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Economic evaluation, human immunodeficiency virus infection and screening: A review and critical appraisal of economic studies

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Objectives: The aim of this study was to review, systematically and critically, evidence used to derive estimates of cost-effectiveness of human immunodeficiency virus (HIV) screening.

Methods: A systematic review was conducted. Searched were **three main** electronic bibliographic databases from 1993 to 2008 using key words including HIV, mass screening, HAART, economic evaluation, cost-effectiveness analysis, modeling. We included studies of sexually transmitted HIV infection in both sexes, including studies comparing diagnostic testing protocols and partner notification. Outcomes included were cases of HIV infection detected, deterioration to the AIDS state, secondary transmission of HIV, the quality-adjusted life-years/survival, costs, and cost-effectiveness of HIV screening.

Results: Eighty-four papers were identified; ten of which were formal economic evaluations, one cost study, three effectiveness studies, and three systematic reviews of HIV prevention programs. The predominant assertion was that HIV screening is cost-effective; methodological problems, such as the preponderance of static models which are inappropriate for infectious diseases, varying perspectives from which the studies were analyzed, and arbitrary threshold incremental cost-effectiveness ratio levels, limited the validity of these findings, and their usefulness in informing health policy decisions.

Conclusions: The majority of published economic evaluations are based on inappropriate static models. This flaw renders the results of these studies as inconclusive and the purported cost-effectiveness of HIV screening debatable. The results of this

This study represents work carried out by Dr. Onome Dibosa-Osadolor in conjunction with Professor Tracy Roberts, for her MSc dissertation in Health Economics and Health Policy at the University of Birmingham. The dissertation was motivated by an earlier study by Tracy Roberts on the NCCHTA funded Chlamydia Screening Studies (ClASS) project. The current work was carried out unfunded. Professor Tracy Roberts is funded by the Higher Education Funding Council for England (HEFCE) at the University of Birmingham. The authors thank Dr. John Saunders for his expert advice on the natural history of HIV.

review could form a basis for consideration of further research and analysis by health economists into the cost-effectiveness of HIV screening.

Keywords: Human Immunodeficiency Virus (HIV), Economic evaluation, Economic modeling

Human immunodeficiency virus (HIV) infection has had an unparalleled and pandemic impact since its discovery in the early 1980s. It has demonstrably changed demographic profiles in the most affected geographical areas by markedly reducing life expectancies, aggravating poverty, and hampering economic growth by annihilating people in their most productive years (3).

Globally, health systems have responded by financing and providing screening services, following the recommendations of economic evaluations which typically suggest HIV screening is a cost-effective use of health resources.

The provision of valid information that can inform health policy requires robust evidence about the cost-effectiveness of the particular programs. Mathematical models such as decision analyses and Markov models which predominate in health economic evaluations (5) assume a constant force of infection and treat individuals independently of each other within their structure (2;5). These models are typically referred to as *Static* and are inappropriate for modeling the impact of an HIV screening program. They cannot account for the dynamics of transmission of the infection which is hinged on its population prevalence per unit time, the duration of the infectious period, the diversity of sexual behavior with its potential for assortment and number of sexual partnerships so formed within the population, as well as the presence of concomitant sexually transmitted infections. These characteristics can only be accommodated in transmission dynamic models (23).

We undertook this review to appraise the methodologies of economic studies of HIV screening carried out before and beyond the advent of the highly active anti-retroviral therapy (HAART) initiative. We assessed and critiqued the mathematical models used in these studies, while expanding on the appropriate model for analysis of HIV infection, to determine the long-term cost-effectiveness of HIV screening. This review is based on the study by Roberts et al. (22) who reviewed and critiqued economic evaluations of *Chlamydia* screening concluding that cost-effectiveness could not be determined by these studies as they had profound methodological flaws; principal among them being the inappropriateness of the mathematical models on which the analyses were based.

MODELING AND HUMAN IMMUNODEFICIENCY VIRUS SCREENING

HIV is predominantly transmitted during sexual intercourse—it is mainly transmitted through heterosexual intercourse but also bisexual and homosexual intercourse. Other

routes for transmission include vertically from an infected mother to child, sharing needles between injecting drug users, and by receiving infected blood products.

