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SEXUAL HEALTH

Interventions aimed at increasing syphilis screening among non-pregnant individuals in healthcare settings: a systematic review and meta-analysis

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ABSTRACT

Syphilis remains a pressing public health concern with potential severe morbidity if left untreated. To improve syphilis screening, targeted interventions are crucial, especially in at-risk populations. This systematic review synthesises studies that compare syphilis screening in the presence and absence of an intervention. A systematic search of four databases was conducted (Medline, Embase, Cinahl and Scopus). The primary outcomes evaluated included syphilis screening, re-screening and detection rates. Findings were synthesised narratively. Where multiple studies were clinically heterogenous, a pooled odds ratio was calculated. Twenty-four studies were included. A variety of interventions showed promise including clinician alerts, which increased syphilis screening rate (OR range, 1.25–1.45) and patient SMS reminders that mostly improved re-screening/re-attendance rates (OR range, 0.93–4.4). Coupling syphilis serology with routine HIV monitoring increased the proportion of HIV-positive individuals undergoing both tests. However, pooling three studies with this intervention using the outcome of syphilis detection rate yielded inconclusive results (pooled OR 1.722 [95% CI 0.721–2.723], $I^2 = 24.8\%$, $P = 0.264$). The introduction of hospital-based packaged testing for screening high-risk individuals is unique given hospitals are not typical locations for public health initiatives. Nurse-led clinics and clinician incentives were successful strategies. Including syphilis screening with other existing programs has potential to increase screening rates (OR range, 1.06–2.08), but requires further investigation. Technology-driven interventions produced cost-effective, feasible and positive outcomes. Challenges were evident in achieving guideline-recommended screening frequencies for men who have sex with men, indicating the need for multifaceted approaches. Wider application of these interventions may improve syphilis screening and detection rates.

Keywords: health facilities and services, HIV, men who have sex with men, screening, sexual health, sexually transmitted infections, syphilis, systematic review.

Introduction

Syphilis poses a significant public health problem. Despite being potentially curable, it often remains asymptomatic and if left undetected, can result in severe morbidity manifesting as cardiovascular syphilis (aortic aneurysm, aortic valvulopathy), neurosyphilis (meningitis, stroke, seizures) or gummatous syphilis (infiltration of any organ and its subsequent destruction).[1]

Syphilis infection increases the risk of human immunodeficiency virus (HIV) acquisition.[2] Moreover, syphilis can increase HIV viral load in individuals already infected, facilitating HIV transmission.[3] Syphilis prevention is therefore of greatest concern in HIV-positive individuals and those with high HIV risk, including men who have sex with men (MSM), transgender people and injecting drug users.[4]

Controlling syphilis outbreaks relies on timely diagnosis and treatment of those infected. Modelling studies indicate more frequent screening of key populations has the potential to improve detection rates.[5–9] This approach would enable earlier treatment and contact tracing, and facilitate health promotion initiatives, thereby reducing community transmission and preventing long-term sequelae associated with untreated syphilis.

Several countries have established guidelines promoting regular syphilis screening for MSM. Guidelines in the United States and Australia recommend screening for syphilis in MSM up to 3 monthly and at least annually for those with fewer risk factors (e.g. not sexually active, in a monogamous relationship).[10,11] However, available data from the United States[12] and Australia[13] indicates the rate of screening for syphilis among MSM does not meet these guidelines.

To address this disparity, research has been conducted into targeted interventions to increase screening of all sexually transmitted infections (STIs) among high-risk populations. Systematic reviews have identified methods to increase STI screening including clinician reminders and patient recall systems that have shown promising results in enhancing overall STI screening.[14–17]

The existing literature lacks comprehensive analysis of interventions specifically targeting syphilis screening, making it challenging to determine optimal strategies and future research directions. This gap is significant given the unique characteristics of syphilis having a primarily asymptomatic course and serious complications. The aim of this review is to evaluate interventions implemented in healthcare settings with the purpose of increasing syphilis screening rates and detection.

Materials and methods

Search strategy

A systematic review of the literature was conducted according to the preferred reporting of items for systematic reviews and meta-analysis (PRISMA) guidelines.[18] The review protocol was registered in PROSPERO, the international prospective register of systematic reviews (CRD42023445995). MEDLINE, Embase, CINAHL and Scopus databases were searched, spanning from their respective creation dates to final searches on 8 July 2023, limited to human studies and those published in the English language. The following keywords, along with synonyms, were used: 'syphilis', 'screening', 'healthcare facilities' (Table 1). Reference lists of included articles were also checked for relevant studies.

Titles and abstracts of all publications from the search were uploaded into Covidence.[19] Two reviewers (LM, MO) independently screened each abstract for inclusion, with a third reviewer acting as a tiebreaker if there was a discrepancy (LH). Full text screening was individually conducted by two reviewers (LM, MO), guided by the inclusion and exclusion criteria.

Eligibility criteria

The PICO (population, intervention, comparison, outcome) framework was used to guide eligibility criteria.[20] Studies of participants who were non-pregnant and asymptomatic for syphilis were included. Screening facilities included sexual health clinics, general practice (GP) and hospitals.

Studies were required to evaluate a clinic- or hospital-based intervention aimed at increasing one or more of the following syphilis-based outcomes: screening rate (proportion of individuals screened); re-screening rate (proportion of individuals who were screening again); or detection rate (proportion of individuals diagnosed with syphilis). A control group or period was required, to ensure comparison to pre-intervention clinical practice. Secondary outcomes, if available, included feasibility (staff burden, resource use, cost analysis) and possible harms of the intervention.

Studies were excluded if they did not include a comparator group or period; reported screening rates in the absence of an intervention; involved STI screening or promotional activities outside of healthcare settings; or were designed to compare sensitivities of different laboratory methods for screening.

Quantitative studies, including randomised controlled trials (RCTs), quasi-experimental, cohort and case-control studies, were eligible for inclusion. Qualitative only studies were excluded from this review as were mathematical modelling studies, review articles, commentaries, editorials, guidelines, and case reports.

Data analysis

Two reviewers (LM, MO) individually extracted data from included articles into a pre-defined template. When completed, data was compared to identify variations in the collected information. Data included study design, study setting, target population, description of the intervention, control groups or periods, outcomes and statistical methods used.

For each study, crude odds ratios (OR), 95% confidence intervals (95% CI) and *P*-values were calculated based on

Table 1. Terms used in the search strategy.

