Modelling Methods of Economic Evaluations of HIV Testing Strategies in sub-Saharan Africa: A Systematic Review

Systematic Review of Modelling Approaches in EEs of HIV Testing Strategies in SSA

Arthi Vasantharoopan[1§], Victoria Simms[2,3], Yuyen Chan[4] , Lorna Guinness[5], Hendramoorthy Maheswaran[6]

1. Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, UK
2. MRC International Statistics and Epidemiology Group, London School of Hygiene and Tropical Medicine
3. Biomedical Research and Training Institute, Zimbabwe
4. Department of Infection Biology, London School of Hygiene and Tropical Medicine, UK
5. London School of Hygiene and Tropical Medicine, UK
6. Institute for Global Health Innovation, Imperial College London, UK

[§]**Address for correspondence and request for reprints:**
Arthi Vasantharoopan
Department of Infectious Disease Epidemiology
Faculty of Epidemiology and Population Health
London School of Hygiene and Tropical Medicine
Keppel Street
London WC1E 7HT (UK)
Tel: + 44 (0) 7446768874
Email: arthi.vasantharoopan.ac.uk

ABSTRACT

Background

Economic evaluations (EEs), a decision-support tool for policy makers, will be crucial in planning and tailoring HIV prevention and treatment strategies especially in the wake of stalled and decreasing funding for the global HIV response. As HIV testing and treatment coverage increase, case-identification becomes increasingly difficult and costly. Determining which subset of the population these strategies should be targeted to, becomes of vital importance as well. Generating quality economic evidence begins with the validity of the modelling approach and the model structure employed. This study synthesizes and critiques the reporting around modelling methodology of economic models in the evaluation of HIV testing strategies in sub-Saharan Africa (SSA).

Methods

The following databases were searched from Jan 2000 – Sept 2020: Medline, Embase, Scopus, EconLit and Global Health. Any model-based EE of a unique HIV testing strategy conducted in SSA presenting a cost-effectiveness measure published from 2013 onwards was eligible. Data were extracted around three components: general study characteristics; EE design; and quality of model reporting using a novel tool developed for the purposes of this study.

Results

A total of 21 studies were included; 10 cost-effectiveness analysis, 11 cost-utility analysis. All but one study was conducted in Eastern and Southern Africa. Modelling approaches for HIV testing strategies can be broadly characterized as static aggregate models (3/21); static individual models (6/21); dynamic aggregate models (5/21); dynamic individual models (7/21). Adequate reporting around data handling was the highest of the three categories assessed (74%), and model validation, the lowest (45%). Limitations to model structure, justification of chosen time horizon and cycle length, and description of external model validation process, were all adequately reported in less than 40% of studies. The predominant limitation of this review relates to the potential implications of the narrow inclusion criteria.

Conclusions

This review is the first to synthesize EEs of HIV testing strategies in SSA. The majority of models exhibited dynamic, stochastic and individual properties. Model reporting against the 13 criteria in our novel tool was mixed. Future model-based EEs of HIV testing strategies would benefit from transparency around choice of modelling approach, model structure, data handling procedures and model validation techniques.

Keywords: HIV; HIV testing; HIV modelling; Economic Evaluation; sub-Saharan Africa

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KEY POINTS FOR DECISION MAKERS

- With the aim of assessing modelling approaches only, (and not the overall quality of the economic evaluation), this review is the first to consolidate and synthesize economic evaluations (EEs) of HIV testing strategies in sub-Saharan Africa.
- Chosen EE methodological approach was essentially evenly split amongst cost-effectiveness analysis and cost-utility analysis; the majority of models exhibited dynamic, stochastic and individual properties.
- Future model-based EEs of HIV testing strategies would benefit from transparency around choice of modelling approach, model structure, data handling procedures and model validation techniques.

1. BACKGROUND

Globally, 38.4 million people are living with HIV, with the burden of disease concentrated in sub-Saharan Africa (SSA) [1, 2] . The UNAIDS 95-95-95 HIV targets – diagnosing 95% of people living with HIV (PLHIV), providing treatment for 95% of those diagnosed, and achieving viral suppression in 95% of those on treatment by 2030 – have helped galvanize testing and treatment efforts since launched in 2014 [3]. Many countries in Eastern and Southern Africa (ESA) have successfully achieved the second and third 95 treatment targets, (with 98% of the West and Central African (WCA) region having achieved the second 95 target). However no country in SSA has met the first 95 (testing) target of having over 95% of PLHIV knowing their status [4]. (Six countries in ESA had achieved at least 90% awareness of HIV status by 2020, and by 2021 80% of PLHIV in WCA knew their status [4].)

HIV testing is the cornerstone of HIV prevention, the conduit to treatment and control, and a key component to ending the HIV/AIDS pandemic. Yet barriers to uptake of HIV testing exist among key populations and demographics in SSA, preventing not only the success of achieving the first 95 HIV target, but access to the HIV care continuum as well. Low socioeconomic status (SES) related barriers such as poverty and poor educational attainment are associated with a lack of HIV knowledge and awareness [5, 6]. Amplified by structural barriers such as large distances to clinics in rural settings, lack of transportation affordability or financial constraints preventing time-off from work, low SES is associated with poor access to, and uptake of, HIV testing services [6, 7]. HIV testing rates in men compared to women are low in SSA. Low HIV risk perception, or conversely engaging in risky sexual behavior, the subsequent fear of a positive HIV status, the lack of trust in healthcare workers' ability to keep status confidential, and the associated stigma of a positive diagnosis are some of the perceived barriers to increasing engagement with HIV testing services in men, in this region [6, 8]. These same challenges, along with the criminalization of sex work and homosexuality have been cited as impediments to accessing HIV testing services among female sex workers, men who have sex with men and transgendered women in the region as well [9, 10]. Legal barriers, i.e. age of consent to access HIV testing independently, compounds to the social and structural barriers preventing HIV testing among adolescents [11, 12]. With domestic funding and international bilateral donations for the HIV response having declined during the pandemic [4], determining and routinely implementing HIV testing strategies capable of reaching and engaging these holdouts, while achieving the greatest benefits at the lowest cost, is urgently needed [13].

