confined to clinics with specialized laboratories [2–4]. Community clinics may not have the capacity to undertake diagnostic testing that requires special equipment and/or extensively trained personnel to perform tests [4, 5]. Many people

delay seeking care at centralized clinics because of stigma, competing demands, and transportation problems [3, 6, 7].

Diagnostic services provided outside conventional settings could help to close this gap. Such services include self-testing, self-sampling, and institutional testing. Self-testing has an individual collect their own specimen and interpret the test result [8]. Self-sampling has an individual collect their own specimen but receive the result from a laboratory [9]. Institutional testing takes place in pharmacies, schools, correctional facilities, or other settings [7, 10, 11]. These new approaches are transforming the field of diagnostic testing by expanding access to testing, empowering individuals, and creating innovative testing models [12].

Previous reviews have mostly focused on self-testing for HIV and self-sampling for sexually transmitted infections (STIs) [13–16]. In addition, studies have not examined how these different diagnostic approaches are shifting power away from centralized testing and toward the patients themselves. Self-testing and self-sampling become particularly advantageous

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in lockdown situations with restricted movement, as seen in the COVID-19 outbreak, where access to health care services and diagnostic testing become limited to medical emergencies. Testing outside of clinics gives greater agency to people and provides an opportunity to develop different service delivery models. The purpose of this study was to examine infectious disease diagnostic testing outside of clinics using a systematic review and meta-analysis.

METHODS

We conducted a systematic review and meta-analysis to identify new models applied to decentralized infectious disease testing. The systematic review was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist ([Supplementary File 1](#)) and conducted following methodology described in the Cochrane handbook [17, 18]. We developed a protocol for the review ([Supplementary File 2](#)), and it was registered in PROSPERO before commencing the review (CRD42019140828).

Search Strategy

We searched 6 databases including PubMed, Embase, Scopus, Web of Science, Global Health, and CINAHL for relevant literature. Search terms were identified by health sciences librarians from the University of North Carolina with experience in search algorithms. Search terms used in the databases included MeSH terms, keywords, and free text ([Supplementary File 3](#)). The search was conducted on July 10, 2019, and updated on August 8, 2019. Our search was not restricted by the year of publication or geographical location. We searched reference lists of articles included for additional citations.

Eligibility Criteria

Original research that compared testing outside of a clinic with a laboratory vs conventional testing in clinics was included. All eligible studies were in the English language and were focused on self-testing, self-sampling, and/or institutional testing for infectious diseases. Studies that compared testing outcomes from interventions and conventional approaches regardless of study design were eligible for pooling. We included data from 14 different infections/infectious diseases including HIV, human papillomavirus (HPV), hepatitis B, hepatitis C, syphilis, chlamydia, tuberculosis, gonorrhoea, filariasis, trachoma, leprosy, dengue, visceral leishmaniasis, and influenza. We excluded systematic reviews, conference abstracts, and studies that lacked a comparator group.

Study Selection

Citations were uploaded into Endnote and de-duplicated. Six reviewers were assigned individual sections for title screening. Next, the 6 reviewers independently assessed the included abstracts assigned to them for full-text reviews. Full-text studies

were evaluated by 2 independent individuals for eligibility and inclusion. Studies with disagreements were sent to a third reviewer and discussed among the group, and a decision was reached to either include or exclude the study.

Data Extraction

We extracted data based on our prespecified outcomes of interest. Data extracted included study design and location, testing site, type of test (self-testing, self-sampling), disease, sample size, linkage to care, test uptake, target population, test payment (out-of-pocket, paid for by research study, etc.), cost-effectiveness, and adverse outcomes reported. We defined linkage to care in HIV and all disease as any follow-up or contact with health care professionals including treatment initiation within 6 months of testing.

Quality Assessment for Included Studies

The quality of studies included for data pooling was assessed using the GRADE approach methodology [19]. For each study, we examined study limitations, risk of bias, consistency, precision, and other factors. The overall findings were assessed as high, moderate, low, or very low.

