ÉCOLE DOCTORALE SCIENCES ÉCONOMIQUES, JURIDIQUES, POLITIQUES ET DE GESTION
Université Clermont Auvergne

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EFFICIENCY IN HEALTH RESOURCE ALLOCATION: THREE EMPIRICAL STUDIES IN EASTERN SUB-SAHARAN AFRICA AND SOUTHEAST ASIA

Thèse présentée et soutenue publiquement le 1er Octobre 2019

pour l'obtention du titre de Docteur en Science Economique

par

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Abbreviations

ACER	Average Cost-Effectiveness Ratio
AFR	Africa Region
ART	Antiretroviral Therapy
ARV	Antiretroviral drug
BAC+	Bacteriologically-Positive
CEA	Cost-Effectiveness Analysis
CHOICE	CHOosing Interventions that are Cost-Effective
CIS	Carcinoma In Situ
DALY	Disability-Adjusted Life Years
DST	Drug Susceptibility Test
DWs	Disability Weights
FLD	First Line Drugs
G6PD	Glucose-6-Phosphate Dehydrogenase
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GCEA	Generalized Cost Effectiveness Analysis
HER2	Human Epidermal growth factor Receptor 2
HH	Household
HIV	Human Immunodeficiency Viruses
HLYs	Healthy Life Years (DALYs averted)
HPV	Human Papillomavirus
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IHME	Institute for Health Metrics and Evaluation
IPTi	Intermittent Preventive Treatment of Infants
IPTp	Intermittent Preventive Treatment of malaria in Pregnancy
ITN	Insecticide Treated Nets
LLIN	Long Lasting Insecticidal Net
LMIC	Low and Middle-Income Countries

LTBI	Latent Tuberculosis Infection
MDGs	Millennium Development Goals
MSH	Management Sciences for Health
MTB	Mycobacterium Tuberculosis
NCDs	Noncommunicable Diseases
NMF	Non-Malaria Fevers
NTPs	National Tuberculosis Programmes
OMS	Organisation Mondiale de la Santé
PAF	Population Attributable Fraction
PMTCT	Prevention of Mother-To-Child Transmission of HIV
PrEP	Pre-Exposure Prophylaxis
PTO	Person Trade-Off
QALY	Quality-Adjusted Life Year
RDT	Rapid Diagnostic Test
RIF	Rifampicin
RTI	Road Traffic Injuries
RTS, S	RTS, S malaria vaccine
SDGs	Sustainable Development Goals
SEAR	Southeast Asia Region
SLD	Second Line Drugs
SMC	Seasonal Malaria Chemoprevention
STI	Sexually Transmitted Infections
TB	Tuberculosis
TIME	Tuberculosis Impact Model and Estimates
TTO	Time Trade-Off
UHC	Universal Health Coverage
UNICEF	the United Nations Children's Fund
VAS	Visual Analogue Scale
VIH	Virus de l'Immunodéficience Humaine
WHO	World Health Organization
XDR	Extensively Drug-Resistant tuberculosis

YLD Years Lost due to Disability

YLL Years of Life Lost

Acknowledgments

To Professor Jérôme WITTWER and Dr. Lionel PERRIER, my sincere gratitude for your availability to report on my thesis.

Dr. Martine AUDIBERT, thank you very much for your trust and for directing this thesis; and to Dr. Hapsatou TOURÉ, I am very grateful to you for agreeing to co-direct this thesis. Thank you for your constant supports.

A very special gratitude to Dr. Taghreed ADAM for all the encouragement, understanding and moreover for being the "suffragante" for my thesis.

With a special mention to Dr. Jeremy LAUER, without whom none of these researches would have been possible. Thank you very much for your trust and thank you to all the colleagues at WHO-CHOICE.

I am also grateful for my parents, sisters, brother, my cousin and friends for their moral supports throughout the period of my thesis.

Summary

Priority setting in health, in the context of Universal Health Coverage, emphasizes three values: improving population health, ensuring equity in access to and quality of services and avoiding impoverishment or underutilization of services as a result of out-of-pocket expenditures. Allocative efficiency can be measured with respect to any one of these values, or with respect to all together by different variants of Cost-Effectiveness Analysis. In this thesis, we use the Generalized Cost-Effectiveness Analysis, a standardized approach developed by the World Health Organization's programme, 'Choosing Interventions that are Cost-Effective' (WHO-CHOICE) that can be applied to all interventions in different settings. This thesis provides a quantitative assessment of allocative efficiency within three health categories: communicable diseases, noncommunicable diseases, and road traffic injuries, focusing on two economically and epidemiologically diverse regions: Eastern sub-Saharan Africa and Southeast Asia. Our objectives are to inform health policy debates, improve the world's body of knowledge on the cost-effectiveness of different interventions by providing more information on the allocative efficiency in those three disease groups and contribute to discussions on Universal Health Care packages.

Keywords: cost-effectiveness analysis, priority setting, universal health coverage, HIV, tuberculosis, malaria, breast cancer, cervical cancer, colorectal cancer, resource allocation, expansion path, impact modelling, intervention costing, road traffic injury, road safety, value for money, WHO-CHOICE

Résumé

La définition des priorités en matière de santé, dans le contexte de la couverture sanitaire universelle, met l'accent sur trois valeurs : améliorer la santé de la population, garantir l'égalité d'accès aux services et la qualité de ceux-ci et éviter l'appauvrissement des usagers ou la sous-utilisation des services par ceux-ci en raison de dépenses non remboursables. L'efficience allocative peut être mesurée par rapport à l'une quelconque de ces valeurs, ou par rapport à l'ensemble, par différentes variantes de l'analyse coût-efficacité. Dans cette thèse, nous utilisons la « Generalized Cost-Effectiveness Analysis », une approche normalisée développée par le programme « Choosing Interventions that are Cost-Effective » de l'Organisation Mondiale de la Santé, (WHO-CHOICE), qui peut être appliquée à toutes les interventions dans différents contextes. En utilisant cette approche, notre travail de thèse fournit une estimation quantitative de

l'efficience allocative des ressources pour trois groupes de problèmes de santé : les maladies transmissibles, les maladies non transmissibles, les accidents de la circulation, en mettant l'accent sur deux régions économiquement et épidémiologiquement différentes : l'Afrique subsaharienne de l'Est et l'Asie du Sud-Est. Nos objectifs étant d'éclairer les débats sur les politiques de santé, d'améliorer le corpus mondial de connaissances sur le rapport coût-efficacité de différentes interventions en fournissant davantage d'informations sur l'efficience de l'allocation de ressources pour les trois groupes de problèmes de santé précités et de contribuer aux discussions sur l'élaboration des programmes de soins de santé universels.

Mots-clés : coût-efficacité, priorités en santé, couverture sanitaire universelle, VIH, tuberculose, paludisme, cancer du sein, cancer du col utérin, cancer colorectal, allocation des ressources, trajectoire d'expansion, modélisation des impacts, évaluation des coûts, accidents de la route, , accidents de la circulation, sécurité routière, WHO-CHOICE.

Résumé substantiel

Les objectifs de développement durable traitent de la couverture sanitaire universelle dans sa cible 3.8. La couverture sanitaire universelle vise à ce que l'ensemble de la population reçoive les services de santé dont elle a besoin sans souffrir de difficultés financières. Elle préconise des politiques de financement de la santé qui veillent à ce que les droits des plus vulnérables ne soient pas négligés tout en promouvant équité, efficience et efficacité. Cependant, les ressources sont limitées et l'établissement des priorités est nécessaire pour définir les interventions pour lesquelles les bénéfices en termes de santé peuvent être les plus importants. Pour l'établissement de ces priorités, l'efficience de l'allocation des ressources en santé peut être mesurée à l'aide de différentes variantes de l'analyse coût-efficacité. Dans ce travail de thèse, nous utilisons la « Generalized Cost-Effectiveness Analysis » (GCEA), une méthode d'analyse coût-efficacité standardisée, développée par le programme de l'Organisation Mondiale de la Santé « Choosing Interventions that are Cost-Effective » (WHO-CHOICE) et qui peut être appliquée à toutes les interventions et contextes. WHO-CHOICE a été lancé en 1998 pour aider les décideurs à fixer des priorités en matière de coûts, d'effets sur la santé et de rapport coût-efficacité des interventions de santé. La GCEA sert à la définition de priorités en produisant des informations sur les interventions de santé offrant le meilleur rapport qualité-prix, aidant ainsi les décideurs à choisir les interventions et les programmes qui optimisent la santé aux vues des ressources disponibles. Ce travail de thèse vise à fournir une évaluation quantitative de l'efficience de l'allocation des ressources pour trois catégories de problèmes de santé : maladies transmissibles, maladies non transmissibles et accidents de la circulation, en mettant l'accent sur deux régions économiquement et épidémiologiquement différentes : : l'Afrique subsaharienne de l'Est et l'Asie du Sud-Est. Cette approche donne un exemple, pour chaque groupe de problème de santé, du rapport coût-efficacité d'une intervention ; nous permettant ainsi d'éclairer les débats sur les politiques de santé, d'améliorer le corpus de connaissances sur le coût-efficacité de différentes interventions en fournissant davantage d'informations sur l'efficience de l'allocation de ressources dans les trois groupes définis et de contribuer aux discussions sur les programmes de soins de santé universels.

Le chapitre I présente les fondements théoriques de la GCEA, sa méthodologie et ses possibilités d'application pour les décideurs. La plupart des analyses coût-efficacité rencontrées dans la

littérature développent une approche incrémentale, consistant à comparer le coût additionnel et l'efficacité additionnelle d'une intervention par rapport à la pratique usuelle. Cette approche comporte des limites, notamment, elle suppose une efficacité de l'intervention actuellement mise en œuvre. Elle omet ainsi l'identification d'éventuelles mauvaises allocations de ressources, qui autrement allouées, auraient pu générer un bénéfice substantiel en termes de santé. Elle présente le risque de pénaliser l'évaluation d'autres interventions en raison des failles déjà préexistantes au niveau du système de santé. Elle peut être hautement contextualisée, son point de départ étant le contexte actuel dans lequel elle est développée ce qui peut limiter sa généralisation à d'autres contextes. La GCEA a été développée et conceptualisée afin de surmonter ces limites. Elle utilise un comparateur commun, un scénario dans lequel tous les impacts des interventions actuellement mises en œuvre sont supprimés. Ce comparateur commun est appelé scénario « nul » et son utilisation par la GCEA présente deux avantages principaux. Premièrement, l'utilisation du scénario « nul » comme hypothèse contrefactuelle permet à la GCEA d'évaluer l'efficacité des interventions actuellement mises en œuvre. Évaluer les inefficiences d'allocation actuelles peut générer des bénéfices significatifs pour la santé, potentiellement plus que la simple identification d'une nouvelle intervention produisant des avantages comparativement moindres pour la santé. Deuxièmement, en supprimant les impacts de l'intervention actuelle, les résultats de la GCEA sont de facto transférables vers d'autres contextes. La GCEA peut constituer une approche forte de l'analyse coût-efficacité dans la mesure où elle n'est pas contrainte par ce qui se fait dans la pratique usuelle, mais pourrait aider à revoir et éventuellement à réviser les choix antérieurs, en donnant aux responsables politiques une base rationnelle s'ils décident d'une réaffectation des ressources vers des interventions plus coût-efficaces. Cette approche généralisée fournira des informations opportunes, accessibles et utiles sur l'efficacité des interventions et peut ainsi éclairer les débats sectoriels sur l'affectation des ressources, pouvant ainsi grandement contribuer à la formulation des politiques de santé.