Economic evaluation (EE) provides a framework to support decision making by comparing the costs and consequences of a program or health intervention to decide whether it represents value for money [14],

and are either trial- or model-based [15]. Model-based EEs are particularly relevant to infectious diseases and numerous modelling approaches are used, ranging from decision trees to static state transition models, (i.e. Markov models, microsimulations), to more complex dynamic models, [i.e. compartmental/transmission models, agent-based models, and discrete event simulations (DES)] [16-18]. The quality of evidence generated by EEs is highly dependent on the validity, accuracy and appropriateness of the model and its inputs. While there is guidance in the literature for model selection [16, 17], the lack of transparency involved in the choice of a modelling approach has been noted [19, 20]. Systematic reviews of EEs of prevention of mother-to-child transmission (PMTCT) and pre-exposure prophylaxis (PrEP) highlight the range of modelling approaches used [21, 22]. Regarding EEs of HIV testing strategies however, no review has been carried out on the various modelling approaches applied, and therefore little is known about the strengths and weaknesses of the different methods within this context. As such, the aim of this systematic review was not to evaluate the expected costs and health gains of HIV testing interventions, but instead, assess the state of the science surrounding model-based EEs of HIV testing strategies conducted in SSA in recent years, by synthesizing and critiquing their reporting of modelling methods. To this end, this review summarized EE methodology employed, identified modelling approaches taken and appraised reporting quality of models used for the decision problem.

2. METHODS

2.1. Protocol and Registration

This study was designed in accordance with the *Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols* (PRISMA) checklist [23]. The protocol for this study was registered in advance on PROSPERO (CRD42020199170).

2.2. Information Sources

Database selection was informed from previous research around efficient combination of databases for identification of EEs in SSA [24]. Medline, Embase and Scopus were chosen. EconLit (a general economics database), and Global Health (focusing on international public health) were also searched, due to the focus of this systematic review being EEs of HIV testing strategies in SSA.

2.3. Search Strategy

The full search strategy is provided in **Appendix** I. The search strategy was derived from the 4 core concepts relevant to this systematic review: HIV; Testing; Modelling; Economic Evaluation. This strategy underwent a peer-review of systematic review search strategies (PRESS) by LSHTM librarians and information specialists. Results were retrieved by combining search terms for the core concepts, accounting for syntax and MeSH terms in all databases, where applicable.

2.4. Eligibility Criteria

Any model-based retrospective or prospective EE of a HIV testing strategy which presented a cost-effectiveness estimate (e.g. cost per DALY/QALY/life year saved/infection averted/positive case identified/HIV death averted), when comparing one *unique* HIV testing modality to any alternative, was eligible. EEs which focused on evaluating the same HIV testing strategy in different contexts, (i.e. frequency for increasing threshold coverage from for example 40% uptake to 80% uptake, or targeted vs universal delivery of the same testing approach), along with EEs focusing on the diagnostic aspects of the same HIV testing strategy (i.e. rapid vs laboratory, confirmatory testing, change in assay types etc.), did not qualify. The search strategy included evaluations of all unique HIV testing modalities, undertaken from all perspectives (e.g. patient, healthcare provider, societal, donor), and all types of economic evaluations (i.e. cost-effectiveness, cost-utility, cost-benefit, cost-minimization, cost-consequence).

All countries and settings were eligible in the initial search to avoid exclusion of potentially relevant articles. Region was screened manually. The search timeframe was from January 1, 2000 to September 16, 2020. After search execution, a systematic review of cost-effectiveness modelling studies of PrEP for

HIV prevention published in 2013 [22], was found. As modelling approaches for evaluating PrEP require incorporation of HIV testing somewhere along the programmatic pathway, and would be comparable to those evaluating HIV testing strategies, all retrieved articles published before 2013 were removed.

2.5. Study Selection

Search results were imported into Endnote X9 for storage and duplicate removal. Titles and abstracts were screened independently by two reviewers, (AV and YC), with disagreements resolved by discussion and consensus, and excluded based on the following criteria: 1.) Unrelated to HIV Testing; 2.) HIV Testing – Epidemiological studies only; 3.) HIV Testing – Costing studies only; 4.) PMTCT interventions focused exclusively on ART provision – excluded as HIV testing is part of any PMTCT program; 5.) Non-English studies; 6.) Full text unavailable (including conference abstracts). EEs meeting the inclusion criteria were reviewed as full-text. High-income or non- SSA countries (as defined by the World Bank) were excluded [25, 26].

2.6. Data Extraction

A multi-component data extraction tool was developed. Firstly, general information including publication date, country of study, population of interest and type of HIV testing strategy assessed was extracted. The second component was based on the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist [27, 28]. Items relating to type of EE and modelling approach, perspective adopted, time horizon, cycle length and discount rate, and outcome measures presented, were extracted. The third component assessed model reporting quality via a novel tool developed, building on the recommendations from ISPOR's Principles of Good Practice for Decision Analytic Modelling in Health-Care Evaluation [29]. Reporting quality was evaluated against three categories – structure, data handling and validation – each differentiated into attributes. Attributes not limited to a specific model type, and having descriptions enabling nominal assessment (i.e. yes/no), were adapted into criteria, (n=13), to evaluate individual model reporting quality of EEs included in this review. (See **Appendix II** for attributes and scoring strategy). Data extraction was completed by one reviewer (AV), and verified by another (HM).