Analysis of Key Outcomes

Data from studies with the prespecified interventions of interest and outcomes with a comparator arm were pooled and analyzed. Studies that fit within thematic areas of interest, had a comparator arm that evaluated out-of-clinic with laboratory testing vs conventional facility testing, and had complete data (on number of participants recruited and number of participants tested) for both comparator arms were eligible for inclusion in the meta-analyses. Meta-analyses of prespecified groups were performed according to the different intervention approaches and outcomes of interest, and unadjusted odds ratios were calculated using Review Manager 5.3. Heterogeneity was assessed with an I^2 statistic [20]. We used a random-effects model in this study to ensure that variance was not underestimated.

RESULTS

The database search identified 21 344 citations, of which 10 958 were nonduplicates. A total of 76 studies were included in the systematic review ([Figure 1](#); [Supplementary File 4](#)). Of the 76 studies, 18 studies were eligible for meta-analysis based on our thematic areas of interest and were pooled. The database search strategy identified 72 studies, and 4 additional studies were identified by hand searching of reference lists. We identified 46 randomized controlled trials and 30 observational studies. Studies focused on HIV (48 studies), chlamydia (8 studies), gonorrhoea (11 studies), syphilis (4 studies), HPV (2 studies), hepatitis (3 studies), and tuberculosis (2 studies). Twenty studies focused on multiple diseases. Twenty-four studies included sexual minorities, 13 studies included testers in remote locations, and