Dans la GCEA, les coûts sont mesurés du point de vue des systèmes de santé — essentiellement toutes les organisations, personnes et actions ayant pour objectif premier de promouvoir, rétablir ou maintenir la santé, quel que soit le payeur (privé ou public). L'évaluation des coûts suppose une capacité constante des systèmes de santé. Cela garantit que les variations de coût-efficacité résultent de différences réelles dans les coûts et les effets des interventions comparées plutôt que d'une mauvaise mise en œuvre ou de l'échec des systèmes de santé. Les coûts sont classés en coûts

liés aux patients, coûts du programme et, le cas échéant, complétés par les coûts liés aux fonctionnements du système de santé. Les coûts liés aux patients sont généralement associés à la prestation de soins curatifs, mais peuvent également inclure certains types d'activités éducatives et de prévention pour la santé. Une approche par ingrédient est utilisée pour mesurer les coûts de chaque intervention. Les coûts du programme sont les coûts nécessaires au développement et à la maintenance de l'intervention de santé en dehors du point de prestation, telle que la formation. Les coûts liés aux fonctionnements du système de santé sont des coûts partagés, telle que la chaîne d'approvisionnement. L'effet sur la santé est mesuré en terme d'Année de Vie Corrigée du facteur d'Invalidité, rapportées dans WHO-CHOICE sous l'acronyme «HLY gained». Les interventions sont incluses dans l'analyse, qu'il s'agisse de recommandations de l'OMS, d'interventions fondées sur les meilleures pratiques ou de programmes d'interventions couramment utilisés sur la période étudiée. L'exclusion d'une intervention n'implique pas qu'elle ne soit pas coût-efficace, mais simplement que l'analyse effectuée n'est pas exhaustive. Les interventions sont analysées individuellement ou en combinaison. L'intervention de santé étudiée peut être préventive, promotionnelle, curative, de réadaptation ou palliative.

Le chapitre II explore l'utilisation de l'approche GCEA pour fournir une évaluation de la performance des systèmes de santé au cours de la première décennie du 21e siècle (2000-2010) en ce qui concerne l'efficacité de l'allocation des ressources sur le VIH, la tuberculose et le paludisme. Il examine le rapport coût-efficacité de quelques interventions sélectionnées notamment sept scénarios pour le paludisme à *P. vivax*, 14 pour le paludisme à *P. falciparum*, 12 pour le VIH et 10 pour la tuberculose, ces interventions sont analysées à 50%, 80% et 95% en termes de couverture de la population ; ainsi que l'ensemble des interventions couramment utilisées au cours de cette période. Ce faisant, notre étude met en lumière l'élaboration et la mise en œuvre de programmes dans ces domaines prioritaires. Afin de calculer l'impact sur la population des différents scénarios d'intervention, les simulations pour le paludisme à *P. falciparum* et à *P. vivax* ont été réalisées à l'aide de la plate-forme OpenMalaria, un programme C ++ open source pour la micro-simulation de l'épidémiologie du paludisme et des impacts des interventions sur la charge mondiale de cette maladie. PopMod, un programme de modélisation de la population développé par WHO-CHOICE, a été utilisé pour combiner les données projetées d'incidence des cas, d'élimination des parasites et les données de mortalité avec les évaluations de l'état de santé. Les simulations pour le VIH ont été réalisées avec le modèle Goals, un modèle compartimental

dynamique développé dans la suite de modèles open source Spectrum. Ce modèle est largement utilisé pour produire des projections des tendances épidémiques ainsi que des projections de l'impact des interventions. Il a été utilisé dans de nombreuses régions, en particulier dans les régions d'Afrique australe et orientale, pour étudier le coût et l'impact des stratégies nationales et autres sur le VIH. Goals simule la transmission du VIH et ses conséquences sur la morbidité et la mortalité chez les populations adultes âgées de 15 à 49 ans. Les simulations pour la tuberculose ont été réalisées avec le « Tuberculosis Impact Model and Estimates » (TIME), un modèle compartimental dynamique développé également dans la suite de modèles open source Spectrum. Ce modèle a été utilisé dans la plupart des contextes de tuberculose, y compris dans les pays où la tuberculose est une maladie opportuniste du VIH, dans des systèmes de santé peu performants, dans les pays à forte charge de tuberculose multirésistante et dans les pays où les programmes de lutte antituberculeuse reposent sur une forte implication du secteur privé. Le programme mondial de lutte contre la tuberculose a utilisé TIME pour produire des estimations de la charge que représentent le VIH et la tuberculose dans le rapport mondial sur la tuberculose. Le modèle TIME reflète les principaux aspects de l'histoire naturelle de la tuberculose, notamment l'infection primaire et latente, la réinfection et la réactivation de la tuberculose latente. La plupart des interventions incluses dans notre étude présentaient un rapport coût-efficacité virtuel inférieur à 100 I$/ HLY. Les interventions les plus rentables étaient les suivantes: les interventions ciblant les travailleuses du sexe (en Asie du Sud-Est) et la circoncision médicale masculine volontaire (en Afrique subsaharienne de l'Est) à 95% de couverture pour le VIH; les soins et contrôle de base (traitement + détection + test de sensibilité aux médicaments) à 50% de couverture pour la tuberculose dans les deux régions; la prise en charge des cas graves de paludisme à P. vivax en Asie du Sud-Est ainsi que du paludisme à P. falciparum en Afrique subsaharienne de l'Est. En outre, l'analyse des interventions couramment mises en œuvre par rapport à la trajectoire d'expansion des interventions coût-efficaces sur cette période permet de conclure à une bonne performance de la communauté mondiale en ce qui concerne ces maladies transmissibles au cours de la première décennie du 21e siècle. Le rôle de l'assistance internationale, financière et technique, a sans doute été essentiel à ces réalisations. Si nous nous référons, par exemple, au dernier rapport mondial de l'OMS sur le financement de la santé, 46% des fonds extérieurs alloués à la santé et 20% des dépenses de santé des gouvernements nationaux allaient à la lutte contre le VIH / sida, paludisme et tuberculose.

Le chapitre III illustre l'utilisation de la GCEA pour calculer le rapport coût-efficacité des interventions contre le cancer du sein, le cancer du col utérin et le cancer colorectal. Alors que la communauté mondiale s'achemine vers la couverture sanitaire universelle, le but de notre étude était de présenter des résultats d'analyses identifiant comment les décideurs peuvent optimiser les bénéfices pour la santé en utilisant les interventions anticancéreuses énumérées à l'annexe 3 du Plan d'action mondial pour la prévention et la lutte contre les maladies non transmissibles 2013-2020. Les interventions incluses dans notre analyse sont basées sur les directives de l'OMS. Ces directives mettent l'accent sur la lutte globale contre le cancer, incluant le diagnostic, la stadification, le traitement multimodal, les soins aux survivants et les soins palliatifs. L'impact pour la santé a été estimé à l'aide d'une simulation déterministe de cohorte à transition d'état (modèle de Markov). Dans ce type de simulation, les stades sains et les stades pathologiques, répartis par âge, sont modélisés comme les états exhaustifs et mutuellement exclusifs d'un modèle de Markov, c'est-à-dire que, à tout moment transversal dans le temps, toutes les personnes de la population appartiennent à un seul et même état. Nos résultats ont démontré que la vaccination contre le papillomavirus humain (deux doses) chez les filles âgées de 9 à 13 ans combinée à la prévention du cancer du col utérin par le dépistage des femmes âgées de 30 à 49 ans au moyen d'une inspection visuelle à l'acide acétique associée à un traitement rapide des lésions précancéreuses en Asie du Sud-Est et la vaccination contre le papillomavirus humain (deux doses) chez les filles âgées de 9 à 13 ans dans l'Est de l'Afrique subsaharienne ont été les interventions les plus coût-efficaces. Pour le cancer du sein, dans les deux régions, le traitement du cancer du sein de stades I et II par chirurgie ± traitement systémique à une couverture de 95% s'est révélé l'intervention la plus coût-efficace. Pour le cancer colorectal, l'intervention la plus coût-efficace était le traitement du cancer colorectal de stade I et II avec une chirurgie ± chimiothérapie et une radiothérapie à une couverture de 95%. Notre étude présente quatre conclusions principales: les interventions de prévention et de contrôle du cancer sont coût-efficaces et peuvent considérablement réduire le fardeau de la maladie dans le monde; une approche progressive dans la mise en œuvre en suivant une trajectoire d'expansion des interventions coût-efficaces peut être utilisée; les interventions sur les cancers à un stade précoce sont généralement plus rentables que celles pour les cancers à un stade avancé; et les programmes de soins palliatifs, considérés comme un droit humain à la santé et recommandés par l'Assemblée mondiale de la Santé, peuvent être mis en œuvre à un coût généralement faible.

Enfin, dans le but d'améliorer la réponse aux accidents de la circulation, le chapitre IV vise à examiner le rapport coût-efficacité d'interventions préventives éprouvées utilisant l'approche GCEA. La Décennie d'action pour la sécurité routière des Nations-Unies a accordé une attention accrue aux accidents de la circulation. La sécurité routière est désormais explicitement traitée dans les objectifs de développement durable 3.6 et 11.2. Notre étude présente des estimations actualisées du rapport coût-efficacité de stratégies que les pays peuvent utiliser pour faire face à la charge mondiale des accidents de la circulation. Notre analyse évalue 13 interventions individuelles et combinées. Elles sont extraites des recommandations du rapport mondial sur la prévention des accidents de la circulation et portent principalement sur les mesures de sécurité routière préalables à l'événement, ciblant les changements de comportement humain, en raison de la disponibilité de données robustes sur leur efficacité et leur faisabilité. Comme dans la précédente analyse WHO-CHOICE, un système dynamique modélisé avec une matrice de Haddon a été utilisé comme cadre de référence pour identifier les facteurs qui ont un impact sur les accidents de la circulation. Un modèle de population multi-états (PopMod) a été utilisé pour estimer les scénarios. Notre étude a montré que, pour prévenir les accidents de la circulation, la combinaison d'interventions individuelles appliquant simultanément de multiples mesures de sécurité routière s'était révélée être le scénario le plus rentable. La législation sur la conduite en état d'ivresse et son application via des tests d'haleine aléatoires des conducteurs aux points de contrôle routiers (en Asie du Sud-Est) et l'application de limitations de vitesse via des caméras mobiles / portables (en Afrique subsaharienne de l'Est) à 80% de couverture étaient les interventions individuelles les plus rentables. Les interventions incluses dans notre étude sont conformes au paquet technique proposé par Save-LIVES publié par l'OMS. Notre analyse permet de conclure que les interventions visant à améliorer la sécurité routière sont coût-efficaces par rapport aux autres mesures de santé publique.

Comme indiqué plus haut, l'utilisation de l'analyse coût-efficacité pour évaluer l'efficience de l'allocation de ressources peut évoluer vers des analyses contextualisées ou des évaluations plus généralisées. La démarche préconisée par la GCEA est de se concentrer sur l'évaluation générale des coûts et des effets sur la santé de différentes interventions. Pour la définition des priorités en matière de santé, les informations coût-efficacité doivent être collectées de manière à permettre aux décideurs d'atteindre le maximum de résultats avec les ressources disponibles et de déterminer le meilleur moyen d'utiliser les ressources supplémentaires si elles deviennent disponibles. Comme

on peut voir ci-dessus, la GCEA fournit des estimations précieuses du rapport qualité-prix des interventions de santé. Elle met l'accent sur l'amélioration de la santé résultant de différents choix quant à la manière d'utiliser les ressources de santé. Cependant, l'amélioration de la santé n'est qu'un objectif du système de santé. Par conséquent, les résultats de la GCEA ne doivent pas être utilisés comme une formule toute faite. Ces résultats doivent entrer dans le débat politique comme étant uniquement un apport parmi d'autres et les décideurs doivent évaluer le compromis entre les coûts de la modification de la combinaison d'interventions courantes et l'impact de différentes combinaisons par rapport aux autres objectifs du système de santé. Ils doivent être pris en compte à côté d'autres facteurs allant au-delà de l'efficacité, tels que l'accessibilité financière, la capacité de mise en œuvre, la faisabilité, l'impact budgétaire et l'équité. Un défi possible à l'approche de la GCEA consisterait à distinguer les inefficiences techniques dans la mise en œuvre d'une intervention donnée de l'inefficience allocative. Nos études traitent de cette question en supposant que les systèmes de santé ont une capacité constante, ce qui garantit que les variations de coût-efficacité résultent de différences réelles de coûts et d'effets des interventions comparées plutôt que d'une mauvaise mise en œuvre ou des échecs du système de santé. Un deuxième défi est la question de savoir comment gérer les coûts supplémentaires liés à la modification des stratégies (par exemple, les coûts de transition) qui peuvent être traités à l'aide de la trajectoire d'expansion programmatique présentée au chapitre II.