2.7. Data Analysis

Descriptive analysis was conducted to present EE methodological features using the CHEERS checklist and to delineate modelling parameters according to HIV natural history (i.e. transmission, progression, treatment). Model reporting around disease process and decision problem presented (structure), consideration of how parameter inputs impacted model outputs (data handling), and accuracy and generalizability of model results (validation), was differentiated across 13 criteria. Six criteria determined

the appropriateness of the model structure for the question modelled, and if structure justifications (cycle length, limitations etc.), were provided. Five criteria from determined the method with which parameters were populated, and their appropriateness. The last two criteria determined whether both an internal and external model validation was conducted. Criteria were evaluated as adequately reported, inadequately reported, not reported, or not applicable (N/A), and presented as a compound bar graph. As pooled results were not intended, risk of bias was not evaluated.

3. RESULTS

3.1. Study Selection

From the years 2000 – 2020, the search strategy yielded a total of 10, 988 records. Following removal of duplicate records (3,813) and articles published prior to 2013, 3,704 records remained. After reviewing title and abstracts, 56 records proceeded to full-text review of which 21 qualified for inclusion (**Figure 1**). (It should be noted that of the 602 titles with no full text (all of which were conference abstracts), review of titles showed 582 were unrelated to HIV testing. Abstract review found 2 of the 20 remaining conference abstracts would have qualified for the systematic review if a full text had been available.)

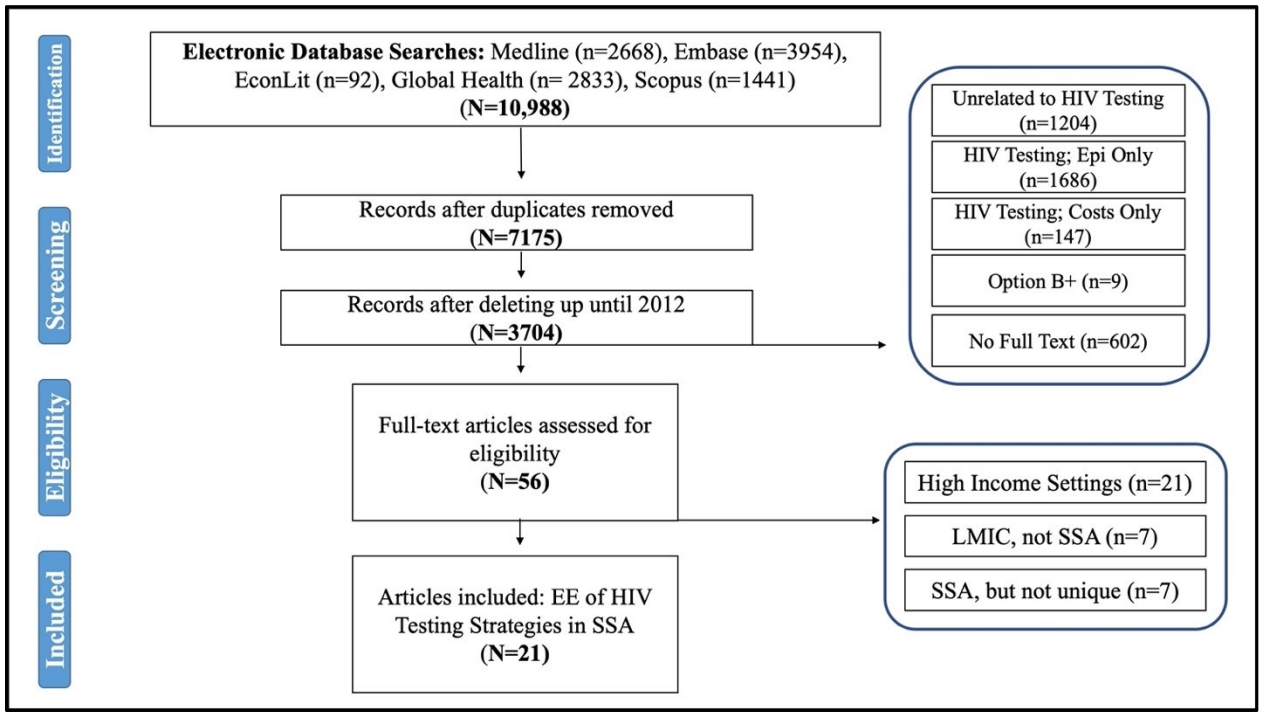

Figure 1. PRISMA flowchart of the inclusion and exclusion process for the systematic review

Option B+ = Initiation of lifelong antiretroviral therapy for all HIV-positive pregnant mothers irrespective of CD4 count
EE = Economic Evaluation
SSA = Sub-Saharan Africa
LMIC = Low and Middle Income Countries

3.2. Study Characteristics

Table 1 summarizes features of the 21 EEs of HIV testing strategies in SSA included in this review. Twenty studies were set in Eastern and Southern Africa, with one multi-country study including two West African countries (Ivory Coast and Sierra Leone) [30]. The most common population of interest was the general adult population (12/21), with varying age ranges considered. The remaining nine studies considered targeted populations. The majority of HIV testing, (12/21), was community-based (including

234 home-based and self-testing). Facility-based testing was the focus in 7/21 studies; while two studies
235 conducted testing in both clinics and the community [31, 32].

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Table 1. Features of Reviewed Economic Evaluations of HIV Testing Strategies in SSA

	STATIC			DYNAMIC		
	Decision Tree (n=3)	**State-Transition: Markov** (n=0)	**State-Transition: Microsimulation** (n=6)	**Compartmental** (n=5)	**Agent-Based** (n=7)	**DES** (n=0)
Model Properties						
Aggregate vs. Individual Deterministic vs. Stochastic	Aggregate (n=3) Deterministic (n=3)		Individual (n=6) Stochastic (n=6)	Aggregate (n=5) Deterministic (n=5)	Individual (n=7) - Deterministic (n=1) - Stochastic (n=6)	
Year of Pub						
2013-2015	3		1	1	2	
2016-2018	0		4	3	2	
2019-2020	0		1	1	3	
Setting						
Eastern Africa	2		2	1	2	
Southern Africa	1		4	3	5	
Other	0		0	1	0	
Pop of Interest						
General/Adult	1		3	3	3	
Pregnant Women and/or couples	2		0	2	1	
Targeted	0		1	0	2	
HIV Testing						
Facility	2		2	1	2	
Community	1		3	4	4	
Both	0		1	0	1	
EE Methodology						
CEA	3		3	2	2	
CUA	0		3	3	5	
Main Outcome						
DALY	0		2	1	5	
QALY	0		1	2	0	
Other	3		3	2	2	