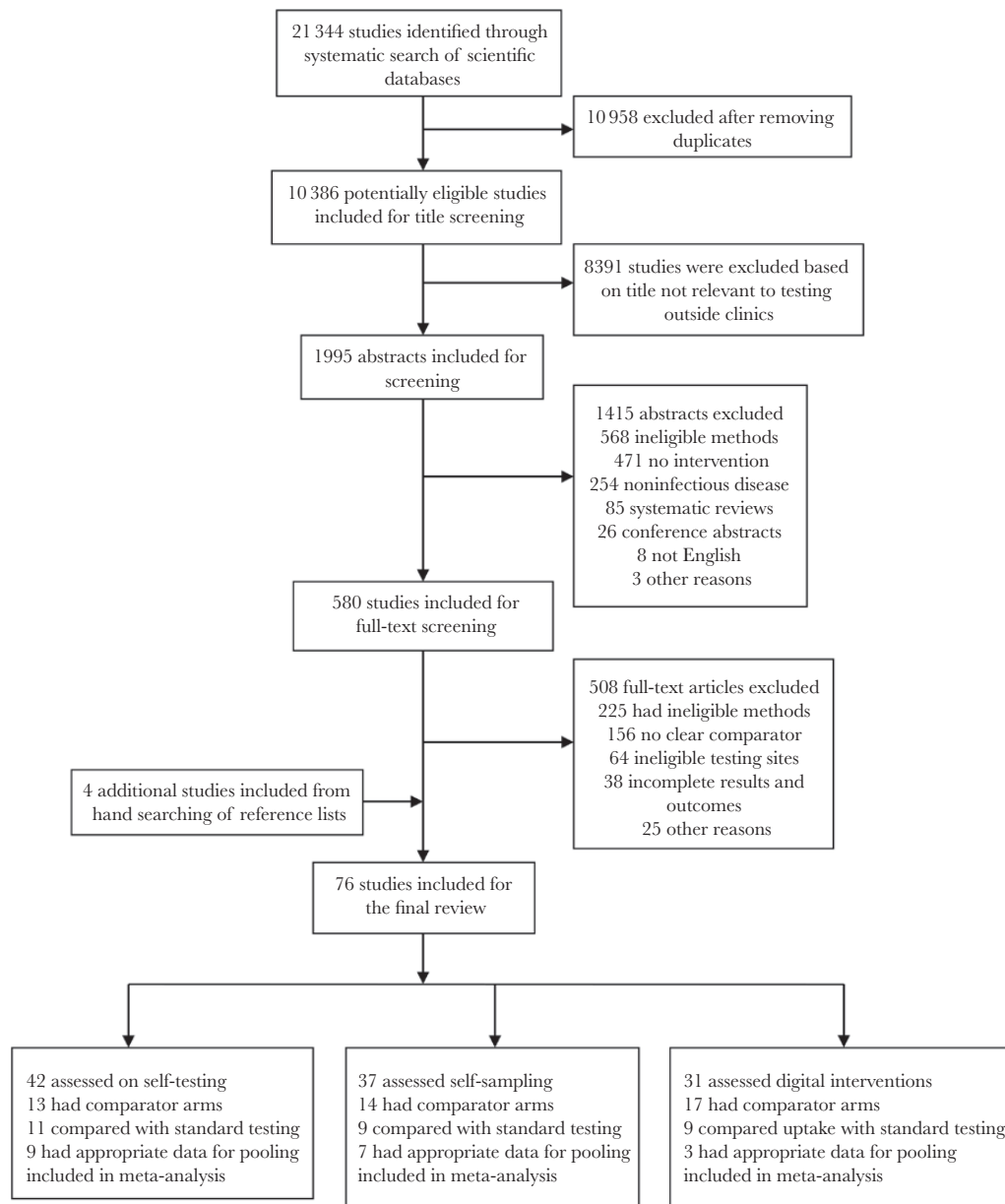


Figure 1. Study selection.

6 studies included first-time testers (Table 1). More than half (55%) of these studies were conducted in LMICs ($n = 42$), and 45% ($n = 34$) were in high-income countries. We observed that testing outside of clinics created new delivery approaches, increased test uptake, empowered testers, and had minimal risks.

HIV self-testing increased test uptake compared with facility-based testing (9 studies in 5 countries: pooled odds ratio [OR], 2.59; 95% CI, 1.06–6.29; $I^2 = 99\%$; $n = 33\,912$) (Table 2, Figure 2) [21–30]. The overall certainty of the evidence was moderate (Supplementary File 5). Self-sampling for STIs (HIV, chlamydia, gonorrhea, hepatitis, and syphilis),

which involved collecting body samples and submitting to a facility for testing, increased test uptake compared with facility-based diagnostic testing (7 studies in 5 countries: OR, 1.74; 95% CI, 0.97–3.12; $I^2 = 95\%$; $n = 14\,256$; moderate-quality evidence) (Figure 3) [31–35]. Testing outside clinics nonsignificantly increased access to diagnostic testing among sexual minorities and people in remote regions when compared with testing in conventional settings (OR, 1.16; 95% CI, 0.88–1.53; $I^2 = 93\%$; $n = 2525$) [35–41]. Four studies in LMICs reported a higher rate of testing in first-time testers among those who participated in testing models outside clinics

Table 1. Characteristics of Studies Included in the Review

Characteristic	No. of Studies
Self-testing	10 (7 LMICs; 3 HICs)
HIV	10
Other STIs	0
Self-sampling	6 (2 LMICs; 4 HICs)
Non-HIV STIs	5
Multiple STIs	1
Digital technology approach	6 (4 LMICs; 2 HICs)
HIV	6
Non-HIV	0
Multiple STIs	0
Study design	
RCT	46 (26 LMICs; 20 HICs)
Observational	30 (14 LMICs; 16 HICs)
Infectious disease	
HIV	48 (36 LMICs; 12 HICs)
Chlamydia	8 (8 HICs)
Multiple diseases	20 (6 LMICs; 14 HICs)
Population type	
Sexual minorities	24 (12 LMICs; 12 HICs)
First-time testers	6 (4 LMICs; 2 HICs)

Abbreviations: LMICs, low- and middle-income countries; HICs, high-income countries; RCT, randomized controlled trial; STI, sexually transmitted infection.

compared with conventional testing [21, 39, 42, 43]. Linkage to care was evaluated in 13 studies (Table 3), most of which were HIV-focused (10 studies, 8 in LMICs). The mean linkage to care rate for HIV within 6 months of testing was 17.3% in the testing-outside-of-clinics groups compared with 16.5% in the facility-based arms.