Introduction

The achievement of Universal Health Coverage (UHC) is addressed by the Sustainable Development Goals (SDG) in its 3.8 target [1]. UHC has been defined as all individuals and communities receiving the health services they need without suffering financial hardship [2]. It advocates for health funding policies to ensure that the rights of the most vulnerable are not forgotten ('no one is left behind'), to promote equity, efficiency and effectiveness [3]. However, resources are finite and priority setting is required to define areas of action where the greatest health gains can be achieved.

Priority setting in health, in the context of UHC, emphasizes three values: improving population health, ensuring equity in access to and quality of services and avoiding impoverishment or underutilization of services as a result of out-of-pocket expenditures. Allocative efficiency[1] can be measured with respect to any one of these values, or with respect to all together by different variants of Cost-Effectiveness Analysis (CEA). In this thesis, we use the Generalized Cost-Effectiveness Analysis (GCEA), a standardized approach developed by the World Health Organization's programme, 'Choosing Interventions that are Cost-Effective' (WHO-CHOICE) that can be applied to all interventions in different settings. WHO-CHOICE was launched in 1998 to help policymakers set priorities with regards to costs, effects and cost-effectiveness of health interventions [4]. GCEA serves priority setting by producing information on health interventions that provide the highest 'value for money' and helps policy makers choose the interventions and programmes, that maximize health for the available resources.

This thesis aims to provide a quantitative assessment of allocative efficiency within the three health categories: communicable diseases, noncommunicable diseases (NCDs), and road traffic injuries (RTIs), focusing on two economically and epidemiologically diverse regions: Eastern sub-Saharan Africa and Southeast Asia. This approach will give us examples of the cost-effectiveness of a common technology set in diverse settings to provide a generalized league table of the cost-effectiveness of interventions for each disease group. The objectives, therefore, are to inform health policy debates, improve the world's body of knowledge on the cost-effectiveness of

[1] Allocative efficiency refers to the optimal choice of interventions' combination to maximize the health of the population, given the level of resources while technical efficiency alludes to the ability to produce given outputs at the most reduced conceivable cost [5].

different interventions by providing more information on the allocative efficiency in those three disease groups and contribute to discussions on Universal Health Care packages.

The thesis chapters are organized as follows:

Chapter I presents the GCEA to provide an understanding of the approach used throughout the thesis, its theoretical foundation, methodology and application for policy makers.

Chapter II explores the use of the GCEA approach to provide an assessment of the performance of global health systems in the first decade of the 21st century (2000-2010) regarding the allocative efficiency of HIV, tuberculosis and malaria. It examines the cost-effectiveness of selected optimal interventions and commonly used intervention packages over this period. In doing so, this study shines a spotlight on the development and implementation of programs in these priority areas.

Chapter III illustrates the use of the GCEA to calculate the cost-effectiveness results for breast cancer, cervical cancer, and colorectal cancer. The purpose of this study was to present results of analyses that identify how decision-makers can achieve maximum health gain using the cancer interventions listed in Appendix 3 of the Global Action Plan for the Prevention and Control of NCDs 2013–2020.

Chapter IV presents updated estimates of the cost-effectiveness of evidence-based, practical strategies that countries can use to address the burden of RTIs. Road safety has been receiving increased attention through the United Nations Decade of Action on Road Safety and is now explicitly addressed in Sustainable Development Goals 3.6 and 11.2. In an effort to enhance the response to RTIs, this study aims to examine the cost-effectiveness of proven preventive interventions using the GCEA approach.

Chapter I: Generalized Cost-Effectiveness Analysis (GCEA)

Generalized Cost-Effectiveness Analysis (GCEA) has been discussed in depth in other literature [5], [6], [7]. This chapter aims only to give an overview on GCEA that pertains to the present thesis, to provide in-hand information on this approach's concepts and benefits.

Concept and theoretical foundation

Numerous guides have been developed throughout the years that recommend CEA to aid decision when allocating scarce resources to health interventions [8], [9], [10], [5], [11], [12]. A CEA evaluates the costs and health effects of a specific health intervention to assess its allocative efficiency regarding the maximization of population health status given a budget constraint. In economic theory, CEA is founded on the belief that health adds to social welfare independently to the consumption of services and non-health goods [5]. CEA in health can be embedded into what is called the Decision Maker's Approach, a theoretical framework that aims to optimize health benefits from a given budget [13]. In this approach, CEA results are intended to inform decision-makers rather than prescribe decisions to be made or strictly prioritize interventions.

Most CEA studies in the literature pursue an incremental approach, where they compare the additional cost of an intervention over current practice with additional benefits. Limitations of such an approach have been discussed elsewhere [6], but two will be recounted here. First, the incremental approach in CEA assumes the efficiency of the intervention currently being implemented, failing to identify existing possible misallocation of resources that could have resulted in a substantial health gain and penalizing other interventions assessment by the possible current health system inefficiency. Second, such study is highly contextualised as its starting point is the current setting in which it is developed; the cost and time involved as well as the possible complexity of the resource allocation models will limit their practical use and generalizability.

GCEA has been developed and conceptualized to overcome those limitations by using a common comparator, a scenario where all the impacts of currently implemented interventions are removed. This common comparator is referred to as the 'null' scenario, and its use by the GCEA presents two main advantages. First, using the 'null' as counterfactual allows the GCEA to evaluate the efficiency of currently implemented interventions. Assessing current allocative inefficiencies may yield significant health gains, potentially more than identifying new intervention that will give smaller benefits in health. Second, by removing the current intervention constraint, the results of

the GCEA will be transferable to other settings. This generalized approach will provide valuable, opportune, affordable and useful information on the efficiency of health interventions to enlighten sectoral debates on resource allocation, which can make a great contribution to health policy formulation.

The 'null' scenario

As with any CEA, the interventions studied must be evaluated against a counterfactual scenario. For GCEA, this common comparator is the 'null' or the scenario of doing nothing. This scenario does not assume that none of the past interventions has ever been undertaken; it depicts what will happen if the interventions currently implemented cease as of today. Consequently, the 'null' represents a transition of the epidemiological profile of disease over time, not a stable epidemiological situation. In addition, the 'null' scenario does not assume that all currently implemented interventions are suppressed, but only those that may affect the disease of interest; for example, for the study on cancer, current interventions on malaria have not been removed.

A back-adjusting approach [5] is applied to measure the impact of the 'null', using the epidemiological information of the interventions currently implemented, their effectiveness and their coverage rates. To do so, the following formulas derived from [5] are used depending on the number of current interventions:

- For a single intervention:

$$\lambda_N = \frac{\lambda_C}{1 - c.e}$$

where

λ_N: null hazard rate (e.g. incidence, remission, case-fatality or disability weight…)

λ_c= current hazard rate

c= current coverage of intervention

e= current effectiveness of the intervention

- For multiple interventions which address the same outcome:

$$\lambda_N = \frac{\lambda_C}{(1 - c_1.e_1) * (1 - c_2.e_2) * \ldots * (1 - c_n.e_n)}$$

Epidemiological information or hazard used depend on the nature of the interventions to remove (e.g. preventive interventions affect the incidence of diseases, curative interventions affect the remission or case fatality rates, rehabilitative and palliative interventions affect the severity).

For communicable diseases, as we will see in the following paper on HIV, tuberculosis and malaria, we use dynamic models; rates are therefore modelled until equilibrium is reached because the effect is not instantaneous.

The time horizon

The choice and influence of time horizon in CEA have been widely discussed in the literature [9], [10], [14], [15]. The time horizon is the duration over which the costs and effects of the interventions studied are measured. The time horizon is identical for all compared interventions. Infectious disease models often apply a long period of implementation to capture changes in disease incidence and transmission dynamics over time following the introduction of the intervention [16]. A long time horizon is needed to fully capture the health impacts associated with preventive interventions, therefore allowing a meaningful comparison with therapeutic and curative interventions; for example, simulating 100-year vaccination intervention is not uncommon [17]. This is even more usual in the economic evaluation of noncommunicable diseases, where conditions are frequently chronic and medications are taken daily until death. As a result, to capture all the costs and effects related to an intervention, the use of a life horizon is much more progressively regular in economic evaluation. The same practice is adopted with GCEA; health effects of the null and interventions are measured over the lifetime of the individuals currently alive, which has been pragmatically defined as 100 years. The same duration is adopted for the costs. This duration allows the GCEA study to capture one generation.

Methodology

Interventions

In economic evaluation, when the defining purpose of an intervention is to improve health, we consider it a 'health intervention' [18]. More precisely, the International Classification of Health Interventions (ICHI) of the WHO defines the health intervention as an 'act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions' [16]. A health intervention can be preventive, promotive, curative, rehabilitative or palliative.

Interventions are included in the analysis whether they are recommendations by WHO or by control experts, best-practice interventions or commonly used intervention packages over a specific period of interest. Exclusion of an intervention does not imply that it is cost-ineffective, but simply that the analysis undertaken is not exhaustive. Interventions are analysed individually or in combination. For each combination, the independence or mutual exclusivity of the combined interventions is considered. Interventions are independent when they can be implemented in the same package, with or without interactions of costs and effects. Conversely, interventions are mutually exclusive when they must replace one another [19].

Interventions costs

The perspective is the point of view adopted to decide which types of costs should be included in the economic evaluation. In GCEA, costs are measured from the perspective of health systems - essentially all organizations, people and actions whose primary intent is to promote, restore or maintain health [20], regardless of the payer (private or public). A constant capacity of the health systems is assumed in the costs evaluation. This ensures that variations in cost-effectiveness result from genuine differences in the costs and effects of the interventions being compared rather than poor implementation or failure of health systems.

An ingredients approach is used to measure the costs of each intervention. In this approach, the quantities of all resources required to deliver the intervention (Q) are multiplied by their unit prices (P).

$$C = Q\ X\ P$$

In its costs valuation, GCEA includes all direct, market-valued costs necessary to provide the health intervention. The costs measured represent the opportunity costs as defined in economics in the sense that the costs represent the value foregone by not using the same resources for something else. However, this excludes all non-monetary patient contributions (e.g. travel time) and potential earnings of patients. In theory, travel time and any other time costs incurred that the patient incurs, related to seeking the intervention, represent an opportunity cost as this time cannot be used to produce consumption in other areas; a similar argument applies to potential earnings as it affects the consumption of services and goods, but both are excluded here on ethical grounds. Their inclusion would prioritize extending the lives of the rich who earn more over the poor [5], [21], [19]. GCEA also excludes costs outside of the health system.

Costs are estimated at different coverage levels for each intervention or combination of interventions, assuming that interventions are first provided to an easy-to-reach population before scaling up to marginal and meagrely populated areas. Combinations of interventions costs are analysed considering any interactions in costs or cost offsets [5].

There are numerous ways of classifying costs. In GCEA, the costs are classified into patient costs and programme costs and, where applicable, supplemented by health system costs [22], [23], [19]. Patient costs are the costs directly related to individual intervention delivery or incurred at the point of delivery. They are usually associated with the provision of curative care but may also include certain types of educational activities for health and prevention. Programme costs are the costs required for the development and maintenance of the health intervention outside of the point of delivery, such as training. Health system costs are shared costs related to health system functions, such as supply chain. Depending on the type of intervention, the cost-driver may differ, with the intervention aimed at behaviour-change in health requiring more programme than patient costs. Table 1 provides a summary of the type of costs that can be included in each classification, derived from [22], [23].