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3.3. Economic Evaluation Overview

EEs only took the form of cost-effectiveness analyses (CEAs) (10/21), or cost-utility analyses (CUAs) (11/21). EEs conducted from the healthcare provider perspective (16/21) were the most common. Where reported, time horizons ranged from 1–50 years. Cycle lengths mostly varied from 1–3 months where applicable and reported. The preferred discount rate was 3% (16/21). Major outcomes of interest reported were: cost per DALY averted (8/21); cost per life year saved (7/21); cost per QALY gained (3/21); cost per HIV transmission/infection averted (2/21); cost per positive HIV case identified (1/21). Characteristics of the EE approaches are detailed in **Table S1** (**Supplementary File**).

3.4. Modelling Approach

Modelling approaches identified included static aggregate models, i.e. decision trees (3/21); static individual models, i.e. microsimulations (6/21); dynamic aggregate models, i.e. dynamic compartmental models (5/21); and dynamic individual models, i.e. agent-based models (7/21) (**Table 2**). All dynamic aggregate (compartmental) models were deterministic in nature (5/21), while all static individual models (microsimulations) were stochastic in nature (6/21). Six of seven dynamic individual models, (agent-based models) were stochastically configured [33].

3.4.1. HIV Transmission

Dynamic models predominantly modelled heterosexual horizontal transmission only (11/12) [32], with two including vertical transmission also [34, 35] (**Table 2**). Three static models modelled vertical transmission, with two (static, individual) including pregnancy and postpartum periods only [36, 37], while the other, (static, aggregate), also included labor [38].

The most frequently incorporated demographic parameter amongst all models was age. Models either: 1.) did not specify cohort age range (5/21); 2.) used varying definitions of adult populations (7/21); 3.) modelled age group as an ordinal variable (9/21). Age-differentiated modelled cohorts were either inclusive of infants, children, adolescents and adults (5/9), or adolescents and adults only (4/9). Two dynamic individual models also considered migration status [35, 39] (**Table 2**).

Static aggregate models, [i.e. (assumed) decision trees (3/21)], modelled HIV transmission via probabilities along event pathways, while static individual models, [i.e. microsimulations) (6/21)], modelled transmission using incidence/prevalence estimates. The number of variables considered in both the contact rate (Beta) and force of infection (Lambda) calculations between both categories of dynamic models varied substantially (**Table 2**). Among both categories of dynamic models [i.e, aggregate-compartmental and individual-agent-based (12/21)], contact rates were usually characterized by

partnerships (6/12), or sex acts per partnership (5/12); the exception being the compartmental model which focused on TB-HIV co-screening, where HIV transmission probability was proportionate to HIV prevalence in the population [40]. Amongst the 12 dynamic models, additional variables included in force of infection calculations were: ART status (8/12); circumcision status (8/12); condom use (8/12); female sex work (4/12); STI co-infection (4/12); and PrEP (2/12).

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Table 2. *HIV Transmission* Variables Among the Models Used in Economic Evaluations of HIV Testing Strategies

Reference	Demographic Parameters	Horizontal Transmission	Vertical Transmission
Static Models – Aggregate [(Assumed) Decision Trees]			
Kim (2013) [38]	Age: Unspecified	*Not Included*	Mother to child transmission probability: - during pregnancy no ARVs - during pregnancy if HAART - if nevirapine given during labor - during labor if acute HIV - during lactation if acute HV - during lactation at 6 months - during lactation at 6 months if on HAART - during lactation at 18 months
Mulogo (2013) [41] *Decision Model Unspecified*	*Model Structure and Parameters Unspecified*	*Model Structure and Parameters Unspecified*	*Model Structure and Parameters Unspecified*
Rutstein (2014) [42]	Age: 15-49 years - Non-age differentiated	Transmission: Heterosexual <u>Transmission Probability</u> - Acute Infection - Chronic Infection - HIV positive: Not on ART - HIV positive: On ART	*Not Included*
Static Models – Individual [Microsimulation]			
Bassett (2014) [43]	Age: 20-46 (assumed) - Non-age differentiated	Transmission: Heterosexual <u>Transmission Probability</u> *Not reported*	*Not Included*
Francke (2016) [37]	Age: Birth-Death - Non-age differentiated	Transmission: Heterosexual <u>Transmission Probability</u> *Not reported*	Maternal HIV Status: - CD4 ≤350/μL or >350μL; receiving or not receiving ART Intrauterine/Intrapartum (1-time risk): - Receiving ART - Not receiving ART Postpartum (monthly transmission risk until weaning): - On ART - Not on ART
Olney (2016 & 2018) [31, 44]	Age: 0-80+	Transmission: Heterosexual	*Not Included*