Testing outside of clinics gives power to all self-testers and self-sample testers (people receiving testing) about when, where, and how to test. One study showed that testing outside of clinics allowed for testing during the evenings, weekends, or holidays [44]. These approaches also allowed testers to test at home, at work, or at another location of their own choosing (3 studies in 3 countries) [26, 35, 45]. Testing outside of clinics allowed testers to give test kits to friends (1 study in 1 country) [22] and refer a partner (spouses and/or sex partners; 7 studies in 4 countries) [21, 24, 30, 46–48].

Innovative test delivery services (through mail services, on-line, pharmacies, schools, or correctional settings) improved test uptake compared with facility-based testing services. Fourteen studies that used local postal systems to mail an entire test kit (self-testing) or specimen collection kit (self-sampling) to the tester showed an increase in testing rates (OR, 1.41; 95% CI, 1.12–1.78; $I^2 = 92%$; $n = 1603$) [33, 34, 36, 46, 49, 50]. Five studies in 4 countries used pharmacies to distribute test-based services (OR, 2.47; 95% CI, 1.85–3.30; $I^2 = 94%$; $n = 1393$) [48, 51–54]. Three studies in 2 countries used schools or other educational settings to distribute diagnostic services (OR, 1.19; 95% CI, 0.68–2.06; $I^2 = 92%$; $n = 203$) [55–57]. Overall, 10 studies used digital interventions to enhance test uptake (Table 4). We

Table 2. Summary of Findings for Quantitative Analysis and GRADE Quality of Evidence Assessment

Intervention	Outcome	No. of Studies (RCT/NRS)	Effect Size (95% CI)	I^2	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality	GRADE Score ^a	
											Not serious	Serious
Self-testing compared with facility-based testing	Test uptake	9 (9/0)	2.59 [1.06–6.29]	99%	Serious	Serious	Not serious	Not serious	None	Moderate	Not serious	Moderate
STI self-sampling compared with facility-based testing	Test uptake	7 (7/0)	1.74 [0.97–3.12]	95%	Not serious	Serious	Not serious	Not serious	None	Moderate	Not serious	Moderate
Digital intervention compared with facility-based testing	STI test uptake	3 (2/1)	3.50 [1.35–9.08]	99%	Serious	Not serious	Not serious	Serious	None	Low	Serious	Low

Abbreviations: NRS, nonrandomized studies; RCT, randomized controlled trial; STI, sexually transmitted infection.
^aFor complete GRADE tables and justification for downgrading quality of evidence, see the Supplementary Data.

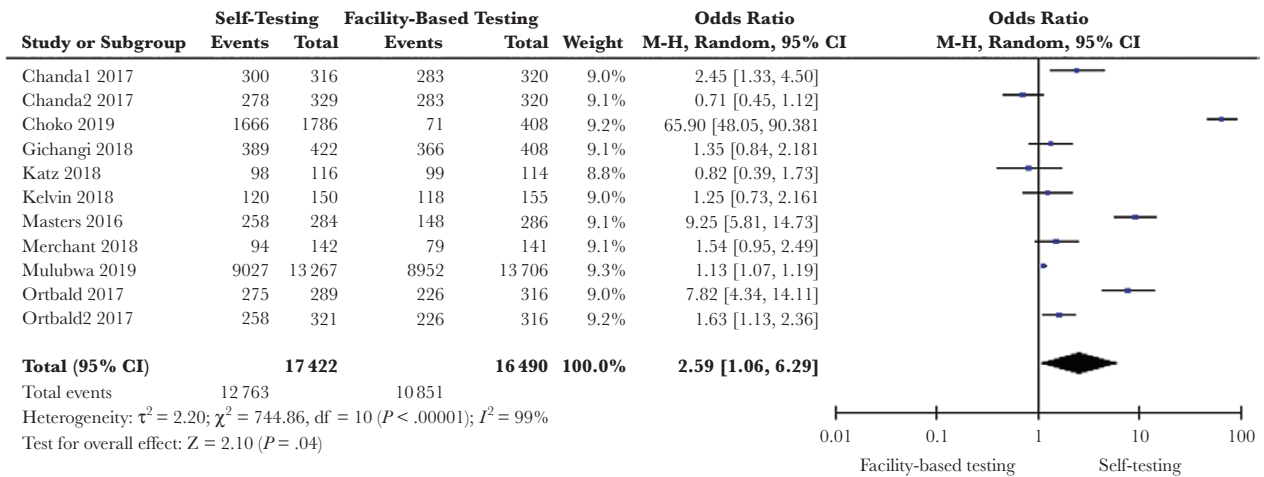


Figure 2. Self-testing compared with facility-based testing.