Table 1: Patient costs, programme costs and health system costs

Costs classification	Inputs
Patient costs	Medicines, diagnostic tests, other consumables
	Behaviour change communication
	Health facility visit unit costs, incorporating health systems costs
Programme costs	Personnel
	Materials and supplies
	Media operating costs
	Transport operating costs
	Equipment operating costs
	Maintenance
	Utilities (e.g. electricity, gas, water)
Health system costs	Supply chain

For patient costs, quantity estimates (Q) are drawn from those used in previous WHO-CHOICE analyses, other published costs or cost-effectiveness studies if quantity details are available or estimated from WHO guidelines for treatment and surveillance after treatment. The quantity results are validated in consultation with experts in the field of the diseases studied. The prices (P) for each input, such as drugs and diagnostic tests, are taken from different sources such as the Management Sciences for Health (MSH) drug price database [24] and in consultation with costing experts. Inpatient and outpatient care or service delivery unit costs, are standardized estimates produced and available at WHO-CHOICE [4]; details on the multivariate regression analysis performed using STATA[2] are available in [25].

For programme costs, full details on the quantity assumptions, price statistical analysis and econometric modelling are published in [19], [26]; estimates are available with WHO-CHOICE. Quantity assumptions are standardized while prices are provided at the level of WHO region [27] and countries. To account for economies of scale and scope, programme costs are scaled by number of interventions and level of coverage. Health system costs like supply chain costs are

[2] STATA is a complete, integrated software package that allows data manipulation, visualization, statistics, and reproducible reporting [80].

theoretically not covered under programme costs in GCEA but applied as a mark-up ratio in the costing process [22].

For transferability across settings, costs are reported in international dollars to account for differences in purchasing power and, where necessary, adjusted over time using the Gross Domestic Product (GDP) price index [28]

Interventions health effects

The denominator of the cost-effectiveness ratio needs to be estimated using an outcome indicator that measures changes in health considering both fatal and non-fatal outcomes. In GCEA, this health outcome is measured using the Disability-Adjusted Life Years (DALY) [29], [30], reported in WHO-CHOICE with the acronym 'HLY gained'.

DALY was first developed during the five-year Global Burden of Disease (GBD) study started in 1988- a joint study between the World Bank, WHO and Harvard School of Public Health [31], [32]. This study aimed to quantify the burden of disease and injury in human populations and define the major health challenges globally through a measure that can also be used for CEA. A preliminary form of DALY was presented and explained in the World Development Report, 1993 [33] which presented estimates of burden of disease and cost-effectiveness of interventions using DALYs as outcome measure, to help set priorities for health spending. Since then, DALY has been refined and used regularly to report on the global burden of disease [34], plan for health research and development and as a measure of the outcome on the CEA, as in the chapters of this thesis.

DALYs introduction in priority setting for health was intended to broaden the scope of measuring diseases in terms of mortality to include an estimate of the impact of morbidity and to make more transparent the ethical dimensions of the quantification of health [35], [36]. The DALYs framework is founded on the combination of two egalitarian principles. First, that the burden calculated for like health outcomes should be the same, i.e. treating like health outcomes as like. This appeals to the most notional concept of fairness in the sense that the contribution of a 30-year-old woman's premature death to the estimation of the disease burden should be the same whether she lives in a rich suburb of New York or in the favelas of Brazil. Second, that the non-health characteristics of the individual affected by a health outcome to be taken into account in

measuring the associated disease burden should be limited to age and sex, those characteristics having the same significance worldwide [35], [37], [36].

Briefly reporting on the comparison of DALYs with other aggregate social measures in the literature, DALY does not indicate the total sum of individual utility lost due to ill health, as the quality-adjusted life year (QALY), for example, would do [35]. Health-related utility includes a more extensive scope of wellbeing that extends beyond the focus on health looked for in DALY. Health, as defined in DALYs, interacts with these other dimensions but can be conceptualized as being distinct from them [5] [38]. DALYs seems to be closer to a measure of health 'capabilities' or 'functioning' using the language developed in [39]. In DALYs, health can be seen as a basic means to achieve well-being, isolating the health problem from any other problem. DALYs measure health and do not incorporate the welfare associated with any income-enhancing properties of an intervention. The concept of DALYs avoids any notion of being satisfied with one's health. Rather, it looks to measure health by the level of hardship experienced by a person in being able to use one's own body [35].

In the DALY concept, any individual is brought into the world with a certain number of life years potentially lived in optimal health. Individuals may lose these healthy life years by dying prematurely or living in health states worse than optimal health. The DALYs metric represent these losses in healthy life years. One lost year of healthy life is equivalent to one DALY.

DALYs corresponding to a disease or health condition are computed as the sum of the Years of Life Lost (YLL) due to premature mortality in the population and Years Lost due to Disability (YLD) for people living with the health condition or its consequence [29].

$$DALY = YLL + YLD$$

DALY as estimated for the GBD studies is a measure of loss whilst it represents a gain measurement in GCEA. To emphasize the refinement between the DALY measure used in GBD and that applied in GCEA, the terminology 'Healthy Life Year' (HLY) gained is used for GCEA.

YLL is a function of the duration of life lost due to a death at each age and the mortality rate. For its calculation, an estimation of how long people should live must be defined. In the GBD study, an expectation of life at each age based on some ideal standard is used, e.g. for GBD 2010, a

synthetic life table constructed from the lowest currently observed mortality rates at each age. In GCEA, the reasoning is different; the need is to measure the YLLs gained by the intervention, which represents the difference of the value of this measure with and without the intervention. Practical examples to illustrate the rationale for this measure can be found in [5] and [40].

YLD is conceptualized as the partial loss of healthy years due to living in a health state worse than optimal health, weighted by the health state severity. While death is not difficult to define, the severity of non-fatal health outcome on one individual is. This severity differs from one individual to another and depends on one's personal characteristics and environment. The 'valuation' of this severity is termed health state valuation or disability weight. It can be estimated using various methods, such as the time trade-off (TTO)[3], person trade-off (PTO)[4], visual analogue scale (VAS)[5] and pairwise comparison[6]. For instance, in the GBD 2010, the disability weights were measured using household surveys conducted in five countries[7] and an open-access survey; the disability weights were then estimated based on paired comparisons of sequelae depicted with brief labels [30]. The severity weight used does not suggest any societal estimation of the value of a person in a disability or health condition, nor does it imply an interpretation of the lived experience of any disability or health. It measures a social inclination for a health state in connection to the societal 'ideal' of good health [5]. In addition to the severity weight, the YLD is also a function of the incidence or prevalence of the disease or health state [30], [29]. In the GBD study, a weight between 0 and 1 is assigned to years lived in health states worse than optimal health, with 0 representing full health. Conversely, the values used in GCEA are the complements of the weight used in the GBD (i.e. 1-health decrement) with 0 representing death and 1, full health.

PopMod [41] and Spectrum [42] population models are used to project and capture the effect of each intervention on the aggregate number of healthy years lived by a population, combining the prevalence, incidence, mortality, severity weight and information on coverage, as well as

[3] TTO: Participants are asked to imagine themselves living in an imperfect health state for a defined number of years. The participants should then indicate how many years in the current health state they would be willing to 'trade off' so as to regain full health [81].
[4] PTO: Participants are asked to trade quality and quantity of life in a hypothetical cohort of disabled and healthy individuals to determine the worth of the disability [31], [82].
[5] VAS: Participants are asked to consider the consequences of living with a disease or a condition for a given duration and scale its severity [83].
[6] Pairwise comparison: Participants are asked to decide who is healthier between two hypothetical individuals in different health conditions [30] [84].
[7] Bangladesh, Indonesia, Peru, United Republic of Tanzania and the United States of America

effectiveness of the intervention. In those population models, people are allowed to move in and out of health states as per the incidence, remission and case-fatality rates. The time spent in each health state is assigned a severity weight using the disability weight from the GBD, as previously indicated. Meta-analyses on effect sizes were used to estimate the magnitude of the effect on disease rates and, if not possible, randomized studies or before/after programme evaluation.

Discounting

In simple terms, to discount is to convert a future value to its present value. One tends to value future costs and effects less than current ones; the farther in the future the costs and effects occur, the lower their value. This underlines the need to adjust the value of the costs and effects for the time at which they occur in economic evaluation. Generally, costs and effects of a health intervention materialize over the time they occur (e.g. a human papillomavirus (HPV) vaccination intervention). However, discounting future costs and health effects of a health intervention can affect their economic evaluation outcome. A growing body of literature has discussed the appropriate discounting rules to apply [43], [44], [45], [46], [47].

Discounting costs may be justified through various uncontroversial reasons [5], [43].

- Opportunity costs – which, as explained earlier, reflect the value foregone by not using the same resources for something else. For example, instead of being spent on the health intervention, the resource could have been invested in another sector of the economy, which would have generated a positive rate of return [48].
- Catastrophic risk – people or society consider that they may not be alive to benefit from future consumption, as well as the likelihood of catastrophe.
- Pure rate of time preference – people or society prefer consumption now to future consumption.
- Consumption growth – if income increase is expected, any increase in consumption has more value now than in the future.

Discounting health effects, however, is one of the controversial topics that emerges from the literature, as health intervention effects are not reported in monetary units. One argument is that if healthcare resources are being discounted, so should health effects, inferring that healthcare resources are ultimately transformed into health [43], [49]. Conversely, ‘health is a unique product

that cannot be traded in overtime, and therefore cannot be invested elsewhere at a real rate of return'– is one of the counter-arguments [50], [43].

The second controversial topic is whether to use an equal or differential rate between health intervention effects and costs. Discounting costs and effects of health interventions at the same rate has been the dominant practice for quite a while and still is [43], [12], [5]. This approach has been supported by two influential justifications. First, the time paradox of Keeler and Cretin [51] arguing that if lower rates for the health intervention effects were used rather than an equal discount rates for the costs and effects of health interventions, decision-makers would indefinitely postpone all health expenditures because the cost-effectiveness ratio of a health intervention would increase with each year it is postponed. Second, the consistency argument of Weinstein and Stason [52] which illustrates that two programs that are identical except in timing must have their costs and effects discounted at the same rate to receive equal priority in decision-making. In the meantime, other publications support the opposite view, namely the concept of differential discounting [53], [54], [55], [46].

Additional to the previous topics, further approaches such as the height of the discount rate [48], [53], [49], [56], [57] and the use of constant or hyperbolic discounting remain a matter of debate in the economic evaluation literature with those in support of constant discounting [58], [59] and against it [60], [61].

For GCEA, results are presented under two scenarios: One applying a differential discount rate, with a zero-discount rate for health intervention effects and a discount rate of 3% [5] for costs, and an alternative scenario with an equal discount rate of 3% [5] for health intervention effects and costs. This will allow for the results to be understood under the two perspectives and will also serve as a sensitivity analysis of the results.

Threshold

In the CEA, the threshold is a standard used to identify the health intervention that, in a given setting, has relatively poor, good or very good value for money. Alongside other considerations relevant to local setting, the threshold can be used as an indication to guide policy makers in their decision making [22].

The conceptual perspectives, methodologies, and general use of thresholds have been largely debated in the economic evaluation literature [62], [63]. Among the arguments common to those who have welcomed a threshold in a CEA is its practicality as an approximation to improve efficiency and that it allows for better transparency and consistency in the decision-making process [64]. The counter-argument claims a lack of empirical and theoretical basis of the recommended thresholds [65], [63]. Of the latter, the most commonly cited are those based upon a country's per capita GDP and the Commission on Macroeconomics and Health's corresponding estimate of the economic value of a year of healthy life [66]. GDP-based thresholds were criticized, because 'people value life in dimensions that extend beyond income' [22], [67].

In its previous analysis, WHO-CHOICE has used the Commission on Macroeconomics and Health's GDP-based thresholds to comment on its CEA results [68]. However, a publication in 2016 [22] clarified WHO-CHOICE's intention to express the results as they were in [68], i.e. only to guide policy-makers on value for money, emphasized the necessity to not use a threshold as a stand-alone criterion for decision-making, recommended against the indiscriminate use of the most common threshold, i.e. three times the per capita GDP per DALY averted, and explained the role of CEA results in the decision-making process. Henceforth, GCEA results are no longer presented as per GDP capita groupings.