	- Age-differentiated into 5-year age stratum: 0-4, 5-9, …, 70-74, 75-79, >80	Transmission Probability HIV Transmission in the model is driven by incidence estimates derived from UNAIDS/Spectrum Software	
Maheswaran (2018) [45]	Age: 16-50+ - Age-differentiated into 5 groups: 16-19; 20-29; 30-39; 40-49; 50+	Transmission: Heterosexual Transmission Probability Dependent on number of individuals who already have the infection, varied by sex and age.	*Not Included*
McCann (2020) [36]	Age: 0-59 - Age-differentiated into 9 groups: 0-2; 3-5; 6-8; 9-11; 12-17; 18-23; 24-35; 36-47; 48-59	Transmission: Heterosexual Transmission Probability *Not reported*	Maternal HIV Status: - CD4 ≤350/μL or >350μL; receiving or not receiving ART Intrauterine/Intrapartum: - Started ART before pregnancy (both chronic and acute maternal HIV) - Started ART during pregnancy (both chronic and acute maternal HIV) - Not on ART (both chronic and acute maternal HIV) Postpartum: - On ART (both chronic and acute maternal HIV) - Not on ART (both chronic and acute maternal HIV)
Dynamic Models – Aggregate [Compartmental]			
Hove-Musekva (2014) [46]	Age: 15-49 - Non-age differentiated	Transmission: Heterosexual Transmission Probability Adjustment factors to contact rate (Beta) that reflect the influence of pre and post-counselling on biological and behavioral processes (that influence risk of transmission) - Behavior change: individual withdrawal from risky sexual activity; i.e. proportion of people using condoms Efficacy of community home based care	*Not Included*
Gilbert (2016) [40]	Age: 15-64 - Non-age differentiated	Transmission: Heterosexual→ (But the aim of the model was to evaluate impact of integrating combined TB/HIV case finding, on HIV/TB Coinfection epidemic) Transmission Probability HIV negative persons: Can acquire HIV at a rate proportional to the HIV prevalence in the population HIV positive: - Not on ART	*Not Included*

		- On ART	
Sharma (2016) [34]	Age: 0-59 - Age-differentiated into 5-year age stratum: 0-4, 5-9,…, 55-59	Transmission: Heterosexual <u>Transmission Probability</u> Estimated by number of sex acts per partnership, per year and the probability of HIV transmission per sex act (and viral load), factoring in the following: Sexual risk group defined by number of (coital acts) partnerships: - Low Risk; Medium Risk; High Risk Circumcision status	<u>Vertical Transmission Probability:</u> HIV Positive women not on ART (have a probability of transmitting to their infants.) - Stratified by CD4 count and viral load If HIV positive, women transition into pregnancy states according to age and CD4 count.
Ying (2016) [47]	Age: 0-59 - Age-differentiated into 5-year age stratum: 0-4, 5-9,…, 55-59	Transmission: Heterosexual Transmission Probability Estimated by number of sex acts per year and the probability of HIV transmission per sex act, factoring in the following: Sexual risk group defined by number of partnerships: - Low Risk; Medium Risk; High Risk Circumcision status PrEP: - No PrEP/on PrEP Condom Use: - Among HIV negative persons - Among PrEP users - Among ART users	*Not Included*
Wall (2020) [30]	Age: 15 – 64 - Non-age differentiated	Transmission: Heterosexual <u>Transmission Probability</u> Discordant couples (among stable couples) Concordant negative couples (among stable couples)	*Not Included*
Dynamic Models – Individual [Agent-Based]			
Cambiano (2015 & 2019); **Phillips (2019)** [48-50]	Age: 15-64 - Age-differentiated into 5-year age stratum: 15-24, 25-34,…, 55-64	Transmission: Heterosexual <u>Transmission Probability</u> Number of condom-less, short term sex partners (in a 3 month period) - Groupings of short term partnerships: none, 1, medium number, high number o Probability of HIV Infection	*Not Included*

		▪ Dependent on HIV prevalence in opposite gender of same age group Long term partnership: - Condom-less sex within 3 duration groups: 1;2;3 (higher class, higher tendency to endure) - HIV positive: Not on ART - HIV positive: On ART Female Sex Worker: >3 sex partners in a 3 month time period Probability of Circumcision	
Smith (2015); Sharma (2018) [35, 39]	Age: ≥ 18 years - Non-age differentiated Migration Status	Transmission: Heterosexual <u>Transmission Probability</u> Sexual Activity: - Coital Frequency Circumcision status Condom use by: - Partnership Type - HIV Status Partnerships: - Long-term/short-term - Concurrent partnerships (up to 2) o (Inc. outside of the community) STI Co-infection (HSV2 and others) CD4 count and ART Status of Partner	*Not Included*
Nguyen (2018) [33]	Patients generated via random draws of characteristics from distributions of *sex* and *age*	Transmission: Heterosexual <u>Transmission Probability</u> Low-Risk Population (88% Proportion): Number of monthly contacts = 4 (via reference) High-Risk Population: Number of monthly contacts=35 (via assumption) Probability of Transmission per Contact: - Acute Infection - Infection, not treated - Treated, Suppressed - Treated, Not Suppressed	*Not Included*

Johnson (2019) [32]	Each simulated individual is randomly assigned an age, sex and race	Transmission: Heterosexual and Homosexual <u>Transmission Probability</u> Probability of Transmission per Sex Act calculated according to relationship, sexual behavior, health and healthcare utilization variables. Relationship variables: - New Partner (sexual mixing pattern – highly assortative) - Marrying Partner - Ending Relationship - Casual Sex - Commercial Sex Sexual behavior variables: - Propensity for Concurrent Partners - Sexual Preference - Number of Current Partners Health variables: - Acquisition of HIV - Acquisition of STI Healthcare variables: - Adoption/Discontinuation of Contraception - Condoms - PrEP - ART - MMC	Mother-to-child transmission simulated; further details not provided

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3.4.2. HIV Progression

Static aggregate models (3/21) did not include any progression-related variables. One dynamic aggregate (compartmental) model also did not represent HIV progression [30]. The remaining 17 models accounted for HIV progression by changes in CD4 count, WHO stage, HIV viral load, and considered hospitalization, occurrence of TB or opportunistic infections (OI) and HIV related mortality. Typically, no more than four variables were represented among individual static models and both types of dynamic models; the exception being one individual static model which accounted for HIV progression through all 6 of the above mentioned categories [43]. All 17 models which incorporated HIV progression variables included HIV-related mortality parameters, followed by CD4 count (16/21), WHO staging (10/21), viral load (7/21), hospitalization (6/21), TB event or OI (4/21). **Table S2 (Supplementary File)** presents an overview of all progression-related variables incorporated into the included models.