Syphilis OR 'treponema pallidum' OR 'treponema pallidum infection' OR lues OR 'syphilitic disorder' OR 'latent syphilis' OR 'latent state syphilis' OR treponematosis OR 'great pox' OR 'txid160'
AND
Screen* OR 'mass screening' OR 'health screening' OR 'early diagnosis' OR 'early detection' OR 'secondary prevention'
AND
Hospital* OR clinic* OR 'health services' OR 'health service' OR 'health facilities' OR 'health facility' OR 'health care services' OR 'healthcare services' OR 'health care service' OR 'healthcare service' OR 'health care facilities' OR 'healthcare facilities' OR 'health care facility' OR 'healthcare facility'

the data available in the published article. Where multiple studies were considered to be clinically heterogenous with the same outcome, a pooled estimate of the odds ratio was generated. STATA ver. 18,[21] was used to conduct a meta-analysis using a random effects model.

Quality assessment

Risk of bias was assessed using the JBI critical appraisal tools.[22] Four instruments were used: checklist for RCTs, checklist for quasi-experimental studies, checklist for cohort studies and checklist for analytical cross-sectional studies. Non-randomised pre-post studies were assessed using the checklist for quasi-experimental studies. These instruments allow for calculation of a bias score ranging from 0 to 100% based on 8–13 questions, which varied by study design. A score of 71% was classified as low risk of bias, 51–70% was moderate risk and 50% was high risk.[23] Two reviewers (LM, MO) individually assessed for bias and in instances of disagreement, a third reviewer acted as a tiebreaker (LH).

Results

Search results

After removing duplicates, 5075 articles were identified, with 24 meeting inclusion criteria (Fig. 1).[24–47] Studies and intervention results are summarised in Table 2. Included studies were conducted in Australia (n = 9), the United States (n = 7), the United Kingdom (n = 6), Canada (n = 1) and China (n = 1). All studies, except one randomised control trial,[31] used an observational design with a pre-intervention comparator period, concurrent control group or both.

Quality assessment

A majority (n = 14) of the 17 cohort studies exhibited a moderate potential for bias. Since these studies were not randomised, they were unable to minimise allocation or selection bias, so did not adjust for potential confounders in analysis. This resulted in systematic differences in baseline characteristics and risk profiles between the intervention and control groups. Similar limitations were observed in the cross-sectional study[43] and two pre-post studies.[27,28] The three cohort studies[26,29,42] with low bias risk all identified and attempted to overcome potential biases through meticulous study design or by employing multivariate analysis.

Three cohort studies[27,28,47] and the cross-sectional study[43] grouped all types of STIs together in their results. For the purpose of this review, it was assumed that the individuals were therefore screened for all STIs, including syphilis. However, due to uncertainty in outcome measurements these studies were deemed moderate risk of bias.

The RCT[31] and three remaining quasi-experimental studies[24,25,30] were of low risk of bias. None of the included studies had high potential for bias.

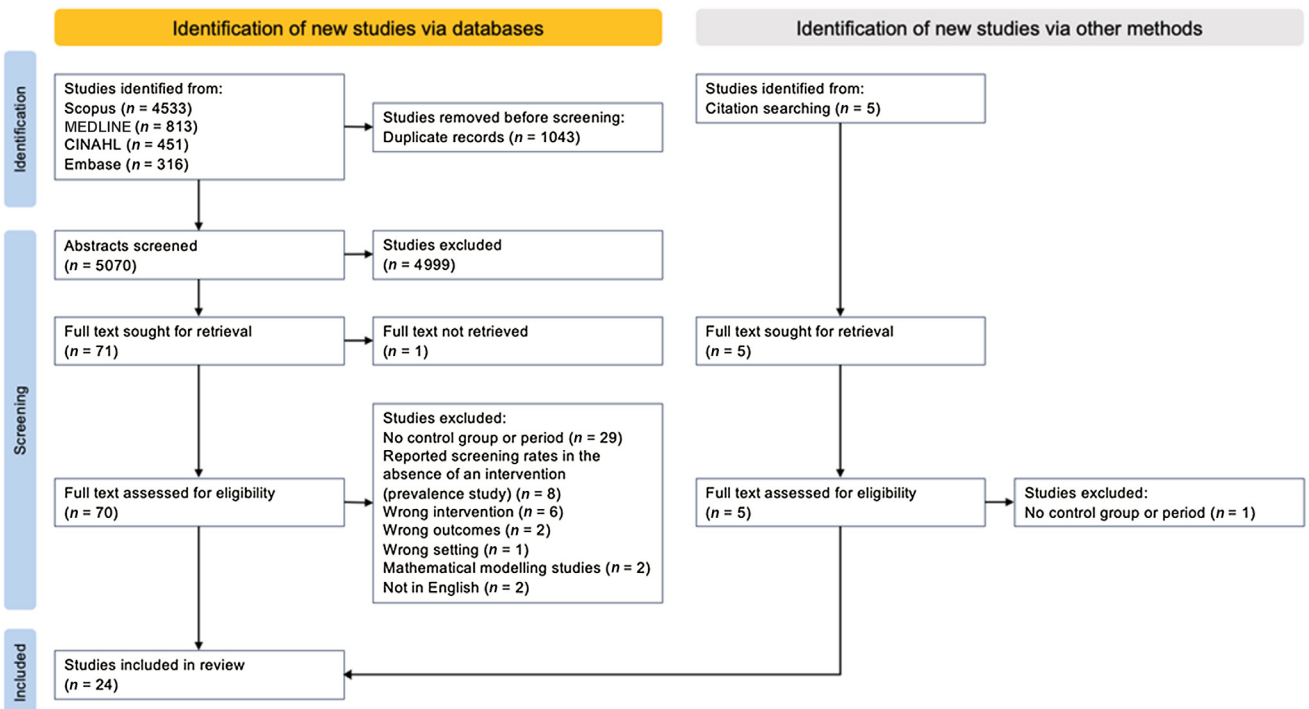

Fig. 1. Flowchart for systematic inclusion of studies according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[18]

Table 2. Studies of clinic- or hospital-based interventions aimed at increasing syphilis screening, re-screening or detection rates.