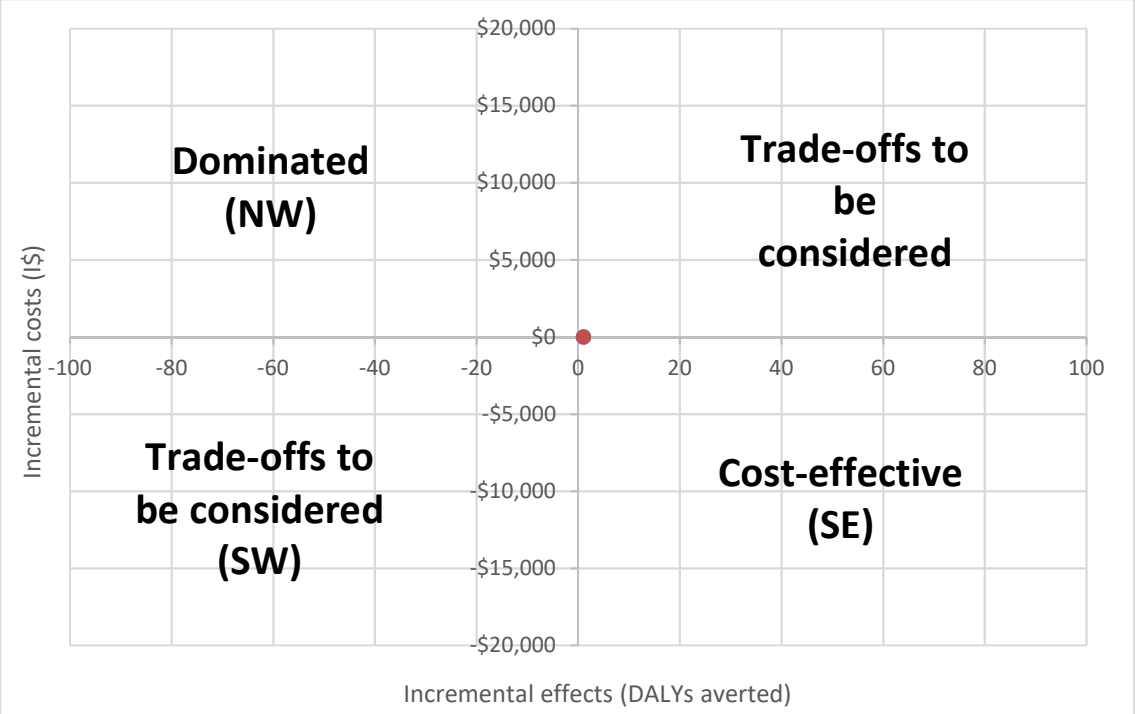
In GCEA, the concept of opportunity cost and trade-offs are the most relevant perspective to consider in the choice of type of cost-effectiveness threshold to use, rather than a rigid cost-effectiveness threshold in the sense that, in considering the implementation of a new intervention, decision-makers need estimates of 'both the health that might be gained elsewhere through the alternative use of the resources needed for the new intervention and the health that is likely to be lost if the new intervention is not used' [22]. Moreover, the use of the 'null' in GCEA contributes to fairness in this choice.

Figure 1 shows the four quadrants that visually represent the incremental cost-effectiveness plane on which the cost-effectiveness decision should be made [69], [70]. The vertical axis divides the plane according to the incremental effects and the horizontal axis according to the incremental costs. Interventions in the southeast quadrant are always considered cost-effective because they are less expensive and more effective; interventions in the northwest quadrant have been

considered ‘dominated’ as more costly and less effective, and those in the northeast and southwest quadrants are those for which a trade-off between costs and effects should be considered.

In GCEA, an intervention would be weakly dominated by other interventions if a combination of these other interventions were more cost-effective. Weakly-dominated interventions can be identified by calculating the incremental cost-effectiveness ratios for each successively costlier intervention – if one of these incremental ratios is lower than the previous one in the increasingly costly and mutually exclusive sequence of interventions, then the precedent is ruled out by weak dominance.

Figure 1: The incremental cost effectiveness plane [69]



NW: Northwest quadrant, NE= Northeast quadrant, SE = Southeast quadrant, SW= Southwest quadrant

GCEA in priority setting

General contribution

The information provided by the results of a GCEA for a set of health interventions represents a key input into the broader task of priority setting.

First, by using the ‘null’ scenario as the counterfactual of the analysis, GCEA can identify not only current inefficiencies in allocation, but also underused or new interventions that can provide good

value for money. Once identified as cost-effective, those interventions can be rapidly disseminated at a global level. Conversely, GCEA can discourage the use of inefficient but broadly used interventions.

Second, GCEA assesses a set of interventions in different combinations at different levels of coverage, taking into account the interactions in the impacts and costs of all the interventions. This process can highlight the efficiency of any individual intervention within any set. In other words, it can show which interventions are a very expensive way to improve health in any combination, or less expensive but more effective.

Third, GCEA can help decision-makers evaluate and possibly improve the performance of their health systems in terms of one goal, namely the level of health. To this end, GCEA defines the sets of interventions providing the best value for money and helps policy makers to choose the interventions that optimize health within the limits of available resources.

Furthermore, GCEA can be used to guide or review financing decisions. One can argue that there should be no attempt to provide cost-ineffective interventions on grounds of efficiency. As a result, GCEA can help inform decisions on full repayment, subsidy, or refusal to cover the costs of providing a service. GCEA could also be used to state the frequency or extent of intervention coverage.

Finally, GCEA can help define priorities for Research and Development. It can be used to estimate the contribution of interventions, or combinations of interventions, to the reduction of a disease burden. If one assumes that all combinations of cost-effective interventions have a relatively small impact on the total burden of a given disease, research into new ways of decreasing this burden may be necessary

As discussed above, GCEA provides valuable estimates of the value for money of the health interventions. It focuses on improvements in health resulting from different choices about how health resources should be used. However, improving health is only one goal of the health system. Therefore, GCEA results should not be used formulaically. They enter the policy debate as one input and decision-makers must evaluate the trade-off in the costs of changing the combination of interventions and the impact of different combinations against other goals of the health system.

They need to be considered alongside other factors beyond efficiency, such as affordability, implementation capacity, feasibility, budget impact and fairness [62].

Contextualization to national setting

To stimulate change where necessary, there is a need to contextualize estimated sub-regional measures of the cost, effects and cost-effectiveness of GCEA to the setting in which the information will be used.

To do so, WHO-CHOICE has developed a new country contextualization tool, 'CHOICE Spectrum' [4], an online contextualization platform which provides countries with the opportunity to quickly develop locally contextual evidence to begin evidence supported priority setting activity or to create a database of cost-effectiveness results for use in an health technology assessment (HTA) decision-making process. Faster and easier to use than previous WHO-CHOICE tools, this tool is freely available for download and supported through user manuals, with technical assistance and peer review options available to WHO member states.

Conclusion

As discussed at the start of this chapter, the use of CEA to assess the allocative efficiency of resource allocations can evolve either towards contextualized analyses or more generalized assessments. Most CEA studies currently observed in the literature are setting-specific; they do not allow an assessment of the current combination of interventions and are based on incremental cost-effectiveness information. The path that GCEA is promoting is to focus on the general assessment of the costs and health effects of different interventions. For sector-wide health priority setting, cost-effectiveness information should be collected in a way that allows policy-makers to achieve as much as they can with the resources available and to identify how best to use additional resources if they become available – GCEA addresses both. By using the 'null' comparator, GCEA can assess the effectiveness of interventions currently implemented in addition to the assessment of new interventions. Moreover, without the various highly variable local decision constraints, the main residual limitation of using GCEA for priority setting is the availability of resources. Removing the current intervention constraint also allows the GCEA results to be transferable to other settings.

The subsequent chapters, therefore, explore the application of the GCEA for each of the three main health categories as briefly introduced earlier in the thesis outline; namely, communicable diseases

in chapter I with *Plasmodium falciparum* malaria, *Plasmodium vivax* malaria, HIV and tuberculosis; noncommunicable diseases in chapter II with breast cancer, cervical cancer and colorectal cancer and road traffic injuries in chapter IV. The choices of each disease included in the analysis were mainly driven by the burden that they represent globally but mainly in the regions studied. Malaria, a preventable and curable disease, causes the death of more than 400,000 people worldwide each year. The African Region bears over 90% of this malaria morbidity, despite the influx of funding received by the control programs, followed by the Southeast Asia Region. More than 200 million cases of malaria have been recorded worldwide, with Plasmodium falciparum being the most prevalent malaria parasite in the African Region, accounting for almost 100% of estimated malaria. Conversely, more than 50% of the Plasmodium vivax cases occurred in the Southeast Asia Region. [71]. HIV has infected more than 70 million people since the beginning of the epidemic, killing more than 30 million individuals. The African region is the most affected, with nearly 70% of people in this region living with HIV, followed by the Southeast Asia region, with about 9.5%. [72], [73], [74]. Millions of people keep getting infected with tuberculosis each year. It is considered to be one of the top 10 causes of death worldwide, with around 50% of tuberculosis mortality occurring in the Southeast Asia region and around 30% in the African Region [75]. Cancer mortality increased by 26% between 2000 and 2015, with a significant increase in Asia and Africa [76]. Cervical cancer and breast cancer are the leading causes of cancer-related deaths among women in the sub-Saharan Africa region, accounting for 23.2% and 19.3%, respectively, of cancer deaths, while colorectal cancer is one of the most common causes of cancer deaths for both sexes around the world [77]. Road traffic injuries represent the tenth leading cause of death among all age groups and are anticipated to become the seventh leading cause of death by 2030. Annually, 1.25 million people die in road accidents around the world. [78] In the African region, the number of road traffic injuries and deaths have increased over the last three decades. [79].

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Chapter II: Priority setting in HIV, Tuberculosis, and Malaria – New Cost-Effectiveness Results for WHO-CHOICE

Submitted to the International Journal of Health Policy and Management (IJHPM) in August 2019

Manuscript Type: Original Article

Title of Manuscript: Priority Setting in HIV, Tuberculosis, and Malaria – New Cost-Effectiveness Results from WHO-CHOICE

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Acknowledgements:

We would like to thank our colleagues from WHO - Communicable Diseases for their review and comments on this paper.

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AHR and JAL conceptualized, designed and drafted the manuscript. AHR, JAL, CP and OJTB acquired the data. AHR collated the database used and performed the cost-effectiveness analysis. AHR, JAL, CP, OJTB and EP contributed to the interpretation of the data, the edit and critical revision of the manuscript.

Conflict of interest:

The contributing authors declare that they have no conflict of interests.

Ethical issues

Not applicable

Abstract

Background

This paper forms part of an update of the WHO-CHOICE programmes. It provides an assessment of global health system performance during the first decade of the 21st century (2000-2010) with respect to allocative efficiency in HIV, TB and malaria, thereby shining a spotlight on programme development and scale up in these MDG priority areas; to examine the cost effectiveness of selected best-practice interventions and intervention packages commonly in use during this period.

Methods

Generalized cost-effectiveness analysis (GCEA) was used to determine the cost effectiveness of interventions for HIV, TB and malaria. Impact modelling was performed using the OpenMalaria platform for malaria and using the Goals and TIME models in Spectrum for HIV and TB. All health system costs, regardless of payer, were included and reported in international dollars. Health outcomes are estimated and reported as the gain in healthy life years due to the specific intervention or combination. Analysis was restricted to eastern sub-Saharan Africa and Southeast Asia.

Results

At the reference year of 2010, commonly used interventions for HIV, TB and malaria were cost-effective, with cost-effectiveness ratios less than I$ 100/HLY saved for virtually all interventions included in this study. HIV, TB and malaria prevention and treatment interventions are highly cost-effective and can be implemented through a phased approach to full coverage to achieve maximum health benefits and contribute to progressive elimination of these diseases.

Conclusions

During the first decade of the 21st century (2000-2010), the global community has done well overall for HIV, TB, and malaria programmes as regards both economic efficiency and programmatic selection criteria. The role of international assistance, financial and technical, arguably was critical to these successes. As the global community now tackles the challenge of universal health coverage, this analysis can reinforce commitment to SDG targets but also the importance of continued focus on these critical programme areas.

Keywords

Cost-Effectiveness Analysis, HIV, Tuberculosis, Malaria, Priority Setting, Universal Health Coverage

Key Messages:

1. Implications for policy makers

- Country level: Continue to scale up comprehensive HIV, TB, and malaria programmes.
- Global level: Continue to provide technical and donor assistance for HIV, TB, and malaria programmes.
- Both: Generalize these practices to the rest of the health system.