defined digital as emails, websites, instant messaging, or related internet approaches. Seven studies found that digital interventions increased the number of people who request diagnostic tests for infectious diseases compared with conventional approaches. Three additional studies evaluated the effect of digital interventions in improving STI self-sampling compared with conventional approaches, with a pooled OR of 3.50 (95% CI, 1.35–9.08; $I^2 = 99\%$; $n = 31\,241$; low quality of evidence) (Figure 4).

In terms of adverse outcomes, 3 studies examined the risks associated with testing outside of clinics. These articles reported on intimate partner violence, coercive testing, and depression and self-harm [24, 52, 58]. The rate of adverse events associated with testing outside clinics was found to be low (0.003% of participants in 2 studies), which was similar to adverse events in facility-based testing. Eight studies in 5 countries examined the cost associated with testing outside of clinics. Three out of 4 studies assessing cost-effectiveness found that testing outside

of clinics was cost-effective compared with facility-based approaches [59–61].

DISCUSSION

Our systematic review found that testing outside of clinics increased diagnostic test access compared with conventional testing. The risks of adverse events associated with testing outside the facility compared with facility-based testing are minimal. HIV self-testing digital interventions increased diagnostic test uptake, and the linkage to care rate was similar compared with conventional approaches. This study expands the literature by summarizing the use of decentralized diagnostic testing for multiple infectious diseases, examining service delivery models not covered in previous reviews, and evaluating linkage to care for diagnostic testing outside conventional settings.

We found that STI self-sampling increased test uptake compared with conventional testing approaches [31–35]. This is

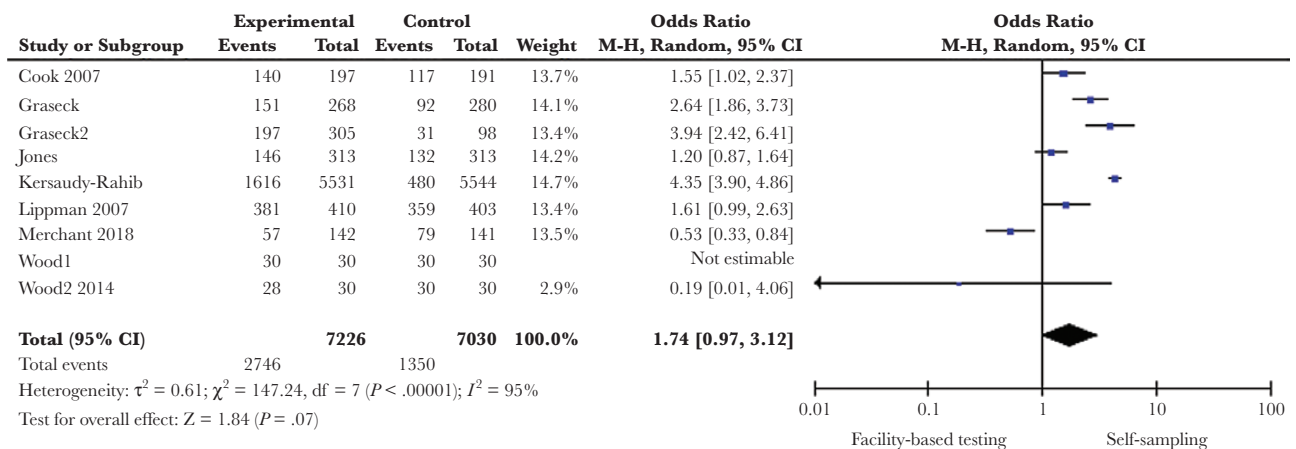


Figure 3. Sexually transmitted infection self-sampling compared with facility-based testing.