3.4.3. ART

ART parameters were abstracted according to five broad categories: 1.) ART Initiation; 2.) Retention in Care; 3.) Viral Suppression; 4.) Loss from Care; 5.) Other. Static aggregate models did not account for ART within branch pathways (3/21). All individual static models (6/6), and all dynamic individual models (7/7) incorporated an ART initiation variable. Amongst dynamic compartmental models, 2/5 did the same, while the other 3/5 dynamic compartmental models did not consider the effects of ART initiation on costs and outcomes. Following ART initiation (15/21), loss from care was the second most commonly included parameter (13/21). No study included ART-related variables from all five categories. **Table S3 (Supplementary File)** presents a summary of all ART-related variables incorporated into the models.

3.5. Model Reporting Quality

Figure 2 depicts the reporting quality of the models.

3.5.1. Model Structure

Model outcomes are conditional upon structural limitations; a lack of transparency around these assumptions and limitations exaggerates their accuracy [29]. Only one study adequately reported all six criteria related to model structure [50], while two did not adequately report any. Relevant inputs/outputs for the decision-making perspective (C1), was adequately reported in fourteen of 21 studies, but for seven studies, it was not clear that input parameters and specifically costs reflected the chosen perspective [51]. It was difficult to assess model structure consistency with available evidence and current understanding of the HIV disease (C2), for 2/21 studies or it was not reported (4/21) [52]. Limitation to model structure (C3), were adequately reported only in 8/21 studies. C3 also had the most studies (8/21), which did not

report on it at all; 5/21 studies mentioned limitations but did not discuss the impact of those limitations on reported outcomes. Justification of time horizon and cycle length (C4), was adequately reported criteria in only 2/21 studies, with the majority of studies (14/21) inadequately reporting the rationale behind their choices. Observations on the final two criteria in the model structure category – simple as possible model structure capable of accurately capturing the underlying disease process (C5) and appropriateness for the question modelled (C6) – similar to C2, were dependent on structure elucidation. Both C5 and C6 were adequately reported in 15 studies, but difficult to assess in the remaining 6 studies since structure complexity and appropriateness was not fully described.

3.5.2. Data Handling

Data handling had the highest proportion (74%) of adequately reported criteria; six studies adequately reported all five criteria. Disclosure of input parameter sources is necessary to determine their suitability [53]; conducting a literature review for key model parameters (C7), was adequately reported 90% of the time. Sensitivity analyses quantify the uncertainty of input parameters and their effects on a model's output [54]. Inclusion of upper and lower bound ranges for input parameters (C8) was adequately reported 81% of the time. Within the data handling category, acceptable data modelling methods in line with biostatistics and epidemiology (C9), was the least adequately reported criteria (62%). Transparency around data transformation for relevant inputs and outputs, (e.g. adjusting for inflation or purchasing power across time and countries; discounting, transformation of health values/scales into quality of life weights), is needed for valid and accurate model outcomes [29]. The same is true for disclosure of data modelling assumptions (C10), which was adequately reported among 14 (of 21) studies (67%). Lastly, consistency between measurement units and population characteristics throughout the model (C11), was evaluated as a summary of reporting across C4, C5, C7 and C9. Seventy-one percent of studies adequately reported this criteria.

3.5.3. Model Validation

Model validation had the lowest percent (45%) of adequately reported criteria. Evidence of internal model validation (C12), where applicable, was adequately reported 79% of the time; four studies did not provide evidence of internal testing and debugging. Failure to report if/how models were calibrated challenges the validity of findings, if the model cannot reproduce observed effects [55]. Evidence of external model validation (C13), (along with C4), was the least adequately reported criterion: adequately reported in 2/19 studies only (11%), inadequately in 7/19 (37%), not reported in 10/19 (53%). Only two of 19 studies accurately reported on both internal and external model validation processes [33, 45], while three studies did not report any validation criteria.