2. Implications for public

Although more needs to be done, coverage levels are higher in HIV, TB and malaria than for other conditions in the regions studied; moreover, overall and on average the right interventions are being done. These observations are not a cause for complacency. Regression to lower levels of epidemic control is possible and in some cases is now being witnessed. International collective action, in conjunction with institutions committed to strengthening domestic actors, has made a convincing case as a global public good for HIV, TB and malaria control, demonstrating international development assistance for health can be transformative when combined with technical assistance about intervention choice and programme development.

Main Manuscript:

Background

The Sustainable Development Goals (SDGs) address universal health coverage (UHC) in target 3.8 [8] [1], [2]. Priority setting in the context of UHC emphasizes three values: improving population health, ensuring equity in access to and quality of services and avoiding impoverishment or underutilization of services as a result of out-of-pocket expenditures [3], [4]. Allocative efficiency can be measured with respect to any one of these values, or with respect to all three together, for example using Extended Cost-Effectiveness Analysis.

Here, we adopt generalized cost-effectiveness analysis (GCEA), an approach used by WHO's programme Choosing Interventions that are Cost-Effective (CHOICE), which has been a global leader in cost-effectiveness analysis in global health since 1998. This GCEA approach has the principal advantage to allow for critical analysis of the package of currently implemented interventions, along with those that may be additionally considered under scaling-up scenarios.

We propose to provide a quantitative assessment of allocative efficiency within three critical diseases areas during the first decade of this century. This historical analysis provides a retrospective evaluation of programme development and scale up during this period. HIV, tuberculosis (TB), and malaria are of interest not only because of the MDGs but also because of the creation of The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund), which contributed to an unprecedented increase in funding towards these infectious diseases.

This paper also forms part of an update of the WHO-CHOICE programme and previous stand-alone analyses of the cost-effectiveness of interventions to combat HIV, TB, or malaria [5], [6] , [7]. As in previous work, we focus here on two economically and epidemiologically diverse regions: eastern sub-Saharan Africa and Southeast Asia [8] in order to have examples of the indicative cost-effectiveness of a common technology set in diverse settings. We stress the word "indicative", since the analysis is regional and has not been contextualized to particular country settings, as would be done for example for national and subnational decision-making, programme

[8] "Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all "

development and priority setting. Rather, we examine how implementation at a macro scale performed relative to global knowledge about best practice during the period 2000-2010.

Given that *Plasmodium falciparum (P. falciparum)* is the most prevalent malaria parasite in the WHO African Region and that most (56%) cases of *Plasmodium vivax (P. vivax)* malaria occur in the WHO South-East Asia Region [9] we focus our analysis on *P. falciparum* malaria, HIV and TB for the eastern sub-Saharan Africa region, and on *P. vivax* malaria, HIV and TB for the South-East Asia region.

Methods

The methods and rationale of GCEA used by WHO-CHOICE have been published elsewhere [10], [11].The principal advantage of GCEA is that it allows for an analysis of the package of currently implemented interventions, along with those that may be considered under alternative or scaling-up scenarios. The cost effectiveness of interventions is examined first individually against a "null" scenario, a counterfactual scenario in which the effects of all currently implemented interventions are removed, and second as packages of interventions defined as combinations of the most cost-effective individual interventions. To allow for comparison and integration of results in a sub-sectoral analysis, common methods and assumptions are applied for HIV, TB, and malaria. Health outcomes are measured and reported as the gain in healthy life years (HLYs) due to a specific intervention or combination thereof. For the calculation of HLYs, disease weights were obtained from the Global Burden of Disease study, 2010 [12]. For costing, all market-traded health system inputs are costed, regardless of payer (i.e. programme costs, service delivery of the intervention, drugs and expendables). Programmes are considered to be implemented for 100 years in the context of a population level model that calculates duration-dependent life-table effects such as healthy life expectancy. A 3% per annum discount rate is applied to costs in all scenarios. HLY are reported both undiscounted and with a 3% per annum discount rate.

The cost effectiveness of disease-specific sets of regional counterfactual scenarios is assessed against a null comparator (no intervention), along with individual and combined interventions, including seven scenarios for *P. vivax* malaria (Table 1), 14 for *P. falciparum* malaria (Table 2), 12 for HIV (Table 5) and 10 for tuberculosis (Table 7). The effects and costs of current (i.e. actual) practice were also assessed relative to this baseline. Interventions are analysed at 50%, 80% and 95% coverages; details for the current scenarios can be found in Tables 3, 4, 6 and 8.

The list of interventions is not exhaustive and excluding an intervention does not imply that it is cost ineffective. The term "current" refers to a representation of the average combination of interventions used in typical countries in the relevant geographical area at year 2010. Some of these interventions, however, do not reflect the recommendations of WHO anymore and up-to-date WHO recommendations can be found in Table 9. Thus, our results are intended to be indicative of average implementation performance relative to the global knowledge of best practice at the time, rather than as prescriptive packages intended for countries to implement now. As noted, our principal objective here is to assess and evaluate retrospectively programmatic performance in HIV, TB and malaria control during the first decade of the 21st century. In addition, in the case of malaria, we also assess the potential cost-effectiveness of the RTSs vaccine in the context of our GCEA framework.

An expansion path shows the steps in programme expansion that a hypothetical decision-maker could follow when maximizing health. However, in constructing such an expansion path, even when maximization of population health is the goal it is presumably important to consider other factors too. We therefore present two expansion paths, one, a health-maximizing expansion path that has no constraints apart from the cost effectiveness of interventions, and, two, a programmatic expansion path that respects the fact that health system resources represent asset-specific investments that cannot be easily substituted. In other words, while an "expansion path" reflects an optimal path for the expansion of health services, the concept of optimal may also include certain criteria for programme acceptability. For example, the concept of bringing a highly cost-effective intervention to full coverage in a given year only to drop it and replace it with a different intervention when higher levels of funding are available the following year can be excluded on programmatic grounds, due to the large fixed costs associated with changing disease control strategies. When such a case is suggested on cost-effectiveness grounds, the programmatic expansion path can be "forced" to adopt the intervention that will subsequently be optimal in this programmatic sense at full implementation. This means that, if a particular technology appears on the expansion path at a certain level of coverage, then for the next steps, we considered only the most cost-effective combination of interventions that also included this particular technology at the same or higher levels of coverage (interventions, albeit, that are potentially less cost effective than available alternatives, implying higher costs but also higher effects). Finally, we note that the concept of an expansion path in either of these guises (health maximizing or programmatic) is at

base only an indicative device to illustrate trade-offs implicitly made by the policy-maker in the course of health system development.

The WHO-CHOICE results are provided at regional level; further contextualization is necessary for individual country-level implementation [13], so our scenarios should be considered only as estimates of (actual) average performance at macro level versus counterfactual idealized practice during the period 2000–2010.

Impact Modelling

Malaria Model

Simulations for *P. falciparum* malaria and *P.vivax* malaria were performed using the OpenMalaria platform [14], an open-source C++ program for micro-simulating malaria epidemiology and the impacts of interventions on disease burden. A WHO-CHOICE population model, PopMod [15], was used to combine projected case incidence, parasite clearance and mortality data with the health state valuations to calculate the population impact of the different intervention scenarios.

All malaria simulations were based on a scenario used earlier [16], [17], [18]. A major innovation compared to the scenario used in [16] is the modelling of fevers with non-malarial aetiology. This scenario with non-malaria fevers (NMF) modelling was adapted to country-specific conditions for the following aspects: seasonality of transmission, history of ITN use, history of case management coverage and intensity of transmission. For *P. vivax*, also the prevalence of G6PD deficiency [19] was taken into account.

Management of severe cases was presumed to be constant over time and among countries of the same region, and the probability of treatment per five-day time step was assumed to be 48% [20], [21]. The per-capita rates of malaria cases and deaths from OpenMalaria were scaled to WHO case incidence estimates per country in 2010 [22]. Similarly, the number of treatments (with or without diagnostic tests), and the number of diagnostic tests, at a given coverage level were also scaled to the WHO estimates of cases.

Interventions against malaria

Insecticide Treated Nets (ITNs) distribution was modelled on an annual basis and their effect was hypothesised to last one year (modelled with a step-wise attrition function). During the year,

no chemical retreatment or physical decay was modelled. Costing of nets, however, was done on the basis of actual estimates of useful life [23].

Case management and diagnostic testing Without testing, fevers without parasites, fevers with incidental parasites (i.e. fevers that occur in people that are not caused by the malaria infection), and malarial fevers (i.e. fevers caused by the malaria infection) have an equal probability of being treated with an antimalarial. With testing, fevers without parasites are not treated. Without G6PD testing, all *P. vivax* positive patients except pregnant women should receive primaquine. With G6PD testing, a status of non-eligibility for primaquine (either due to G6PD deficiency, or due to policy regarding primaquine treatment) was assigned at birth with a pre-set probability dependent on the proportion of hemizygous men in the population.

RTS,S malaria vaccine was modelled as was previously done by Swiss TPH for the Malaria Vaccine Initiative [24]. While this vaccine is not recommended by WHO, it is a potential new intervention included in this study for illustrative purposes, drawing on previous modelling conducted for WHO.

Table 1: Interventions included in the analysis for P. vivax malaria

#	Scenario name	Description
1	CMS	Management of severe cases
2	ITN	Insecticide-treated bed nets
3	CMS_ITN	Management of severe cases + Insecticide-treated bed nets
4	CMU_CMS	Management of suspected uncomplicated cases + Management of severe cases
5	CMU_CMS_ITN	Management of suspected uncomplicated cases + Management of severe cases + Insecticide-treated bed nets
6	CMUPQX*_CMS	As #4 with primaquine only given to non-G6PDd° males
7	CMUPQX*_CMS_ITN	As #5 with primaquine only given to non-G6PDd° males

°G6PDd: Glucose-6-phosphate dehydrogenase (G6PD) deficient

*PQX: G6PDd testing in males, non-deficient males receive primaquine, and all others (G6PDd males and all females) do not receive primaquine.

Table 2: Interventions included in the analysis for P. falciparum malaria

#	Scenario name	Description
1	CMS	Management of severe cases
2	ITN	Insecticide-treated bed nets
3	CMS_ITN	Management of severe cases + Insecticide-treated bed nets
4	CMU_CMS	Management of suspected uncomplicated cases + Management of severe cases
5	CMU_CMS_ITN	Management of suspected uncomplicated cases + Management of severe cases + Insecticide-treated bed nets
6	CMS_RTSS	Management of severe cases + Malaria vaccine with RTS, S
7	ITN_RTSS	Insecticide-treated bed nets + Malaria vaccine with RTS, S
8	CMS_ITN_RTSS	Management of severe cases + Insecticide treated bed nets + Malaria vaccine with RTS,S
9	CMU_CMS_RTSS	Management of suspected uncomplicated cases + Management of severe cases + Malaria vaccine with RTS, S
10	CMU_CMS_ITN_RTSS	Management of suspected uncomplicated cases + Management of severe cases + Insecticide treated bed nets + Malaria vaccine with RTS,S
11	CMU_D*_CMS	As #4, but treatment seeking fever cases RDT° tested
12	CMU_D*_CMS_ITN	As #5, but treatment seeking fever cases RDT° tested
13	CMU_D*_CMS_RTSS	As #9, but treatment seeking fever cases RDT° tested
14	CMU_D*_CMS_ITN_RTSS	As #10, but treatment seeking fever cases RDT° tested

*D: Diagnostics; ° RDT: Malaria rapid diagnostic test

Table 3: Population in need and current coverage for P. vivax malaria

Interventions	Population in need	Current coverage (%)	References
Case management	All- age population, men and women living in malaria endemic areas	52	[20], [21], [25]
ITN		21	

Table 4: Population in need and current coverage for P. falciparum malaria

Interventions	Population in need	Current coverage (%)	References
Case management	All- age population, men and women living in malaria endemic areas	40	[20], [21], [26]
ITN		58	

HIV Model

Simulations for HIV were performed with the Goals model, a dynamic compartmental model developed in the open-source Spectrum suite of models [27], [28], [29], [30], [31], [32]. The Goals model is widely-used to produce projections of epidemic trends as well as projections of the impact of interventions. It has been used in many regions, particularly in the Southern and Eastern African region, to study the cost and impact of national and other HIV strategies.