Study	Study design	Setting	Study population	Intervention	Time after intervention	Control	Outcome(s)	Control group		Intervention group		Statistical findings calculated by reviewers		Risk of bias
								n/N	%	*n/N*	%	Crude OR (95% CI)	*P*-value	
Reminder systems														
Bissessor *et al.*[24]	Pre-post	STI clinic, Australia	MSM	Pre-appointment computer-assisted self-interview risk assessment. System-generated clinician alert to test high-risk MSM (>10 sexual partners in previous 12 months) for syphilis.	12 months.	Before intervention: 12 months.	Screening rate (any risk)	2787/3902	71.42	2949/3893	75.75	1.25 (1.13–1.38)	<0.001	Low
							Screening rate (high-risk)	1559/2017	77.29	1282/1445	88.72	2.31 (1.9–2.8)	<0.001	
							Detection rate of early syphilis in high-risk MSM	31/2017	1.54	58/1445	4.01	2.67 (1.72–4.17)	<0.001	
							Proportion of early syphilis diagnoses that were asymptomatic	5/31	16.13	31/58	53.45	5.97 (2.01–17.71)	0.0013	
Scarborough *et al.*[25]	Quasi-experimental	STI clinic, US	HIV-positive MSM	Self-completed pre-appointment risk assessment provided to doctor during consultation.	3 months.	Before intervention: 3 months.	Screening rate	213/437	48.74	211/364	57.97	1.45 (1.1–1.92)	0.0093	Low
Bourne *et al.*[26]	Cohort	STI clinic, Australia	HIV-negative MSM	HIV/STI screening SMS reminder: 3–6 months post-appointment.	9 months.	(1) Before intervention: 9 months.	HIV/STI re-screening rate within 9 months	544/1753	31.03	460/714	64.43	3.1 (2.5–3.8)[A]	<0.001	Low
						(2) Concurrent control.		322/1084	29.70	460/714	64.43	4.4 (3.5–5.5)[A]	<0.001	
						(2) Concurrent control.	Detection rate	8/1084	0.74	36/714	5.04	7.14 (3.3–15.46)	<0.001	
Burton *et al.*[27]	Pre-post	STI clinic, UK	Patients at risk for STIs (current acute STI, attending for emergency contraception, sex workers, MSM and those in the window period for HIV)	STI screening SMS reminder: 2–12 weeks post-appointment.	8 months.	Before intervention: 8 months. Risk factors matched.	Re-attendance rate for STI screening within 4 months	92/266	34.59	90/273	32.97	0.93 (0.65–1.33)	0.691	Moderate

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Table 2. (*Continued*).

Study	Study design	Setting	Study population	Intervention	Time after intervention	Control	Outcome(s)	Control group		Intervention group		Statistical findings calculated by reviewers		Risk of bias
								n/N	%	*n/N*	%	Crude OR (95% CI)	*P*-value	
Nyatsanza *et al.*[28]	Pre-post			Same as above (Burton *et al.*[24]). More personalised text message including patient's first name and additional clinic contact details.	8 months.	(1) Before both interventions: 8 months. Risk factors matched.	Re-attendance rate for STI screening within 4 months	92/266	34.59	149/266	56.02	2.41 (1.7–3.42)	<0.001	Moderate
						(2) Before intervention: 8 months. Patients who received generic text message.	Re-attendance rate for STI screening within 4 months	90/273	32.97	149/266	56.02	2.59 (1.83–3.67)	<0.001	
Zou *et al.*[29]	Cohort	STI clinic, Australia	MSM	SMS reminders 3-, 6- or 12-monthly, depending on patient preference.	19 months.	Concurrent control.	Re-attendance rate for STI screening within 12 months	978/1382	70.77	3-monthly: 587/656	89.48	3.51 (2.67–4.63)	<0.001	Low
										6-monthly: 264/301	87.71	2.95 (2.05–4.24)	<0.001	
										Any: 885/997	88.77	3.26 (2.6–4.1)	<0.001	
							Median number of subsequent clinic visits (range)	1 (1–16)	n/a	3-monthly: 3 (1–36)	n/a	n/a	<0.001[B]	
										6-monthly: 2 (1–14)	n/a	n/a	0.001[B]	
										Any: 3 (1–36)	n/a	n/a	<0.001[B]	
							Re-screening rate for syphilis	384/978	39.26	3-monthly: 393/587	66.95	3.13 (2.53–3.88)	<0.001	
										6-monthly: 137/264	51.89	1.67 (1.27–2.19)	<0.001	
										Any: 545/885	61.58	2.48 (2.06–2.99)	<0.001	
							Detection rate of early syphilis at subsequent visits	15/978	1.53	3-monthly: 19/587	3.24	2.15 (1.08–4.26)	0.0287	
										6-monthly: 5/264	1.89	1.24 (0.45–3.44)	0.6805	
										Any: 25/885	2.82	1.87 (0.98–3.56)	0.0586	
							Detection rate of early latent syphilis at subsequent visits	4/978	0.40	3-monthly: 10/587	1.70	4.22 (1.32–13.52)	0.0153	
										6-monthly: 2/264	0.76	1.86 (0.34–10.2)	0.4755	
										Any: 12/885	1.36	3.35 (1.08–10.42)	0.037	

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Table 2. (*Continued*).

Study	Study design	Setting	Study population	Intervention	Time after intervention	Control	Outcome(s)	Control group		Intervention group		Statistical findings calculated by reviewers		Risk of bias
								n/N	%	*n/N*	%	Crude OR (95% CI)	*P*-value	
Change in clinic screening guidelines														
Bissessor *et al.*[30]	Pre-post	STI clinic, Australia	HIV-positive MSM	Syphilis serology included with routine HIV monitoring: 3–6-monthly.	18 months.	Before intervention: 18 months.	Median number of syphilis tests per man per year	1	n/a	2	n/a	n/a	n/a	Low
							Detection rate of early syphilis	14/444	3.15	48/587	8.18	2.74 (1.49–5.03)	0.0012	
							Proportion of early syphilis diagnoses that were asymptomatic	3/14	21.43	41/48	85.42	21.48 (4.76–96.96)	<0.001	
Burchell *et al.*[31]	Randomised control trial	Four HIV clinics, Canada	HIV-positive males	Syphilis serology included with routine HIV monitoring: 3–6-monthly Randomised stepwise introduction at different clinics.	6 months. Data given for step 5 when all clinics had the intervention.	Before intervention: 6 months. Data given for step 1 when all clinics were control.	Mean syphilis tests per man per year	0.53	n/a	2.02	n/a	2.03 (1.85–2.22)[C]		Low
							Detection rate of early syphilis		0.90		3.20	1.25 (0.71–2.20)[C]	>0.05[B]	
							Proportion screened at least once per year		36.40		79.40	3.73 (3.21–4.32)[C]		
Callander *et al.*[32]	Cohort	GP clinic, Australia	HIV-positive MSM	Syphilis serology included with routine HIV monitoring: 3–6-monthly Implemented in late 2006.	1 year. Data given for 2007, remains consistent over next 3 years.	Before intervention: 1 year. Data given for 2005.	Mean syphilis tests per man per year	1.14	n/a	2.32	n/a	n/a	<0.001[B]	Moderate
							Proportion screened ≥3 times per year	87/877	9.92	281/691	40.67	6.22 (4.76–8.14)	<0.001	
							Proportion with no syphilis tests per year	240/877	27.37	20/691	2.89	0.079 (0.05–0.13)	<0.001	
							Proportion of HIV viral load tests accompanied by syphilis serology		50.00		88.00		<0.001[B]	