HIV infection, like *Chlamydia*, is often asymptomatic. As a consequence, many people remain unaware of their infection until they develop symptoms related to advanced immunosuppression and AIDS. This delay in diagnosis not only limits access to life-saving HAART, but there is also evidence to suggest that people who are not aware of their diagnosis are disproportionately responsible for the onward transmission of HIV (15).

The natural history of HIV infection suggests that typically once a person is exposed to HIV and becomes infected, approximately 1–6 weeks later between 50 and 80 percent of people will feel unwell with perhaps one or more symptoms of fever, headache, rash, or ulceration of the oropharynx, general aches and pains, etc. Most people feel better within a few weeks; hence they and their doctors think they had a bout of the flu and miss an opportunity to screen for the disease. However, this is one of the most infectious periods due to high levels of the circulating virus in the bloodstream. As a result of this and because they are unaware of their HIV status, at-risk sexual behaviors continue and onward transmission occurs (15). The asymptomatic phase can vary in length before the development of AIDS. Without treatment, the immune system declines leaving people open to life-threatening infections (combination of HIV and these infections is called AIDS) and then death. People are again very infectious at this stage due to high levels of the virus in the blood.

A fundamental understanding required for the construction of a mathematical model for any infectious disease is the natural history of infection, because one of the main purposes of the model is to depict the rate of transmission through a defined community. Therefore, in the application of mathematical models to the economic evaluation of a screening program for HIV, the most relevant characteristics are associated with disease transmission. The costs and effectiveness of the intervention, should be accounted for as far as possible within the structure of the model before the potential impact of the screening program can be analyzed (9;22).

METHODS

For ease of comparison this review was based on a similar study by Roberts et al. (2006) (21). We searched three main electronic bibliographic databases from 1993 to 2008 using keywords search strategy that included words such as HIV or HIV infection, mass screening, HAART, economic

Table 1. Criteria for Quality Assessment

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- The research or study question should be explicit, implicit, or evident; its economic significance and social relevance should be elucidated, and the perspective or standpoint of the study should be stated and justified
 - The alternative health interventions being compared should be described vis-à-vis their costs and outcomes, and the underlying principle governing the ultimate choice of an intervention should be stated
 - The type of economic study performed should be clearly stated and it should be appropriate to the stated objectives of the research question within an appropriate time horizon
 - All sources of effectiveness data should be explicit or implicit and methods of data analysis and extraction should be outlined
 - The primary outcome measure of the study should be explicit, implicit or evident
 - The quantities of resources used should be stated independently of the unit costs of these resources; the currency and/or currency conversion rates as well as any inflation motivated price adjustments should be documented
 - An appropriate and validated discount rate should be documented
 - Incremental analysis should be performed when two or more alternatives are being compared
 - The modeling type used in the study should be characterized, described, and should be appropriate for the study question
-

evaluation or cost-effectiveness analysis or cost benefit analysis and modeling.

Inclusion Criteria

Participants. Individuals of both sexes at risk of exposure to the human immunodeficiency virus.

Interventions. All available interventions for screening for HIV, including both nonselective and selective opportunistic and population-based screening programs.

Outcomes. The outcomes of interest were the cases of HIV infection detected by screening; major outcomes averted such as deterioration to the AIDS state and secondary HIV transmission, the quality-adjusted life-years (QALYs)/survival, costs, and cost-effectiveness of HIV screening.

Studies Reviewed. Formal economic evaluations; such as cost-effectiveness analyses, cost-benefit analyses and other studies which assess the effectiveness of HIV screening with a focus on assessment of costs likewise. Studies reporting cost-effectiveness of HIV screening in pregnancy, screening of blood products, and screening of injecting drug users were excluded from this systematic review.

Selection of Papers for Review

The selection of papers for review was fashioned after a similar methodology used by one of the co-authors (T.R.) of this review and described in detail elsewhere (21).