Goals simulates transmission of HIV and its morbidity and mortality consequences for adult populations aged 15–49 years, which are structured into five risk categories: stable couples (men and women reporting a single partner in the last year), multiple partners (men and women with more than one partner in the last year), female sex workers and clients, men who have sex with men (MSM), and people who inject drugs (PWID). These groups are based on risk stratifications available in publicly available data sources, such as Demographic and Health Surveys (DHS) and AIDS Indicator Surveys (AIS), as well in behavioural surveys. HIV transmission in Goals is explicitly calculated from behavioural (e.g. age at first sex, number of sexual partners and number of sex acts per sexual partner) and biomedical (e.g. ART, condom use and VMMC) characteristics.

Goals is directly linked to the AIDS Impact Model (AIM) module in Spectrum, which is used annually to produce national HIV burden estimates towards the Global AIDS report [28], [29]. Goals uses the HIV progression structure in AIM, in which HIV progression is captured through

movement in CD4 categories, which form the basis of ART eligibility criteria, ART initiation and ART coverage levels and is also the basis of mortality patterns.

AIM also estimates the effects of programs preventing mother-to-child transmission [33], [34]. AIM further calculates corresponding epidemic patterns for children (0–14 years) and models HIV progression for adults above 49 years.

Interventions against HIV

The impact of behavioural interventions for HIV is represented by an impact matrix which summarizes the impact of key behavioural interventions (e.g. community mobilization, mass media campaigns, condom distribution programs, outreach to key populations) with respect to the reduction of condom non-use, reduction of number of partners, and increase in age at first sex for the populations outlined above, based on meta-analysis of research studies [33], [34], [35], [36].

In addition to these behavioural factors, HIV transmission risk further depends on biomedical factors including ART use, VMMC, the prevalence of other sexually transmitted infections (STIs) and the use of pre-exposure prophylaxis (PrEP).

Interventions in Goals can change any of these factors, and thereby affect HIV transmission risk and the future course of the epidemic.

To apply intervention structure of the Goals model to our CHOICE scenarios, we constructed three ART scenarios in which eligibility for ART is progressively relaxed. In the first scenario ART is provided to all children two years and younger, to all other children under the age of 15, to all adults (15 years and older) with CD4 count below 350 cells/uL and Option B+ (ART continued after a pregnancy during which ART is initiated) is followed in the PMTCT program. The second scenario is the same except that a CD4 count below 500 cells/uL replaces CD4 350 cells/uL in the definition of the first scenario. In the third scenario CD4 count is removed as an eligibility criterion and ART is applied as prevention (the so-called TasP strategy). All these strategies assume HIV testing services as part of ART enrolment process. Testing is an entry point and it matters who gets testing as services and impact depend on this.

The list of interventions is extended through voluntary male circumcision (VMMC), STI treatment, behavioural interventions (mass media, condom distribution and youth-based programs)

as well as outreach programs to high-risk groups (FSW and their clients, PWID and MSM outreach). Three combination scenarios are defined by adding all of these interventions to the three ART scenarios.

Table 5: Interventions included in the analysis for HIV

#	Scenario name	Description
1	FSW	Female Sex Workers and clients
2	PWID	People Who Inject Drugs community outreach and peer education
3	MMCO	Mass Media communication designed to increase demand and improve use of COndoms, and condom provision
4	MSM	Interventions targeting Men who have Sex with Men
5	VMMC	Voluntary Male Medical Circumcision
6	YFI	Youth Focused Interventions
7	ART3	HIV testing services + Antiretroviral therapy for all HIV positive adults with CD4 < 350, all HIV positive children =<2 yrs, children>2 yrs with CD4 <350, pregnant women Option B+
8	ART5	HIV testing services + Antiretroviral -therapy for all HIV positive adults with CD4 < 500, all HIV positive children =<2 yrs, children>2 yrs with CD4<500, pregnant women Option B+
9	TASP	HIV testing services + Antiretroviral therapy Treatment AS Prevention for all HIV positive adults, children and PMTCT* Option B+
10	CB1	ART3 + MMCO + FSW +PWID + MSM +YFI + Management of Sexually Transmitted Infections +VMMC
11	CB2	ART5 + MMCO + FSW +PWID + MSM +YFI + Management of Sexually Transmitted Infections +VMMC
12	CB3	TASP + MMCO + FSW +PWID + MSM +YFI + Management of Sexually Transmitted Infections +VMMC

*PMTCT: Prevention of mother-to-child transmission

°pregnant women Option B+: lifelong antiretroviral therapy treatment giving to HIV-positive pregnant women regardless of CD4 count or WHO clinical stage [37]

Table 6: Population in need and current coverage for HIV

Intervention	Population in need	Current coverage (%)		References
		Eastern sub-Saharan Africa	Southeast Asia	
Female sex workers and clients	Female sex workers aged 15-49 years	31	67	[38], [39], UNGASS reports, data collected for the UNAIDS global report (analogous to the TB reports) and data collected for the Resource Needs Model exercises
PWID community outreach and peer education	People Who Inject Drugs aged 15-49 years (male and female)	10	33	
Mass media	Population aged 15-49 years (male and female)	29	31	
Condom provision	Population aged 15-49 years (male and female)	27	28	
Men who have sex with men	Men who have sex with men aged 15-49 years	25	28	
Voluntary male medical circumcision	Population aged 10-19 years (male)	70		
Youth focused interventions	Population aged 15-49 years (male and female) and STI symptomatic	60	18	
STI° management	Population aged 15-49 years (male and female) and STI symptomatic	36	23	
HIV testing services	Population aged 15-49 years (male and female)	23	4	

*STI Sexually Transmitted Infections

TB Model

Simulations for TB were performed with the Impact component of the TB Impact Model and Estimates (TIME) model, a dynamic compartmental TB model developed in the open-source Spectrum suite of models [27], [40].

TIME is used by TB policymakers and national TB programmes (NTPs) to develop strategic responses and strategies for TB and to produce projections that inform funding applications. The model has been used in most TB settings, including in countries where TB is driven by HIV, in weak health systems, in countries with high MDR-burden and in countries where TB programs depend on a high level of private-sector involvement. The Estimates component of TIME was used by the Global TB Programme to produce estimates for HIV-TB burden towards the Global TB Report.

The TIME model reflects key aspects of the natural history of TB including primary and latent infection, re-infection and re-activation of latent TB. Smear positivity, negativity and smear conversion is explicitly handled. TIME also accounts for the characteristics of paediatric TB, treatment history and drug resistance. It has additional structure for HIV/ART which mimics the structure of the Spectrum AIDS Impact Model (AIM) module to directly use its HIV programmatic data. TIME includes two generic strains by MDR status: susceptible and resistant to treatment. Resistance can be acquired during treatment upon transmission, at rates that distinguishes it from the susceptible TB type in the model.

Interventions against TB

A description of the TIME model and its parametrization can be found in the technical appendix of [40]. Interventions in TIME are structured according to a general care-and-control cascade for TB, which is further structured by HIV and MDR status as relevant. The cascade starts with a screening rate which is defined for smear-positive cases, and relative screening rates are specified for smear-negative and TB susceptible cases. Diagnosis of TB is defined by sensitivity and specificity values which are used to characterise the most widely-used and WHO-recommended diagnostic tools in diagnostic pathways for TB. Estimates of diagnostic sensitivity and specificity used in TIME are based on those discussed in [41], [42], [43].

Following screening and diagnosis, cases are linked to care at a specified acquisition rate and then treated at a specified success rate. The model does not explicitly handle a delay between diagnosis and treatment. Coverage, sensitivity and specificity of drug susceptibility tests (DST) for treatment naïve and previously treated cases are specified. These inputs characterize MDR diagnosis and notification, including notification of non-MDR cases as MDR due to non-perfect specificity of DST.

The model has a detailed structure for active case finding and household-based contact tracing for children and adults as well as subsequent links to preventive therapy (IPT) for cases identified with latent TB on the basis of a detailed testing algorithm. Prioritized access to ART for HIV-positive TB cases is explicitly linked to ART enrolment numbers from the Spectrum AIM model.

To apply intervention structure of the TIME model to this CHOICE analysis, we constructed a basic care-and-control scenario which comprise screening (of all population dimensions, including

smear, HIV and MDR-status), detection (including DST to find MDR among new and retreatment cases) and treatment for non-MDR and MDR case (including cases that are false diagnosed due to non-perfect specificity). Note that the different components of this basic care cascade cannot be individually studied in this analysis approach, but rather only as packages.

The basic scenario package has two variations. One representing a traditional diagnostic algorithm of symptomatic screening, followed with smear microscopy or clinical diagnosis and culture for MDR diagnosis. A second scenario represents a recommended design for future diagnostic algorithms which are projected to change to an increasing and dominant use of X-ray for screening and rapid molecular tests such GeneXpert for diagnosis of non-MDR and detection of rifampicin resistance, and by assumption diagnosis of the general MDR strain in our model.

Core interventions recommended in the End TB Strategy [44] and the Global Plan to End TB 2016-2020 [45] are added to the basic care-and-control cascade. First is preventive therapy for HIV-positive TB cases not on ART and on ART with latent TB infection (LTBI). Then preventive therapy for children ages (0-14) with LTBI found in the context of household screening of index cases. Finally, we added ART prioritization for notified HIV-positive TB cases, irrespective of CD4 count.

This overall intervention structure is kept general and do not address specific activities or implementation approaches that are necessary to implement the package. In different TB contexts screening rates might be increased through active case finding and enhanced passive case finding in specific groups at high risk of TB infection (e.g. diabetics, prisoners, miners, and so on). Community health workers are often employed to improve high treatment success. We made no assumptions regarding these types of underlying activities that are required to achieve the coverage levels of the intervention packages studied.

We also made no assumption regarding the future trend of the number of tests that will be needed to find one case, and kept the value fixed at 10, which is considered an average value. Generally, it is expected that this value will increase as more aggressive screening policies are adopted by national TB programmes. These are considered too context specific to specify here.