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Table 2. (*Continued*).

Study	Study design	Setting	Study population	Intervention	Time after intervention	Control	Outcome(s)	Control group		Intervention group		Statistical findings calculated by reviewers		Risk of bias
								n/N	%	*n/N*	%	Crude OR (95% CI)	*P*-value	
Cheeks *et al.*[33]	Cohort	STI clinic, US	HIV-positive MSM	Syphilis serology included with routine HIV monitoring: 3–6-monthly	15 months.	Before intervention: 15 months.	Detection rate of early syphilis	4/58	6.90	29/187	15.51	2.48 (0.83–7.37)	0.1028	Moderate
Winston *et al.*[34]	Cohort	Hospital out-patient HIV clinic, UK	HIV-positive individuals	Syphilis serology included with routine HIV monitoring: 3–6-monthly	12 months.	Before intervention: 12 months.	Proportion with CD4 count and syphilis serology performed		3.00	2266/2670	84.87	n/a	n/a	Moderate
Cohen *et al.*[35]	Cohort				12 months (2nd year of intervention).	Before intervention: 12 months.	Proportion with CD4 count and syphilis serology performed		3.00	2389/2655	89.98	n/a	n/a	Moderate
					12 months (2nd year of intervention).	1st year of intervention: 12 months (Winston *et al.*[31]).	Proportion with CD4 count and syphilis serology performed	2266/2670	84.87	2389/2655	89.98	1.6 (1.36–1.89)	<0.001	
							Detection rate of asymptomatic syphilis	26/2670	0.97	40/2655	1.51	1.55 (0.95–2.56)	0.0813	
Trubiano *et al.*[36]	Cohort	Hospital out-patient HIV clinic, Australia	HIV-positive individuals	Syphilis serology included with routine HIV monitoring: 3–6-monthly	4 months.	Before intervention. 4 months.	Proportion with HIV viral load and syphilis serology performed	136/574	23.69	317/574	55.23	3.97 (3.08–5.12)	<0.001	Moderate
							Proportion of HIV viral load tests accompanied by syphilis serology	175/762	22.97	417/743	56.12	4.29 (3.43–5.36)	<0.001	
							Detection rate of syphilis (any stage)	4/574	0.70	18/574	3.14	4.61 (1.55–13.72)	0.006	

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Table 2. (*Continued*).

Study	Study design	Setting	Study population	Intervention	Time after intervention	Control	Outcome(s)	Control group		Intervention group		Statistical findings calculated by reviewers		Risk of bias
								n/N	%	*n/N*	%	Crude OR (95% CI)	*P*-value	
Guy *et al.*[37]	Cohort	Three GPs, two STI clinics, two hospital outpatient HIV clinics, Australia	HIV-positive MSM	*Opt-out*: Four clinics where syphilis serology included with routine HIV monitoring: 3–6-monthly *Opt-in*: One clinic where clinicians ordered syphilis serology when patients agree (perceived self-risk). *Risk-based*: Two clinics where clinicians offer syphilis serology only to patients they deemed high-risk. *Timing*: three clinics introduced opt-out interventions in April 2006, September 2006 and January 2008. The rest had the same policy throughout study period.	1 year. Data given for 2007, remains consistent over next 3 years.	Before intervention: 1 year. Data given for 2006.	Mean number of syphilis tests per man per year	1.3	n/a	2.2	n/a	n/a	<0.01[B]	Moderate
							Proportion screened ≥3 times per year		15		36.00		<0.01[B]	
							Proportion of HIV viral load tests accompanied by syphilis serology		37		63.00		<0.01[B]	
					Opt-out interventions: 1 year. Data given for 2010.	Concurrent control groups (opt-in and risk-based clinics). Data given for 2010.	Proportion screened ≥3 times per year in 2010		Opt-in: 39		Opt-out: 48		0.12[B]	
									Risk-based: 8.4				<0.01[B]	
							Proportion screened ≥3 times per year in 2010		Opt-in: 74		Opt-out: 87		<0.01[B]	
									Risk-based: 22				<0.01[B]	
Rieg *et al.*[38]	Cohort	Two HIV clinics, US	HIV-positive MSM	Patients enrolled into the study to have syphilis screening 6-monthly (total of three visits).	18 months. Data given for 0, 6 and 12 months.	Concurrent control (same population). Data given for 0 and 12 months.	Proportion of syphilis infections diagnosed	11/16	68.75	16/16	100.00	8.5 (0.9–80.03)[D]	0.0614	Moderate
Tang *et al.*[39]	Cohort	Two STI clinics and one GP, US	HIV-negative MSM (and transgender women) on PrEP	Patients were enrolled to be tested for syphilis 3-monthly (total of four visits). Offered free PrEP as incentive.	16 months. Data given for 3, 6, 9 and 12 months.	Concurrent control (same population). Data given for 6 and 12 months.	Proportion of syphilis infections diagnosed	43/54	79.63	54/54	100.00	15 (1.88–119.85)[D]	0.0106	Moderate

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Table 2. (*Continued*).