The search was carried out in June 2008. The main investigator for the review (O.D.) followed the methods that have been described in detail elsewhere (21). All stages of the review were overseen by a second investigator (T.R.). The quality of the economic evaluations being reviewed was assessed based on criteria derived from a synopsis of previously published guidelines (Table 1) (21). Studies which failed to meet more than two criteria were excluded, those which failed to meet two criteria were reviewed and relevant deductions were extracted, while those which failed to meet one or less than one criterion were subjected to a full review and critique.

RESULTS

The search identified eighty-four papers (see Figure 1), thirty-eight of which were considered potentially relevant. Twenty-five papers were fully reviewed and those papers which were categorized as economic evaluations or cost studies containing some useful information, classified as (C) but not fully meeting the inclusion criteria were excluded. There were ten formal economic evaluations, one cost study, three effectiveness studies, and three systematic reviews of HIV prevention programs. The models used in the different studies were also reviewed and documented.

Studies of Human Immunodeficiency Virus Screening Programs

Fourteen studies, of the seventeen selected for the review, were specifically designed with respect to HIV screening programs. One of these fourteen studies also explored the benefits of partner notification, as a consequence of screening, in limiting the spread of HIV. The general characteristics of these studies are summarized in Table 2. Of these fourteen studies, thirteen were model based, three were effectiveness studies, and one was a cost study. Most of these studies used rapid HIV antibody testing and found nonselective opportunistic screening programs to be cost-effective.

Static models predominated with only two studies using transmission dynamic models in their analyses (4;27). Vickerman et al. (27) evaluated the benefits of selective population screening for HIV and other sexually transmitted diseases and concluded that screening using rapid point of care tests was more cost-effective than the prevailing syndromic management of potentially infected female commercial sex workers. Using a Bernoulli (stochastic transmission) model, Bos et al. (4) analyzed the economic impact of selective opportunistic screening of sexually transmitted diseases (STD) clinic attendees and concluded that screening was cost-effective presuming that behavioral modification would be a consequence of detected HIV sero-positivity.