Table 3. Studies Reporting Linkage to Care in Diagnostic Testing Outside Clinics

Study	Location	Target Population	Disease	% Linked to Care (Intervention vs Control Group)	Linkage to Care Time Point
MacPherson et al. 2014 [29]	Malawi	Adults	HIV	2.2% vs 0.7%	6 mo
Morano et al. 2014 [84]	USA	General population	HCV	93.8% vs 18.2%	1 mo
Parker et al. 2015 [85]	Swaziland	General population	HIV	34.0% vs N/A	6 mo
Kelvin et al. 2019 [43]	Kenya	Female sex workers	HIV	14.0% vs 9.3%	2 mo
Chanda et al. 2017 [52]	Zambia	Female sex workers	HIV	51.9% vs 61.1%	4 mo
Reddy et al. 2016 [73]	USA	MSM	HIV	73% vs N/A	6 mo
Meehan et al. 2017 [61]	USA	University students	Chlamydia	74% vs 50%	Not stated
Miller et al. 2017 [82]	France	Young adults (aged 17–24 y)	HIV	85.1% vs 35.1%	Not stated
Barnabas et al. 2016 [70]	S/A Uganda	Men (aged 16–49 y)	HIV	74% vs 66%	9 mo
Ortblad et al. 2017 [23]	Uganda	Female sex workers	HIV	8.3% vs 8.2%	4 mo
Choko et al. 2019 [21]	Malawi	Pregnant women	HIV	10% vs 4%	1 mo
Green et al. 2018 [39]	Vietnam	MSM	HIV	81% vs 69.1%	Not stated
Johnston et al. 2018 [86]	Canada	General population	HIV	63.2% vs 29.3%	Not stated

Abbreviation: MSM, men who have sex with men.

consistent with a global literature suggesting patient preference for self-sampling [62–64]. Self-sampling kits require minimal technical skills, may be cost-effective, and diversify testing locations [65, 66]. Self-sampling could enhance early detection of many STIs for which self-testing is not available [67, 68]. This approach could simplify and streamline the process of diagnostic testing [69].

We found that HIV self-testing digital interventions increased testing rates compared with conventional approaches in 6 studies [25, 38, 43, 70–72]. This finding is consistent with earlier literature on promoting HIV self-testing [33, 73] but to our knowledge has not been the focus of previous systematic review findings. This finding is consistent with earlier studies that report that advertising free HIV self-testing kits on dating websites, mobile phone apps, and social media platforms helped to reach more men who have sex with men (MSM). This also simplified and increased access to many first-time testers when compared with testing in conventional health facilities [74–76].

Although digital interventions may be preferred by some key populations, this approach relies on self-reporting results, which may reduce the validity of the findings [77, 78]. However, external validation can be obtained through built-in interpretation programs to reduce bias due to self-reporting of test results. It is therefore important for digital self-testing strategies and models to incorporate linkage-to-care services such as real-time online supervised testing, digital tracking of test kit utilization, and provider-initiated follow-up calls or other interventions [21, 79, 80].

We observed a similar rate of linkage to HIV care after testing outside of clinics compared with conventional facility-based testing. This finding may be a result of who chooses to test outside of clinics and is similar to an observation made in a Copenhagen study [81], but has not been the focus of systematic reviews. Although other research has shown lower linkage to HIV care following self-testing [23, 29, 39, 82], recent studies suggest that embedding HIV self-testing with health provider-initiated

Table 4. Use of Digital Technology Across the Testing Continuum

Digital Technology Across the Testing Continuum				
Digital Technology	Promote Testing (Demand Generation)	Focus Testing Services (who Should Be Tested)	Order and Receive Self-Testing or Self-Sampling Kit	Results Notification/Instructions and Counseling
Websites, email	Katz 2018 [25] Kersaudy-Rahib 2017 [33] Jenkins 2012 [55]	Jenkins 2012 [55]	Jenkins 2012 [55]	Wang 2018 [71]
Social media	Katz 2018 [25]			
Mobile apps	Wray 2018 [38] Zhu 2019 [72]			
Text messages	Barnabas 2016 [70] Kelvin 2018 [26] Kelvin 2019 [43]	Kelvin 2018 [26] Kelvin 2019 [43]		Barnabas 2016 [70]
Remote monitoring sensors	Wray 2018 [38]			Wray 2018 [38]