Study	Study design	Setting	Study population	Intervention	Time after intervention	Control	Outcome(s)	Control group		Intervention group		Statistical findings calculated by reviewers		Risk of bias
								n/N	%	*n/N*	%	Crude OR (95% CI)	*P*-value	
Hospital-based packaged testing														
Lipps *et al.*[40]	Cohort	Emergency department, US	ED patients who required STI testing	Educational materials provided to emergency physicians, automated daily reports with results of all syphilis tests and a dedicated STI 'order set' that emergency physicians could use to order all STI-related tests when diagnosis of one/more was suspected.	12 months.	Before intervention: 12 months	Average number of syphilis tests ordered per month in ED	4	n/a	108	n/a	IRR 30.7 (26.8–35.2)[E]	<0.001[B]	Moderate
							Average number of positive syphilis tests per month in ED	0.63	n/a	4.4	n/a	IRR 7.02 (4.66–10.61)[E]	<0.001[B]	
Marks *et al.*[41]	Cohort	Three hospitals, US	Individuals hospitalised with serious injection-related infections	Checklist of recommendations to add to patient's chart for screening patients with invasive infections secondary to injection-related infections.	13 months.	Before intervention: 6 months.	Screening rate	48/123	39	163/271	60.15	2.36 (1.52–3.65)	<0.001	Moderate
Enhancing existing health infrastructure														
Snow *et al.*[42]	Cohort	GP clinic, Australia	MSM	Introduction of a sexual health nurse for STI screening.	1 year.	(1) Before intervention: 1 year.	Screening rate	837/1385	60.43	951/1460	65.14	1.22 (1.05–1.42)	0.0095	Low
						(2) Concurrent control. A different GP practice.	Screening rate	2260/4728	47.80	951/1460	65.14	2.04 (1.8–2.3)	<0.001	
Hamlyn *et al.*[43]	Cross-sectional	STI clinic, UK	HIV-positive individuals	Introduction of nurse-led clinic for HIV-positive patients within a larger STI clinic.	Audit of 100 consecutive patients. Retrospective data from 18 months (from clinic opening).	Before intervention: audit of 100 consecutive patients. Time period of retrospective data collection not stated.	Proportion of individuals undergoing STI screening at HIV diagnosis	39/100	39.00	52/100	52.00	1.69 (0.97–2.97)	0.0657	Moderate
							STI screening rate within 12 months preceding the audit	26/100	26.00	46/100	46.00	2.42 (1.34–4.4)	0.0035	

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Table 2. (*Continued*).

Study	Study design	Setting	Study population	Intervention	Time after intervention	Control	Outcome(s)	Control group		Intervention group		Statistical findings calculated by reviewers		Risk of bias
								n/N	%	*n/N*	%	Crude OR (95% CI)	*P*-value	
Kelly *et al.*[44]	Cohort	Twelve GP clinics, UK	Heterosexual patients (asymptomatic, >18 year olds) who accessed this service	Training program for GPs and nurses to deliver sexual health care. Previously, done by genitourinary medicine clinics.	Data given for May (start) and October (6 months in).	Before intervention: 1 month. Data given for January.	Screening rate for all four STIs (gonorrhoea, chlamydia, HIV, syphilis)	January: 0/131	0	May: 21/121	May: 17.36	28.75 (3.81–216.9)[D]	0.0011	Moderate
										October: 48/144	October: 33.33	66.68 (9.05–491.32)	<0.001	
Zhang *et al.*[45]	Cohort	Multiple clinics or hospitals, China	Individuals who were drugs users or at risk for syphilis for other reasons (determined by healthcare provider)	Monetary incentive for healthcare providers to screen and treat syphilis. Introduced in 2011.	1 year. Data given for 2015.	Before intervention: 1 year. Data given for 2010.	Screening rate at 'voluntary counselling and testing centres'	32,877/71,162	46.20	68,012/69,259	98.20	63.51 (59.94–67.3)	<0.001	Moderate
							Screening rate at 'methadone maintenance treatment clinics'	9836/18,419	53.40	17,921/19,737	90.80	8.61 (8.14–9.1)	<0.001	
Utilising other screening programs to promote syphilis screening														
Barbee *et al.*[46]	Cohort	STI clinic, US	MSM	STI self-testing program for chlamydia and gonorrhoea. Then, patient directed to laboratory for syphilis serology, ordered through standing order forms.	1 year.	Before intervention: 1 year.	Screening rate	962/1520	63.29	976/1510	64.64	1.06 (0.91–1.23)	0.4403	Moderate
Botes *et al.*[47]	Cohort	STI clinic, Australia	HIV-positive MSM	Anal cytology screening program for anal cancer. Also offering STI screening.	3 months. Includes those who opt-out.	Before intervention: 3 months.	Screening rate of STIs	67/328	20.43	123/353	34.84	2.08 (1.47–2.95)	<0.001	Moderate
							Number syphilis diagnoses	0	n/a	4	n/a	n/a	n/a	

[A]Calculated by authors, after adjusting for differences in baseline characteristics.
[B]Calculated by authors, data for calculation not available in the published article.
[C]Calculated by authors, after adjusting for time.
[D]1 added to all cells.
[E]Incident rate ratio calculated by authors.

Interventions and outcomes

The primary outcome of 11 studies was screening rate,[22,26,34,37,41–47] and two others emphasised detection rate.[27,30] Other included studies reported both screening and detection rates, ($n = 4$),[24,31,35,36] re-screening rates ($n = 2$)[26,29] and re-attendance rate ($n = 2$).[27,28] Studies measuring re-attendance rate were included because their goal was for patients to re-attend specifically for STI screening, including syphilis.

Two cohort studies[38,39] reported detection rate at different monthly intervals, with participants serving as their own controls. One cohort study[34] reported average number of syphilis tests conducted per month in an emergency department. As this outcome is comparable to screening rate, the study was included.