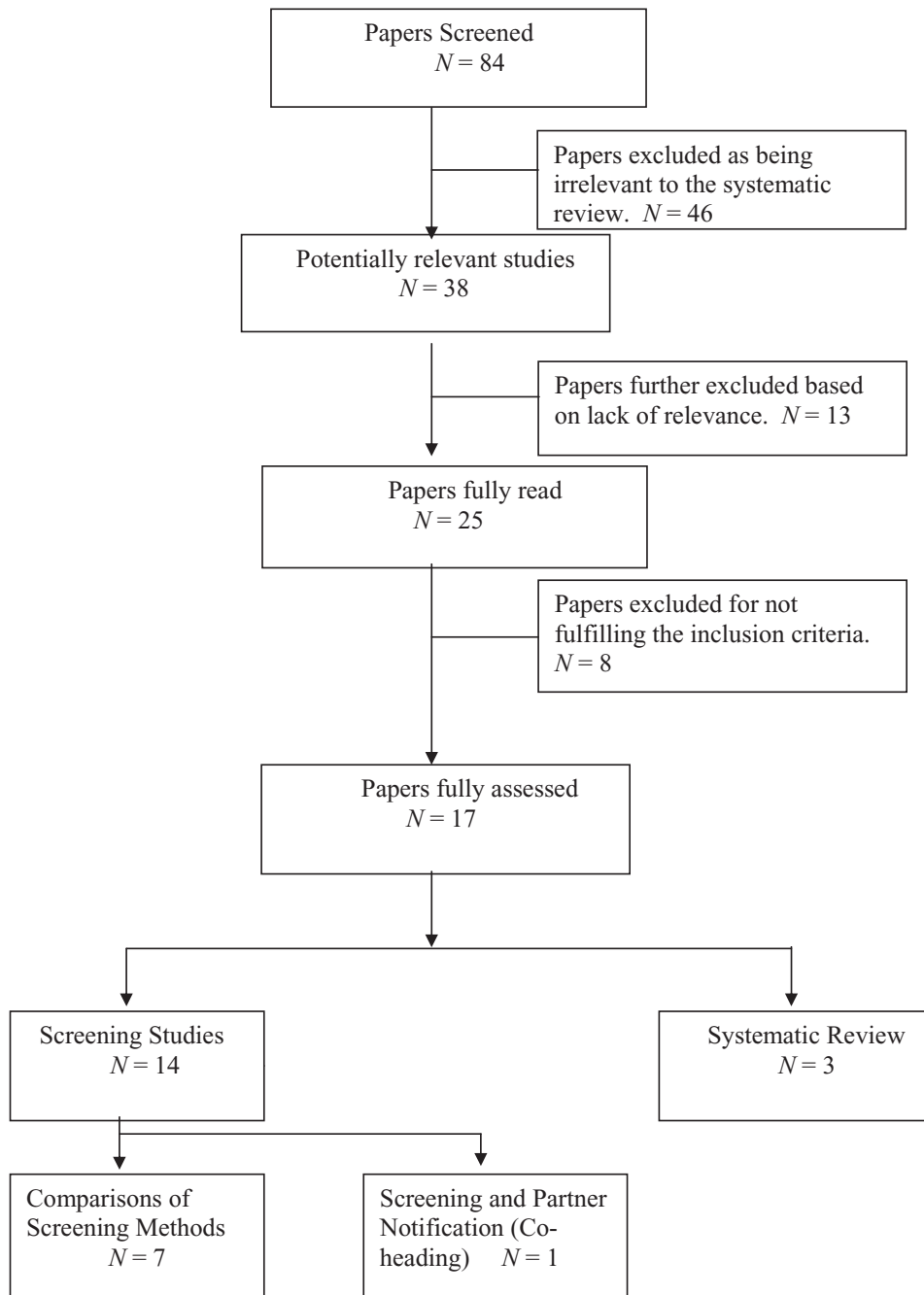


Figure 1. Algorithm depicting selection of economic evaluations of HIV screening.

Diagnostic Testing Studies

Seven studies addressed diagnostic testing protocols used for HIV detection. The studies were categorized as those analyzing the cost-effectiveness of enzyme linked immunosorbent assay (ELISA) or enzyme immuno-assay (4;28;29), those exclusively evaluating rapid testing protocols (18) and those comparatively analyzing both protocols (4;6;17). Two of these studies used transmission dynamic models to evaluate the cost-effectiveness of rapid antibody testing protocols

as well as ELISA testing protocols (4;27), while the other five studies were based on static models.

The studies unanimously concluded that HIV screening by any means is cost-effective. The majority of the papers (57 percent) concluded that rapid antibody testing for HIV with immediate patient notification is more cost-effective than alternative tests which give results over a protracted period (approximately 2 weeks); and they result in a higher percentage of patients being appropriately linked to care (6;17;18;27).

Table 2. Summary of the Characteristics of the Economic Evaluations of HIV Screening in Chronological Order

First author; year	Target population	Model type	Outcomes	Use of HAART	Main study conclusions
Fang; 2007 (8)	M&F	Static	Life expectancy	Yes	Effectiveness Study. Screening should be expanded to minimize delays in diagnosis.
Holtgrave; 2007 (11)	M&F	Static	HIV infections and transmissions averted	Yes	Screening is cost-effective. Targeted counseling and testing performs better than opt-out testing from an effectiveness and public health perspective.
Walensky; 2007 (28)	M&F	n/a	QALY	Yes	Review of economic evaluations of HIV screening. Screening is cost-effective.
Paltiel; 2006 (17)	M&F	Static	QALY, HIV cases detected, transmissions averted	Yes	Routine HIV screening is cost-effective; except when the prevalence of undetected infection is below 0.2%.
Vickerman; 2006 (27)	F	Dynamic	Number of HIV cases averted	n/a	Screening is cost-effective. Rapid Ng/Ct POC more cost-effective than existing syndromic management.
Coco; 2005 (6)	M&F	Static	QALY, secondary transmission averted	Yes	Expanded testing for primary HIV infection may be cost-effective.
Paltiel; 2005 (18)	M&F	Static	QALY	Yes	Routine voluntary HIV screening once every 3 to 5 years is cost-effective; except in settings of lowest prevalence.
Sanders; 2005 (24)	M&F	Static	QALY	Yes	Screening is cost-effective; even at prevalence rates substantially less than 1%.
Walensky; 2005(a) (29)	M&F	none	HIV cases detected	n/a	
Walensky; 2005(b) (28)	M&F	Static	QALY	Yes	Although screening is cost-effective; limited funds allocated to client notification and linkage to medical care are a better value for money.
Walensky; 2005(c) (30)	M&F	Static	QALY	Yes	Routine in-patient HIV screening is cost-effective; even at undiagnosed prevalence rates of 0.1%.
Ekwueme; 2003 (7)	M&F	Static	HIV cases detected	n/a	
Bos; 2001 (4)	M&F	Dynamic	QALY; secondary transmissions	Yes	Universal HIV screening of STD clinic attendees is cost-effective.
Varghese; 1999 (26)	M&F	Static	QALY;	Yes	Counseling and screening is cost saving.
Holtgrave; 1996 (12)	M&F	n/a	QALY; HIV cases detected; secondary transmissions prevented	No	
McCarthy; 1993 (16)	M&F	Static	Life expectancy	No	Screening is cost-effective at prevalence rates of 0.5% or more.