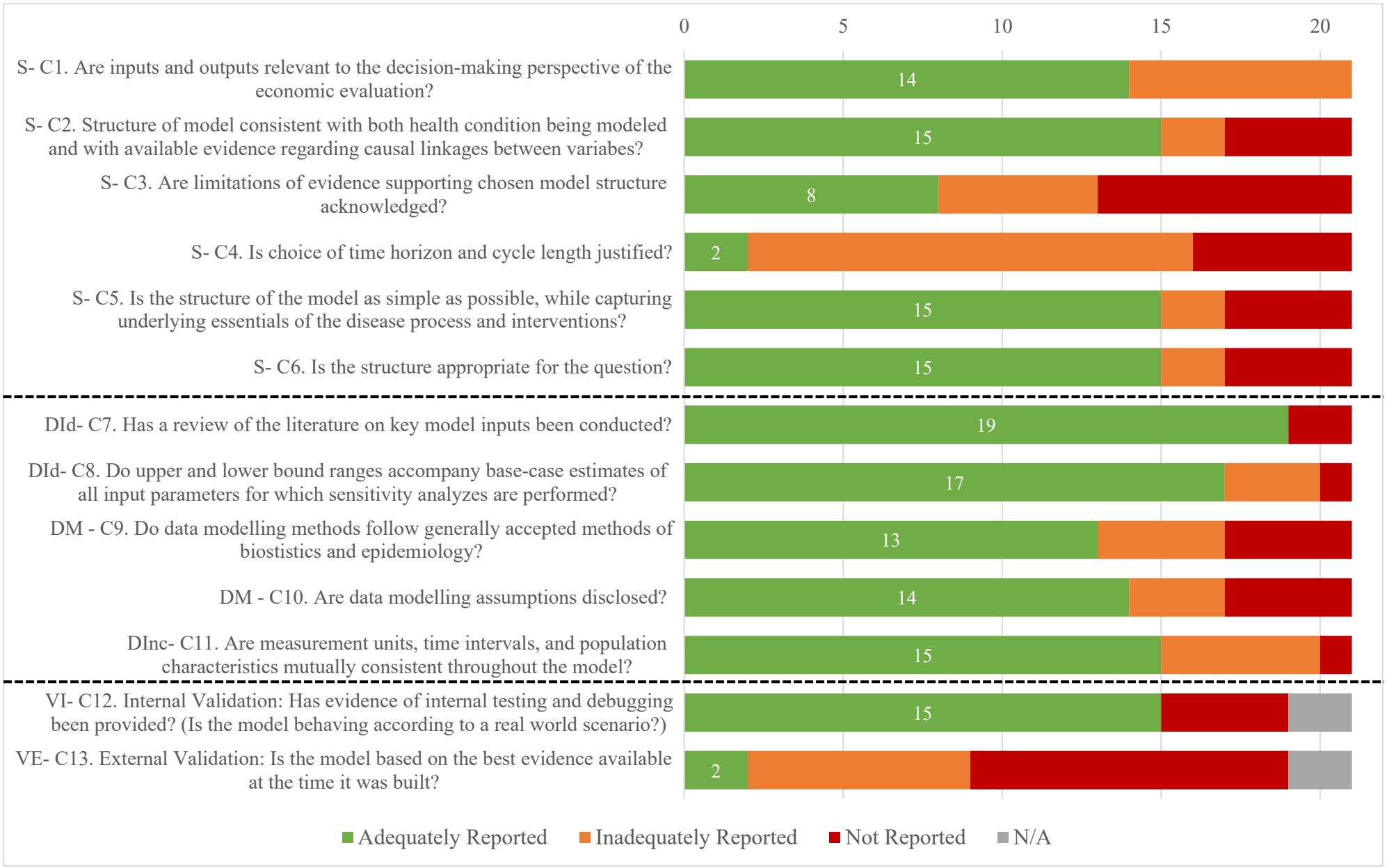

Figure 2. Assessment of Model Reporting Quality

Models were assessed against a total of 13 criteria (developed around ISPOR's Principles of Good Practice for Decision Analytic Modelling in Health-Care Evaluation), and were gauged against a 3 point scale: Adequately reported; Inadequately reported ; Not reported.

- *Model Structure* – 6 criteria (C1 – C6)
- *Data Reporting* – 5 Criteria from 3 sub-categories: Data Identification (C7, C8); Data Modelling (C9, C10); Data Inclusion (C11)
- *Validation* – 2 Criteria from 2 sub-categories: Internal Validation (C12); External Validation (C13)

4. DISCUSSION

This systematic review sought to determine how EEs of HIV testing strategies in SSA have been conducted, and to namely highlight what modelling approaches have been used to do so. Spanning 2013 to 2020, 21 economic evaluations of HIV testing strategies were included; all were either CUAs (11/21), or CEAs (10/21). EE modelling approaches fell into four categories: 1.) Static aggregate (3/21); 2.) Static individual (6/21); 3.) Dynamic aggregate (5/21); 4.) Dynamic individual (7/21). When graded against model reporting criteria adapted from ISPOR guidelines, 6 of 13 criteria were adequately reported at 70% or above. Except for one model, all economic evaluations were confined to East and Southern Africa, where the largest HIV burden resides. There was no discernable relationship between testing approach, modelling approach and location.

In line with previous reviews [56, 57], the included models were classified according to the following properties: Static vs Dynamic; Deterministic vs Stochastic; Aggregate vs Individual.
The majority of papers represented the disease process dynamically (n=12), favoured stochastic functions (n=12), and individual population representation (n=13). There were no cohort-based Markov models or DES included. This finding was aligned with results from a systematic review of EEs of adult male circumcision which did not have any Markov-modelled evaluations [58], but not with the results of two other systematic reviews of EEs [of PrEP [22] and PMTCT [59]], which did. The 'memoryless' Markovian property, while well suited for chronic diseases [60], may not be appropriate for HIV prevention decision problems where transitioning to the next state is dependent on the previous one, and accounts for this lack of Markov models for HIV testing.

A key challenge was discerning the authors' intention behind the use of modelling terminology; for example, both microsimulations and agent-based models were referred to as 'individual-based' models. Standardization of mathematical model reporting in terms of explicit categorization of the above-mentioned three properties may provide clarity for future researchers seeking to replicate an approach for their decision problem, and consequently a better understanding of its appropriateness and applicability for their specific context.

Six of 21 models in this review were static. Static models have less data and computational requirements than dynamic models, yet a disadvantage is that a constant force of infection disregards real-world contact and mixing patterns, as well as variable risk within partnerships [61]. For HIV, dynamic models are conceptually more desirable than static ones [21]. However, if a static model predicts that an intervention is cost-effective, a dynamic model will as well [56]. A comparison between a dynamic transmission

model and a well-known static HIV model - the 'Modes of Transmission'(MOT) model – found that when the MOT model structure was equivalent to that of the dynamic model, the static model estimates improved [62]. The validation also cited the quality of data as another key to improving the MOT model's outputs [62]. Depending on parameter availability and quality, a static model might be an acceptable alternative if structure (i.e. natural history/health states and parameters), inputs (data sources) and model outputs (i.e. cost-effectiveness measures), are standardized. A first step would be to produce a limited number of cost-effectiveness measures (i.e. cost per DALY or QALY only), to reduce variability within outcomes presented by various modelling approaches, thereby facilitating comparability. A more ambitious next step would entail universal accessibility of datasets (ideally in a repository) to aid in reproducibility of parameter inputs and facilitate a higher research standard.

Viral load is widely considered the most important risk factor in HIV transmission, and a good proxy indicator for ART monitoring, highly sensitive to treatment adherence and failure [63]. However, a review of HIV mathematical models found that only 6% (i.e. 17 of 279) of models incorporated a viral load parameter [63]. This may be in part due to lack of data access, especially in low-income settings where monitoring CD4 count rather than viral load was historically the norm [64]. Only seven of the 21 included studies (33%), incorporated a viral load parameter under the HIV progression category, and three of them were from a single working group using the same model [48-50]. Moving forward, inclusion of a viral load parameter may help homogenize structural/natural history considerations, consequently advancing HIV model standardization.