The studies covered various interventions to increase syphilis screening, such as reminder systems for clinicians ($n = 2$)[24,25] and patients ($n = 4$),[26–29] changes in clinic guidelines for combined HIV and syphilis screening ($n = 8$)[30–37] or increased screening frequency ($n = 2$),[38,39] syphilis serology inclusion in hospital-based packaged testing ($n = 2$),[40,41] improving health infrastructure ($n = 4$),[42–45] and utilising other screening programs for syphilis screening promotion ($n = 2$).[46,47]

Reminder systems

The implementation of self-reported risk assessments for MSM was conducted by Bissessor *et al.*[24] with a computer-assisted self-interview and by Scarborough *et al.*[25] with paper forms, to be completed prior to their appointment at STI clinics. Clinicians were notified of high-risk MSM either through a computer alert (Bissessor *et al.*) or by reading the risk assessment form (Scarborough *et al.*). Both interventions increased the screening rate, compared to a pre-intervention control period (Bissessor: 2787/3902 (71.42%) vs 2949/3893 (75.75%), OR 1.25 [95% CI 1.13–1.38], $P < 0.001$) (Scarborough: 213/437 (48.74%) vs 211/364 (57.97%), OR 1.45 [95% CI 1.1–1.92], $P = 0.0093$). Compared to the control period, Bissessor *et al.* also demonstrated an increased proportion of MSM diagnosed with early syphilis (31/2017 (1.54%) vs 58/1445 (4.01%), OR 2.67 [95% CI 1.72–4.17], $P < 0.001$) of which a higher proportion were asymptomatic (5/31 (16.13%) vs 31/58 (53.45%), OR 5.97 [95% CI 2.01–17.71], $P = 0.0013$).

Four studies introduced SMS reminders for patients to return to the clinic for STI re-screening at varying time intervals ranging from 2 weeks to 12 months.[26–29] Burton *et al.*[27] and Nyatsanza *et al.*[28] describe this intervention at the same clinic over consecutive years. Only Nyatsanza *et al.* reported an increase in the proportion of patients re-attending the clinic compared to the pre-intervention period (OR 2.41 [95% CI 1.7–3.42], $P < 0.001$). The distinguishing factor between these studies was that Nyatsanza *et al.* used personalised text messages, whereas Burton *et al.* employed generic texts.

Bourne *et al.*[26] demonstrated an increased re-screening rate of patients for STIs, including syphilis, compared to both a pre-intervention (544/1753 (31.03%) vs 460/714 (64.43%), OR 3.1 [95% CI 2.5–3.8], $P < 0.001$) and concurrent control group (322/1084 (29.7%) vs 460/714 (64.43%), OR 4.4 [95% CI 3.5–5.5], $P < 0.001$). Detection rate also increased compared to the concurrent control group (8/1084 (0.74%) vs 36/714 (5.04%), OR 7.14 [95% CI 3.3–15.46], $P < 0.001$).

Zou *et al.*[29] showed an increased re-screening rate among men receiving 3- and 6-monthly reminders compared to men in the concurrent control group, with the highest re-screening rate (393/587 (66.95%)) in those receiving 3-monthly reminders. Compared to men in the concurrent control group, men receiving the 3-monthly reminders had a significantly higher detection rate of early syphilis (15/978 (1.53%) vs 19/587 (3.24%), OR 2.15 [95% CI 1.08–4.26], $P = 0.0287$).

Change in clinic screening guidelines

The inclusion of syphilis serology with routine blood tests performed for HIV-positive patient monitoring (3–6-monthly) was demonstrated by multiple studies to varying effects. The mean or median number of syphilis tests per individual per year increased in all studies that measured this outcome.[30–32,37]

Three studies assessed the effectiveness of this intervention by measuring the proportion of HIV viral load tests that were accompanied by syphilis serology. All of these favoured the intervention, demonstrating an increase in this proportion during the post-intervention period compared to the pre-intervention period.[32,36,37] Guy *et al.*[37] implemented this intervention at seven clinics using different strategies: four used an opt-out strategy where syphilis serology was automatically added to laboratory requests, one clinic relied on clinicians to order syphilis serology (opt-in) and at two clinics, clinicians offered syphilis serology only to patients they deemed high-risk (risk-based). In the final year of the study period, the proportion of HIV viral load tests accompanied by syphilis serology was highest in clinics with opt-out strategies (87%) compared with opt-in (74%) and risk-based (22%). Of note, all other studies with this intervention used an opt-out method, except for Trubiano *et al.*[36] which employed an opt-in method.

Screening rate was determined as the proportion of individuals who underwent both a HIV viral load or CD4 test and syphilis serology during the study period. Trubiano *et al.*[36] demonstrated that compared to the pre-intervention period, there was an increased proportion of individuals having both tests (136/574 (23.69%) vs 317/574 (55.23%), OR 3.97 [95% CI 3.08–5.12], $P < 0.001$). Winston *et al.*[34] showed a more substantial difference (3% vs 2266/2670 (84.87%), all raw numbers not provided). Compared to Winston *et al.*, Cohen *et al.*,[35] which reports the second year of the same intervention shows a further increase in this value (2266/2670 (84.87%) vs 2389/2655 (89.98%), OR 1.6

[95% CI 1.36–1.89], $P < 0.001$), demonstrating continued success of the intervention over time.

Burchell *et al.*[31] conducted a RCT over 3 years implementing linked syphilis screening with HIV monitoring and reported an increase in the proportion of men screened at least once per year (36.4% vs 79.4%, OR 3.73 [95% CI 3.21–4.32]) compared to a pre-intervention control period. Results regarding the detection rate of early syphilis compared to the pre-intervention period were inconclusive (0.9% vs 3.2%, OR 1.25 [95% CI 0.71–2.20]). The other studies that reported early syphilis detection rate were non-randomised studies and could be impacted by bias. Bissessor *et al.*[30] showed a significant increase in the detection of early syphilis (14/444 (3.15%) vs 48/587 (8.18%), OR 2.74 [95% CI 1.49–5.03], $P = 0.0012$), whereas Cheeks *et al.*'s[33] results favoured the intervention but were inconclusive (4/58 (6.9%) vs 29/187 (15.51%), OR 2.48 [95% CI 0.83–7.37], $P = 0.1028$). The pooled OR for this outcome was 1.722 [95% CI 0.721–2.723] and had low heterogeneity ($I^2 = 24.8\%$, $P = 0.264$) (Fig. 2).

Cohort studies by Rieg *et al.*[38] and Tang *et al.*[39] both enrolled MSM for more frequent syphilis screening. Rieg *et al.* compared 12-monthly screening (serving as the control) to 6-monthly screening, revealing that 18 individuals with early syphilis infections at 6 months would have potentially remained infectious for an additional 6 months. Tang *et al.* compared 6-monthly to 3-monthly screening and showed that diagnosis of 11 early syphilis infections would have been delayed. Only Tang *et al.* showed significant increase in the proportion of syphilis infections diagnosed at 6-monthly versus 3-monthly intervals (43/54 vs 54/54, OR 15 [95% CI 1.88–119.85], $P = 0.0106$). Both studies had a small sample size.