NSO, non-selective opportunistic screening; NSP, non-selective population screening; SO, selective opportunistic screening; SP, selective population screening; HAART, highly active antiretroviral therapy; MOA, major outcome averted; F, female; M, male; QALY, quality-adjusted life-years; HIV, human immunodeficiency virus infection; n/a, not applicable; STD, sexually transmitted diseases; Ng/Ct POC, *Neisseria gonorrhoeae/Chlamydia trachomatis* point of care.

The general characteristics and summaries of details of these studies are presented in Supplementary Table 1, which can be viewed online at www.journals.cambridge.org/thc2010022.

Partner Notification Studies

One paper investigated the benefits of partner notification as an adjunct to counseling and screening programs for HIV prevention (26). The study used a decision model to simulate the introduction of partner notification into an existing HIV

counseling and testing program and concluded that partner notification piggy-backed onto a screening program is cost saving both from the providers and societal perspectives. The characteristics of this study are summarized in Supplementary Table 2.

Other Characteristics of the Studies

Overall the studies used long-term outcomes to measure benefits of HIV screening. The majority of studies reported their

results in generalizable outcome measures such as QALYs or life-years gained (LYG). The exceptions are Fang et al. (8) who reported their results in life expectancy, Holtgrave (11) who reports in terms of infections and transmissions averted, Walensky et al. (29), and Ekwueme et al. (7) who reported their studies in terms of number of cases of HIV detected. The two studies which were based on transmission dynamic models were also reported with respect to secondary cases averted. Coco (6) and Varghese et al. (26) considered the benefits of HIV screening on secondary cases averted and HIV transmission from infected index patients to their partners, but based their analysis on static decision analysis models.

When evaluating HIV screening from the third party payer's perspective, Coco (6) reported in terms of cost per case of primary HIV infection detected. Quality of life data were derived from widely published studies of health states and health utilities which were robust in their analyses (7;13;20;25). Bos et al. (4) estimated the additional years of life gained from screening as a function of HIV detection during at least 3 years of the asymptomatic phase.

For many of the studies that reported incremental cost-effectiveness ratios there was no discussion of a predetermined acceptable threshold but their results were typically interpreted as being cost-effective (11;17;27;28).

DISCUSSION

Within the limits of the electronic bibliographic databases and journals searched, several economic studies which assessed various aspects of HIV screening were identified and subsequently reviewed. The unanimous conclusion of all studies identified was that HIV screening was cost-effective. The study that considered partner notification as an adjunct to screening suggested that it was cost saving. Rapid HIV antibody testing was found to be both clinically efficacious as well as cost-effective.

Paying specific attention to the UK environment, the review unearthed a dearth in economic studies of HIV screening programs. This finding was particularly disconcerting considering the evidently rising incidence of HIV among adults in the United Kingdom as reported by the Department of Health in 2008. Three UK studies were identified on antenatal screening programs, but these studies are not critiqued in the current review because the wider population effects are not relevant and a static model is appropriate for such evaluations (1;10;19).