While recommendations and classifications exist [16, 17, 29, 65], model structure taxonomy and reported rationale for modelling approach in the literature is inconsistent and non-transparent, evidenced by the inadequate reporting around certain model structure criteria observed. No study stated their rationale for choice of model used. Without disclosure of reasons behind model choice, assessing criteria around appropriate model structure for question (C6), was difficult and subjective. Oftentimes, limiting factors to modelling approach and structural considerations are largely contextual, such lack of data, ease of use and technical aptitude hinging on resource availability [66]. Brief explanations accompanying modelling decisions would help modellers determine if a structure is appropriate for replication in future evaluations. The 2022 update to the CHEERS statement encourages researchers to explain their reasoning behind model-based decisions [28]. Future researchers would benefit from closely adhering to the updated CHEERS checklist as it would strengthen the accuracy and validity of both methodology and results generated, and aid the audience (other researchers, policy makers etc.) understand the context of all decisions made. Journals compulsorily requiring a completed 2022 CHEERS checklist alongside EE manuscripts might increase transparency in EE modelling and facilitate the modification, reusability,

reproducibility of existing models, and analyses as a whole, thereby reducing redundancy and limiting resource use.

Reporting around data handling was the highest of the three model appraisal categories. Across the 21 studies, the proportion of adequately reported criteria in this category ranged from 62% (C9) to 90% (C7). However, scarcity of externally validated models, or at the very least, adequate reporting around external validation, (C13, 11%), is a cause for concern. This questions model generalizability and results upon which policy decisions are made, and the likelihood that predicted effects would occur outside of the study [55, 67]. This is particularly problematic in the HIV context, where drivers of epidemics vary substantially according to population and region. ISPOR's good modelling practices cites the need for a formal process evaluating external validity of models [55]. The difficulty of establishing a formalized process may account for the rarity of evaluating external model validation [68]. The structuring of research reporting itself might also contribute to the problem. The focus almost always lies on the results of the modelling study – i.e. how cost-effective the intervention was, how many DALYs were averted etc. – and rarely is space and time given to the model itself. Peer-review processes would benefit from better guidelines for model reviews. ISPOR's modelling practice recommendations are a great starting point, however, evidenced by the difficulty encountered in adapting the guidelines into an actionable format for the purposes of this systematic review, they would benefit from a structural overhaul to become more user-friendly and executable. Altering the format to resemble the resulting tool (**Appendix II**) may be useful for future modellers and reviewers, irrespective of research area, and could facilitate higher quality economic evaluations.

When reviewing the results of this systematic review, the following limitations must be considered. Modelling methods are complex and terminology used vaguely and interchangeably adds to the confusion. There is a possibility of incorrect interpretation of model components due to variation and inconsistent use of terminology. However, explicitly attempting to categorize models according to three fundamental properties – static vs. dynamic; deterministic vs. stochastic; aggregate vs. individual – possibly mitigated some of the misunderstanding. While no study was excluded solely based on the availability of English text, relevant model-based evaluations of HIV testing strategies based in WCA, under-represented in this review and a largely Francophonie area, may have been missed if a translated abstract did not accompany the manuscript, as the search strategy (and accompanying terms) were in English. Though database selection was informed via research findings [24], omitting other relevant databases (e.g. Web of Science, grey literature databases etc.), and excluding studies without full text (as a detailed methods section outlining model structure and parametrizations was necessary to abstract relevant data for this review), may have prevented gaining a holistic and representative view of model-

based economic evaluations of unique HIV testing strategies in SSA. Additionally, the search timeframe did not include studies published in 2021 and 2022, potentially hampering the ability to observe any recent modelling-based trends in EEs of HIV testing strategies (in SSA), that may be forming. Finally, the scope of this review excluded the possibility of exploring the potential policy implications of the studies included; future research may entail assessing the overall quality and conclusions of these EEs and their impact on HIV testing recommendations and policy implementation within SSA.

5. CONCLUSION

No single modelling approach and structure will ever fully represent HIV disease transmission and the impact of testing. Similarly, while standardization of HIV testing models would facilitate generalizability and reproducibility of results in the region, economic modelling studies are conducted within a specific context or setting to answer a distinct question or policy consideration. Models are further limited by practical and real-world data considerations. Therefore, generating quality evidence via economic evaluations begins with the validity of the modelling approach chosen and the model structure employed. Conducting an economic evaluation of a HIV testing strategy via an agent-based model – a dynamic, stochastic, individual representation capable of calculating nuanced interactions and mixing patterns while accounting for variability and changes over time – would be ideal. However, most settings, especially SSA suffer from constraints related to data and resources, at which point static and compartmental models can be as effective, particularly if future researchers and modelers adhere to several key recommendations. Namely: 1.) rationalization and explanation of model-based decisions surrounding model structure, parametrizations and analytic components in line with the 2022 updated CHEERS statement; 2.) explicitly highlight model structure, data handling procedures and processes for both internal and external validation of models using the tool generated by this systematic review as a frame of reference; 3.) facilitate data sharing; 4.) generate at least one summary measure of population health (cost per DALY or QALY) to facilitate policy implementation comparison and decision making across the spectrum of health technologies.

DECLARATIONS

Ethics Approval and Consent to Participate

Not applicable: data in this review was obtained from previously published studies.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request. Search strategy available in appendix. Code availability not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Author Contributions

AV, LG, HM and VS conceptualized the study and developed methods. AV and HM developed data collection tools. AV and YC executed data acquisition. AV and HM analyzed data. First draft of the manuscript was written by AV and all authors commented on subsequent versions. All authors have read and approved the final draft and declare no competing interests.

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