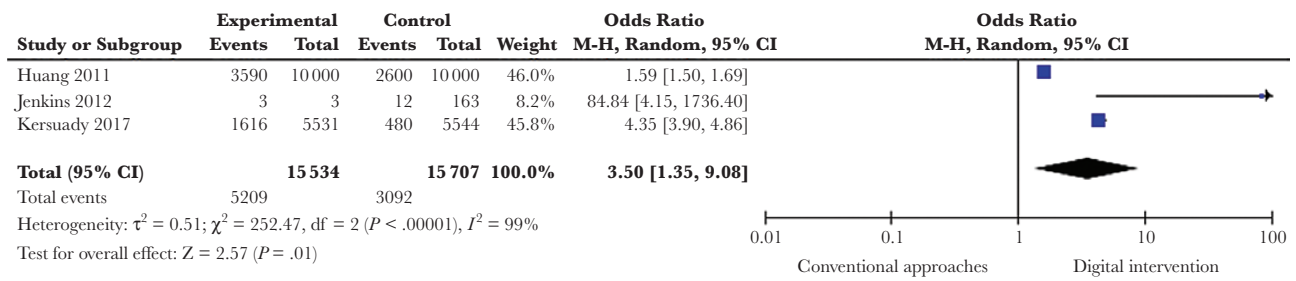


Figure 4. Use of digital interventions to promote infectious disease testing.

follow-up can enhance linkage to care [83]. There is still a need to improve linkage to HIV care after self-testing.

Our study has several important implications. From the policy viewpoint, this work demonstrates that the use of digital technology in testing outside clinics is a useful strategy for improving infectious diseases screening and linkage to care, and policies that aim to promote the use of these strategies are needed. These models may be especially useful for diseases associated with stigmatization such as HIV and other STIs, but many studies focus on HIV. Also, testing outside clinics will be a key strategy for continued testing in future pandemic situations where lockdowns and restricted movements are implemented. There is a need for more studies on the implementation of these strategies for other infectious diseases apart from STIs. Second, from the research perspective, we found that studies that aimed to evaluate the cost-effectiveness of decentralized diagnostic testing are limited, with most of these focusing on HIV infection alone. Future studies are needed to evaluate the cost-effectiveness, barriers, and facilitators of these approaches.

This study also has some limitations. First, very few studies have examined the risks and adverse outcomes associated with testing outside of clinics [24, 52, 58]. Further post-trial research is needed to fully understand the risks associated with testing outside of clinics. Second, none of the included studies provided testing to persons living with disabilities. This is another opportunity for expanding the impact of testing outside of clinics. Third, the number of studies for each outcome included in this study was low, and we noted that substantial heterogeneity across studies exists. Fourth, we only pooled the unadjusted results of the included studies, which may make the results biased. However, in most included studies, the participants in the conventional service group and the decentralized diagnostic testing group were reported to be comparable. Additionally, for studies that had multiple intervention arms compared with 1 control group, variance may have been underestimated.

CONCLUSIONS

Testing outside of clinics provides an opportunity to expand access to diagnostic testing for infectious diseases and give power to testers through innovative delivery models. Testing outside

of clinics can reach the last mile of many health systems, driving access for hard-to-reach groups in diverse LMIC settings. The modest evidence on adverse events suggests that these occur at a similar rate in facility-based testing. Further implementation research and scale-up of effective decentralized models in LMIC settings are needed.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. C.B. and J.T. developed the original idea for this study. E.K., G.M., W.T., N.F., D.W., and S.B. conducted the literature screening. J.S.W. did the literature search, and J.D.T., N.P.P., C.B., S.J.L., and R.S. were responsible for the study design. E.K., G.M., N.F., D.W., and S.B. did the data extraction, and W.T. did the analysis and created figures. E.K. and J.D.T. wrote the first draft of the manuscript. E.K., G.M., W.T., and J.D.T. wrote the report, and all authors reviewed and approved the final version.

Patient consent. This study only included a secondary data analysis and, as a result, did not require patient consent.

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