HIV is an infectious disease that causes worldwide devastation. The evidence presented in this study does not purport to suggest that screening individuals and treating for this disease is not good value for money. However, the findings of this review raise questions on the validity of the reported assertions made by the authors of some papers because many of the assertions are underpinned by economic studies which had methodological flaws. Principally, the models which were predominantly used in the assessments were inappropriate

for modeling the dynamics of infectious diseases. Indeed the methodological flaws, if absent might lead evidence to show that the results supporting cost-effectiveness is actually understated and that screening is even more cost-effective than the available results suggest. Alternatively, model-based economic evaluations that use an appropriate modeling approach may highlight with more precision, where the resources should be targeted, to what groups, how often or suggest other alternative but cost-effective policies.

Strengths and Limitations

The strengths of this study are that, to date and to our knowledge, this is the only review of economic studies of HIV screening to address the appropriateness and quality of the models used in the studies. This is particularly important vis-à-vis the study by Roberts et al. (2006) on *Chlamydia* screening as congruent concerns and matters surrounding both areas of study can be underscored. A limitation of the review is the limited scope of the search. There will exist some databases that have not been searched and some studies not identified. However, our approach was pragmatic, and the studies identified are recently published and in main stream journals.

Comparison With Other Studies

Three other published systematic reviews in the area of HIV were identified: two focused on HIV prevention inclusive of screening (12;14) and one specifically reviewed screening studies (28).

Hornberger et al. (14) reviewed and comprehensively summarized studies of HIV prevention and management from 1980 to 2005. Outcome measures which the authors considered legitimate were the QALYs or LYGs. While the review presented comprehensive literature-based evidence on the cost-effectiveness of HIV screening, among other HIV prevention strategies, it also highlighted methodological flaws in economic studies reviewed such as varying cost-effectiveness thresholds and questionable evidence on effectiveness of the individual strategies. However, the authors did not critique the approaches to modeling used in the economic analyses reviewed and did not highlight this as a limitation.

Walensky et al. (28) reviewed the methods and results of economic studies of HIV screening in various clinical settings in the United States. The review corroborated the conclusions of existing studies, but neither the methodology nor the strengths and limitations of their review were discussed by the authors.

One of the earliest reviews of economic studies identified by the current study was by Holtgrave et al. (12). The author reviewed economic studies of domestic HIV screening programs from 1990 to 1995 across different populations based on age, gender and level of risk; from individualistic, governmental and societal perspectives. The

author did critique the modeling approaches used in some of the studies and he buttressed the fact that economic studies should be based on clearly described and appropriate models. Given the relative age of this review compared with that of Walensky et al. (28) and Hornberger et al. (14), the point made by Holtgrave in regard to the modeling is both pertinent and advanced. However, it is also apparently ignored or at best misunderstood by the subsequent published studies.

The published reviews did support some of the findings of this review, such as the variance in acceptable threshold levels and the incomparability in measures of outcome.

POLICY IMPLICATIONS

National and international HIV screening policies are today informed by the results of erstwhile and current economic evaluations of screening interventions. Given the widespread devastation caused by this disease, such a finding is disappointing to say the least. It is not the objective of this study to suggest that current policies are not good value for money or that the current strategies are misplaced. However, future research must use the appropriate methods to support the vast investments made to treat this disease and to ensure resources are targeted appropriately.

Although the economic evaluations of HIV screening included in this review have unequivocally lauded the cost-effectiveness of screening, and such support may well be correct, these assertions were predominantly informed by static-model-based economic evaluations.

Thus, this review contends that, on the basis of the studies identified, the most efficient use of available resources to combat HIV may not exist in current strategies. This review presents a prominent example of situations where economic analysts apply their standard toolkit or the most current or fashionable approach to research questions which is simply inappropriate. Such examples risk jeopardizing the importance of health economics and leaving champions of the discipline poorly placed to object when economic evidence is ignored in policy making. For these reasons, this review principally maintains that health policy in the area of HIV screening should be informed by studies carried out by multi-disciplinary teams which include competence in economics, modeling and the epidemiologists who understand the natural history of the disease. Good quality economic evidence to decision makers is essential if the efficient and appropriate use of scarce resources is to be achieved.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Supplementary Table 2

www.journals.cambridge.org/thc2010022

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CONFLICT OF INTEREST

Both authors report having no potential conflicts of interest.

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