Hospital-based packaged screening

Lipps *et al.*[40] introduced a dedicated STI order set which included syphilis serology for emergency physicians for use in patients being tested for other STIs, resulting in an increase in the average number of syphilis tests ordered per month (4 vs 108, IRR 30.7 [95% CI 26.8–35.2], $P < 0.001$) and average number of positive syphilis tests per month (0.63 vs 4.4, IRR 7.02 [95% CI 4.66–10.61], $P < 0.001$) compared to a pre-intervention period.

Marks *et al.*[41] targeted individuals hospitalised with serious injection-related infections, implementing a standardised checklist of screening recommendations that could be inserted into a patient's electronic medical record by their treating infectious diseases physician. This resulted in an increase in syphilis screening rate (48/123 (39%) vs 163/271 (60.15%), OR 2.36 [95% CI 1.52–3.65], $P < 0.001$).

Enhancing existing health infrastructure

The studies by Snow *et al.*[42] and Hamlyn *et al.*[43] both implemented nurse-led STI clinics for at-risk populations (MSM and HIV-positive individuals, respectively) in different settings (GP practice and STI clinic, respectively). Snow *et al.* demonstrated a rise in syphilis screening rates compared to both a pre-intervention period (837/1385 (60.43%) vs 951/1460 (65.14%), OR 1.22 [95% CI 1.05–1.42], $P = 0.0095$) and a similar GP practice without a sexual health nurse (2260/4728 (47.8%) vs 951/1460 (65.14%), OR 2.04 [95% CI 1.8–2.3], $P < 0.001$). Hamlyn *et al.*'s audit reported an increase in STI screening rate (26/100 (26%) vs 46/100 (46%), OR 2.42 [95% CI 1.34–4.4], $P = 0.0035$).

Kelly *et al.*[44] trained general practitioners and practice nurses in Ireland to screen for STIs, traditionally done by genitourinary clinics. Monthly asymptomatic heterosexual patient screenings for four STIs (gonorrhoea, chlamydia, HIV, syphilis) increased (0/131 vs 21/121, OR 28.75 [95% CI 3.81–216.9], $P = 0.0011$), with sustained increase over the 6-month study period.

Zhang *et al.*[45] introduced a pay-for-performance scheme to incentivise healthcare providers to screen and treat syphilis. Compared to a pre-intervention period, screening rates increased at testing centres (32,877/71,162 (46.2%) vs 68,012/69,259 (98.2%), OR 63.51 [95% CI 59.94–67.3], $P < 0.001$) and methadone maintenance treatment clinics (9836/18,419 (53.4%) vs 17,921/19,737 (90.8%), OR 8.61 [95% CI 8.14–9.1], $P < 0.001$).

Utilising other screening programs to promote syphilis screening

Barbee *et al.*[46] introduced a self-testing program for chlamydia and gonorrhoea for MSM, and Botes *et al.*[47] introduced an anal cytology screening program for anal cancer for HIV-positive MSM. While not the primary focus

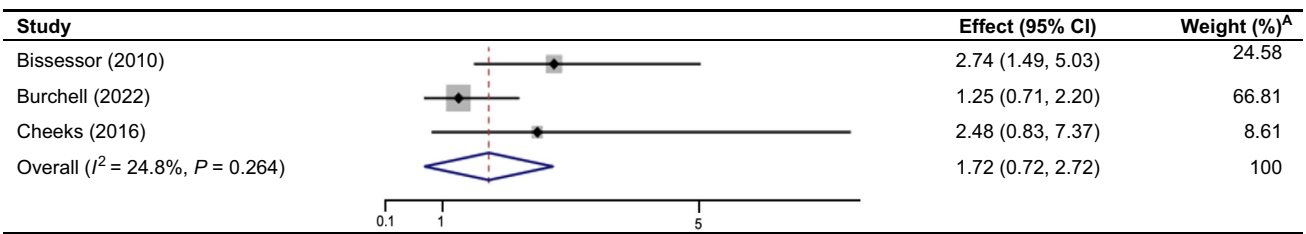

Fig. 2. Forrest plot of odds ratios of early syphilis detection rate in studies which combine syphilis screening with regular HIV monitoring.

of the study, both offered the participating clients to be screened for syphilis using a blood test. There was no change in syphilis screening rate in Barbee *et al.* (962/1520 (63.39%) vs 976/1510 (64.64%), OR 1.06 [95% CI 0.91–1.23], $P = 0.4403$), however Botes *et al.* showed an increased syphilis screening rate after introduction of their anal cytology screening program (67/328 (20.43%) vs 123/353 (34.84%), OR 2.08 [95% CI 1.47–2.95], $P < 0.001$).

Secondary outcomes

Few studies reported the feasibility of their interventions. Scarborough *et al.*[25] found that a paper-based risk assessment was low-cost but time-consuming for clinic staff, leading to discontinuation of this intervention to adopt an electronic sexual history instrument such as Bissessor *et al.*[24] SMS reminders were low-cost, automatic and required minimal labour,[26,29] although no formal cost-benefit analysis was reported.

Adding syphilis serology to HIV monitoring was practical using automatic opt-out methods, avoiding additional staff time or handling.[30,35] Trubiano *et al.*[36] faced challenges with their opt-in strategy, struggling to motivate clinicians to screen all MSM attending the clinic for routine review. Overall, this strategy was reported as low cost.[30,32] Rieg *et al.*[38] supported this with a cost analysis, demonstrating the annual costs of screening every 6 versus 12 months did not differ substantially (USD10,640 vs USD10,681 per asymptomatic STI detected).

The use of packaged testing in hospital was acceptable to medical providers,[40,41] simple and inexpensive.[41]

Kelly *et al.*[44] reported that providing STI screening in primary care is approximately 1.5-times less expensive than if the same case mix of patients had been seen in secondary care services. The pay-for-performance scheme described by Zhang *et al.*[45] had a mean cost of USD39,000 annually.

No other studies reported feasibility or costs. No studies reported harms of screening.

Discussion

The studies included in this review provide evidence supporting a diverse array of interventions aimed at increasing syphilis screening, with most focusing on tailored approaches for at-risk populations. Technology played a significant role in the reviewed interventions, including clinician alerts, SMS reminders and packaged testing with HIV monitoring or in hospital with other investigations. Computer-assisted self-interviews proved useful for collection of sexual histories and consenting for SMS reminders.

Electronic clinician alerts were deemed more feasible than paper-based methods.[24,25] These alerts could also be applied in hospital settings, as shown in a study outside the scope of this review that alerted emergency physicians to screen for syphilis in patients living in high-prevalence areas or with a history of drug use.[48] SMS reminders for re-screening are known to be accepted in a sexual health context,[49,50] with personalised messages more effective than generic ones.[27,28] Once established, these technology-based approaches required minimal staffing and ongoing costs, making them efficient and sustainable solutions for increasing syphilis screening rates.

Incorporating syphilis serology with regular HIV monitoring proved an effective strategy to increase the number of syphilis tests per year and screening rate among HIV-positive individuals. An opt-out method is particularly successful.[37]

The degree of benefit of linked screening with HIV monitoring in increasing detection rate may be influenced by changes in syphilis incidence and study location. Despite inconclusive meta-analysis results with a pooled OR of 1.722 (0.721–2.723), the clinical significance of the intervention remains notable. Cheeks *et al.*[33] found 3–6-monthly screening identified 27 additional infections that would have otherwise remained undetected until annual syphilis screening. Identifying syphilis infections in the early phase allows for more timely treatment, reducing the period of infectiousness and preventing potential sequelae.

Syphilis screening guidelines suggest 3-monthly screening for MSM,[10,11] including those who are HIV-positive,[51] which results in four screening episodes annually. Australian HIV monitoring guidelines advise HIV-positive individuals undergo viral load and CD4 count tests 3–6-monthly, potentially extending to annually if virally suppressed.[52] Although coupling syphilis screening with HIV monitoring for MSM is convenient and cost effective, it is unlikely to achieve the recommended 3-monthly syphilis screening frequency as per guidelines. This is supported by the included studies, which reveal the mean or median number of screening episodes annually for HIV-positive MSM ranging between 2 and 2.32.[30,32,37] Therefore, multiple methods of increasing syphilis screening may be required, such as pairing this strategy with reminder systems, incentives or employing a dedicated sexual health nurse. Zou *et al.*[29] reports that 3-monthly SMS reminders for MSM correspond with a median of three screening episodes annually, although still falling short of guideline recommendations.

HIV-negative MSM may also require further targeted interventions to achieve 3-monthly screening. A current method used in Australia involves screening this population for syphilis on provision of 3-monthly HIV pre-exposure prophylaxis (PrEP) prescriptions.[53] This has proven effective, as a 2017 Australian study reported 99% of HIV-negative individuals were screened for syphilis 3-monthly when provided with PrEP.[54] A systematic review revealed that globally, the majority (70%) of PrEP programs offer 3-monthly syphilis screening, with lower availability of testing observed primarily in low-income countries.[55]

Increased syphilis surveillance in hospitals is noteworthy, given their non-traditional role in public health initiatives. This approach becomes especially important for at-risk populations (illicit drug users, cultural subpopulations) who

may not access regular healthcare services elsewhere. Recent cross-sectional studies have detailed the implementation of routine syphilis screening in emergency departments, leading to new syphilis diagnoses.[56–58]

Methods to encourage clinicians to screen for syphilis may be beneficial, such as introduction of a sexual health nurse,[42] incentives[45] and education of best practice screening for syphilis.[40,41,44] As described by Snow *et al.*,[42] general practitioners may have been more inclined to initiate screening, knowing a nurse was available to conduct the tests and spend additional time with these patients, facilitating better adherence to screening guidelines.

The inclusion of syphilis screening in other screening programs or interventions has potential to enhance their public health benefit and merits further investigation, such as integration with cervical cancer screening or HPV vaccine campaigns for at-risk individuals.

Increasing syphilis screening involves two key aspects: initiatives directed at healthcare facilities, as discussed in this review, and efforts targeted at patients themselves to promote attendance to these additional services or to secure consent for reminders and opt-out testing. While not the focus of this review, these interventions hold equal importance. Kelly *et al.*[44] and Barbee *et al.*[46] describe using posters and pamphlets within clinics to advertise their new services. Zou *et al.*[29] employs the use of computer-assisted self-interview to acquire consent for SMS reminders, taking the opportunity to advise MSM of the current syphilis epidemic and its often asymptomatic nature to encourage uptake. Promoting syphilis screening to at-risk populations has been extended through innovative methods such as advertising through mobile dating applications[59–61] and social media marketing campaigns.[62–66] During an epidemic, patient incentives, such as offering free PrEP in exchange for syphilis screening as demonstrated by Tang *et al.*,[39] could prove valuable. To address the challenge of increasing syphilis screening, a synergistic approach that combines both healthcare driven, and patient-centred strategies is essential.

Strengths and limitations

This review used robust and systematic methodology, minimising bias through meticulous study selection. Data extraction and quality assessment were independently conducted by two researchers, adding further rigour. It addresses a gap in the existing literature by focusing on enhancing syphilis screening in non-pregnant individuals, offering valuable insights for future intervention development and implementation.

There are limitations to this review. Although syphilis testing has been referred to as 'screening,' in many cases, it is unclear whether the individuals were indeed asymptomatic or had symptoms and were receiving diagnostic testing rather than screening. Even in studies where the individuals were described as asymptomatic, complete examinations to document symptoms were often not performed. Reasons for non-compliance with interventions in individual studies were often not recorded. For instance, there was no information on why some individuals declined to receive SMS reminders or why some HIV monitoring tests were not accompanied by syphilis serology.

Most studies were observational, so causality between the interventions and outcomes cannot be definitively established. The effectiveness of the interventions across different populations remains uncertain. The review's lack of representation of low-income countries due, in part, to language restrictions hinders generalisability to setting with potential implementation barriers including access to technology, staff availability and costs of universal screening.

Owing to the clinical heterogeneity of the interventions and various outcomes, pooled outcomes could not be determined for all results to provide a summary effect. Our meta-analysis was limited by the inclusion of different study designs (non-randomised and RCT).

Conclusion

The studies included in this review offer valuable insights into the diverse approaches for increasing syphilis screening. It is important that the benefits of early detection and averting potential morbidity is balanced by the cost of routine screening strategies. Notably, interventions involving reminder systems or syphilis grouped with HIV monitoring should undergo cost-effective analysis to fully assess their impact as they appear to have only modest operating costs. Future research and wider adoption of these interventions in at-risk populations could mitigate the burden of syphilis.

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