Table 7: Interventions included in the analysis for tuberculosis

#	Scenario name	Description
1	B2	Treatment (FLD+SLD) +Detection (Xpert +X-ray+ Culture) +Drug susceptibility testing
2	B2_AX	Treatment (FLD+SLD)+Detection (Xpert + X-ray +Culture) +Drug susceptibility testing + ART° prioritization for TB cases
3	B2_AX_PX_PXC	Treatment (FLD+SLD) +Detection (Xpert + X-ray +Culture) +Drug susceptibility testing + ART° prioritization for TB cases + Preventive therapy + Preventive therapy for children
4	B2_PX	Treatment (FLD +SLD) +Detection (Xpert + X-ray +Culture) +Drug susceptibility testing +Preventive therapy
5	B2_PXC	Treatment (FLD +SLD) +Detection (Xpert + X-ray +Culture) +Drug susceptibility testing + Preventive therapy for children
6	B1	Treatment (FLD +SLD) +Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing
7	B1_AX	Treatment (FLD +SLD) +Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing + ART° prioritization for TB cases
8	B1_AX_PX_PXC	Treatment (FLD +SLD) +Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing + ART° prioritization for TB cases + Preventive therapy + Preventive therapy for children
9	B1_PX	Treatment (FLD +SLD) +Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing + Preventive therapy
10	B1_PXC	Treatment (FLD +SLD) +Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing + Preventive therapy for children

°ART: Antiretroviral therapy; FLD: First line drugs, SLD: Second line drugs

Table 8: Population in need and current coverage for Tuberculosis

Interventions	Population in need	Current coverage (%)		References
		Eastern sub-Saharan Africa	Southeast Asia	
Detection		73	65	
Screening	All age population, men and women			Screening rate is a fitting parameter
Algorithm sensitivity and specificity	TB susceptible and active TB cases, as applicable to diagnostic method			[41], [42], [43]
Drug sensitivity test	Active new and previously treated TB cases			[46], [47]
Treatment	Active TB cases, with diagnosis and linked to care	85	80	[46], [47]
ART prioritization	HIV-positive TB cases, not on ART	80	40	[46], [47]
Preventive therapy	Ages 15+, men and women, LTBI cases	40	40	[46], [47]
Preventive therapy for children	Ages 0-14, LTBI cases	23	50	[46], [47]

Table 9: WHO recommended interventions

Disease	Category	Intervention	References
HIV	Prevention	Male and female condoms and lubricants	[48]
		Harm reduction for people who inject drugs	[48], [49]
		Antiretroviral-based prevention: pre-exposure prophylaxis, post-exposure prophylaxis, prevention of mother-to child transmission, antiretroviral therapy that achieves viral suppression.	[48], [50]
		Prevention of HIV infection in infants	[48]
		Voluntary medical male circumcision	[48]
		Injection and blood safety	[48]
		Behaviour change interventions (specific to particular population groups including adolescent girls and young women)	[48]
		Prevention and management of gender-based and sexual violence	[48]
	Testing	HIV testing	[48], [51], [52]
	Treatment and Care	Expand antiretroviral therapy coverage	[48], [50]

		Prevent and manage HIV and tuberculosis coinfection	[48]
		Prevent and manage HIV and viral hepatitis coinfection	[48]
		Address other HIV coinfections	[48]
		Prevent and manage HIV drug resistance	[48]
		Provide person-centred chronic care for people living with HIV	[48]
	Comprehensive package for key populations (men who have sex with men, people who inject drugs, people in prisons and other closed settings, sexworkers and transgender people)	Comprehensive condom and lubricant programming	[49]
		Harm reduction interventions for substance use (in particular needle and syringe programmes and, opioid substitution therapy and naloxone distribution)	
		Behavioural interventions	
		HIV testing and counselling	
		HIV treatment and care	
		Prevention and management of co-infections and other co-morbidities	
		Sexual and reproductive health interventions	
Tuberculosis	Prevention	Preventive treatment of persons at high risk, and vaccination against TB	[53], [54]
	Detection	Early diagnosis of TB including universal drug susceptibility	[53]

		testing, and systematic screening of contacts and high risk groups:	
		Rapid molecular test: Xpert® MTB/RIF assay (Cepheid, USA)	[55]
		Sputum smear microscopy	[55]
		Culture-based methods	[55]
		First-line Line Probe Assays LPAs	[55]
		Second-line LPA	[55]
		DST by phenotypic or genotypic methods should be done for all persons with bacteriologically confirmed TB	[53]
	Treatment and Care	Treatment of all people with TB including drug resistant TB, and patient support	[53], [56]
		Collaborative TB/HIV activities, and management of co-morbidities	[53], [57]
Malaria	Prevention	Insecticide–treated mosquito nets (ITNs)/ Long lasting insecticidal nets (LLINs) or Indoor residual spraying (IRS)	[58]
		Intermittent preventive treatment of malaria in pregnancy (IPTp)	[59], [60]
		Intermittent preventive treatment of infants (IPTi)	[61]

	Seasonal malaria chemoprevention (SMC) or Intermittent preventive treatment of children (IPTc)	[62]
Testing	Rapid Diagnostic Tests (RDTs) or microscopy	
Treatment	Treatment of blood-stage infection (for *P.falciparum* and *P.Vivax*)	
	Treatment of liver-stage infection (not applicable for *P.falciparum* and includes G6PD testing for confirmed cases of *P.Vivax*)	[63]
	Treatment of severe malaria	

Intervention Costs

We used a framework developed for WHO-CHOICE for costing interventions. This framework includes patient-level delivery costs, programme costs, and other health system costs, regardless of payer (e.g. private or public). We developed the costing estimates under the assumption that health system capacity is available to support the interventions. The quantities of resources assumed used at patient level were based on adherence to WHO treatment guidelines. Programme costs were calculated in a standardized way, as reported in [64]. Costs were discounted at 3% per annum, and capital expenses annualized over the lifetime of the good. All prices are reported in 2010 international dollars. Costing details for each programme area can be found in Tables 10, 11, 12 and 13.

Table 10: Intervention costing assumptions for P. vivax malaria

Patient costs (*regional average unit costs per person reached - I$ 2010)	
Management of uncomplicated cases	6.33
Management of severe cases	173.91
Insecticides-treated bed nets (ITNs)	5.47

* Prices of drugs from various sources: MSH database: **http://erc.msh.org/**, UNICEF LLIN data (2014). UNICEF supply catalogue (2012) and WHO-CHOICE price database. Unit costs include logistics, wastage, and freight and insurance (when relevant). Consumables required for management for severe cases include those needed for pre-referral treatment, hospital treatment, and post-discharge follow-up.

Table 11: Intervention costing assumptions for P. falciparum malaria

Patient costs (*regional average unit costs per person reached - I$ 2010)	
Management of suspected uncomplicated cases	2.06
Management of suspected uncomplicated cases (without diagnosis)	1.41
Management of severe cases	57.55
Insecticides-treated bed nets (ITNs)	5.47
RTS,S	7.25

* Prices of drugs from various sources: MSH database: **http://erc.msh.org/**, UNICEF LLIN data (2014). UNICEF supply catalogue (2012), WHO/IVB/06.15 [65] and WHO-CHOICE price database. Unit costs include logistics, wastage, and freight and insurance. Consumables required for management for severe cases include those needed for pre-referral treatment, hospital treatment, and post-discharge follow-up.

Table 12: Intervention costing assumptions for HIV

Patient costs (I$ 2010) (regional average unit costs per person reached)	**Eastern sub-Saharan Africa**	**Southeast Asia**
Youth-focused interventions	12.22	13.97
Female sex workers and clients	8.78	28.29
Men who have sex with men	9.30	32.82
[1]IDU community outreach and peer education	6.60	21.80
Condom provision	0.50	0.15
[2]STI management	9.19	34.07
Voluntary counselling and testing	12.48	31.73
Voluntary male circumcision	56.26	58.11
[3]PMTCT screening	4.43	3.74
PMTCT ARVs	597.23	986.63
Mass media (per campaign)	0.95	0.95
Service Delivery	100.77	54.95
[4]ART		
Labs	33.23	259.50
[5]ARVs - 1st line	130.35	128.65
ARVs - 2nd line	308.34	518.33
Pre-ART	118.74	233.93
Non-ART care and prophylaxis	302.70	302.70
Palliative Care	236.14	236.14

[1] IDU: Injecting drug users, [2]STI: Sexually Transmitted Infections, [3] PMTCT: Prevention of Mother-to-Child Transmission of HIV, [4]ART: Antiretroviral therapy, [5]ARVs: Antiretroviral

Table 13: Intervention costing assumptions for TB

Patient costs (I$ 2010) **(regional average unit costs per person reached)**	**Eastern sub-Saharan Africa**	**Southeast Asia**
Detection		
Smear microscopy		
Diagnostic test for passive TB case finding, BAC+ cases	1.20	1.20
Diagnostic tests for adults in HH-contact tracing	1.20	1.20
Diagnostic tests for children in HH-contact tracing	1.20	1.20
Diagnostic test for retreatment cases	1.20	1.20
Diagnostic test for child cases, BAC+ cases	1.20	1.20
Diagnostic test for HIV+ cases, BAC+ cases	1.20	1.20
Test to monitor treatment for new cases	1.20	1.20
Test to monitor treatment for retreatment cases	1.80	1.80
Test to monitor treatment for MDR-TB cases	7.21	7.21
Culture		
Diagnostic test for passive TB case finding, BAC+ cases	10.59	10.59
Diagnostic tests for adults in HH-contact tracing	10.59	10.59
Diagnostic tests for children in HH-contact tracing	10.59	10.59
Diagnostic test for smear negative or Xpert negative	10.59	10.59
Diagnostic test for extra pulmonary TB	10.59	10.59
Diagnostic test for child cases, BAC+ cases	10.59	10.59
Diagnostic test for HIV+ cases, BAC+ cases	10.59	10.59
Test to monitor treatment for new cases	21.17	21.17
Test to monitor treatment for retreatment cases	31.76	31.76
Resistance testing for new cases (FLD)	10.59	10.59
Resistance testing for retreatment cases (FLD)	10.59	10.59
Resistance testing/monitoring for MDR-TB cases (FLD)	127.03	127.03
Resistance testing/monitoring for MDR-TB cases (SLD)	127.03	127.03
Resistance testing for HIV+ cases	10.59	10.59
Resistance testing for child cases	10.59	10.59
Resistance testing for MDR-TB contact tracing	10.59	10.59
Molecular: Xpert		
Diagnostic test for passive TB case finding, BAC+ cases	9.98	9.98
Diagnostic tests for adults in HH-contact tracing	9.98	9.98
Diagnostic tests for children in HH-contact tracing	9.98	9.98

Diagnostic test for smear negative TB	9.98	9.98
Diagnostic test for extra pulmonary TB	9.98	9.98
Diagnostic test for child cases, BAC+ cases	9.98	9.98
Diagnostic test for HIV+ cases, BAC+ cases	9.98	9.98
Test to monitor treatment for new cases	19.96	19.96
Test to monitor treatment for retreatment cases	29.94	29.94
Resistance testing for new cases	9.98	9.98
Resistance testing for retreatment cases	9.98	9.98
Resistance testing for MDR-TB cases	119.76	119.76
Resistance testing for HIV+ cases	9.98	9.98
Resistance testing for child cases	9.98	9.98
Resistance testing for MDR-TB contact tracing	9.98	9.98
X-rays, Full Chest		
Screening for passive TB case finding, BAC+ cases	10.00	10.00
Diagnostic tests for adults in HH-contact tracing	10.00	10.00
Diagnostic tests for children in HH-contact tracing	10.00	10.00
Screening for smear negative TB	10.00	10.00
Screening for extra pulmonary TB	10.00	10.00
Screening for child cases, BAC+ cases	10.00	10.00
Screening for HIV+ cases, BAC+ cases	10.00	10.00
Test to monitor treatment for new cases	20.00	20.00
Test to monitor treatment for retreatment cases	30.00	30.00
Test to monitor treatment for MDR-TB cases	30.00	30.00
Treatment		
First line treatment		
First-line TB drugs, Initial treatment (adults)	30.93	30.93
First-line TB drugs, Initial treatment (children)	24.12	24.12
First-line TB drugs, Retreatment	98.90	98.90
MDR and XDR TB		
Second-line TB drugs	1,866.24	1,866.24
XDR treatment	7,602.00	7,602.00
MDR-Adverse events &Palliative care	120.00	120.00
XDR-Adverse events &Palliative care	120.00	120.00
Collaborative TB and HIV/AIDS interventions		
HIV testing and counselling	4.80	4.80

Prioritization of ART for TB-HIV co-infected	110.00	110.00
Isoniazid preventive therapy for adults and children with HIV and on ART without TB	5.43	5.43
Isoniazid preventive therapy for adults and children with HIV and not on ART without TB	5.43	5.43
Preventive Therapy for Adults and Children through HH-contact tracing		
Preventive therapy for children without TB	5.43	5.43
Preventive therapy for adults without TB	5.43	5.43
MDR Case Management		
MDR Case Management	11,886.99	7,135.00
Health Systems Costs		
First line: Hospitalization and Ambulatory Care	23.69	55.66
Second line: Hospitalization and Ambulatory Care	1,366.60	2,854.58

Results

Tables 14, 15, 16, 17, 18 and 19 show the costs, effects and cost-effectiveness of the different interventions. These tables present only the most cost-effective interventions on the two expansion paths for each of the disease areas. Interventions that are "dominated" i.e. are more costly or less effective, are presented in Appendix 1. Figures 1-6 show the steps reflecting the programmatic path that a hypothetical decision maker could follow for the expansion of service. Both the health-maximizing and the programmatic expansion path are presented. However, we consider the programmatic expansion path for the main results, while also discussing where relevant the implications of the health maximizing expansion path.

HIV Results

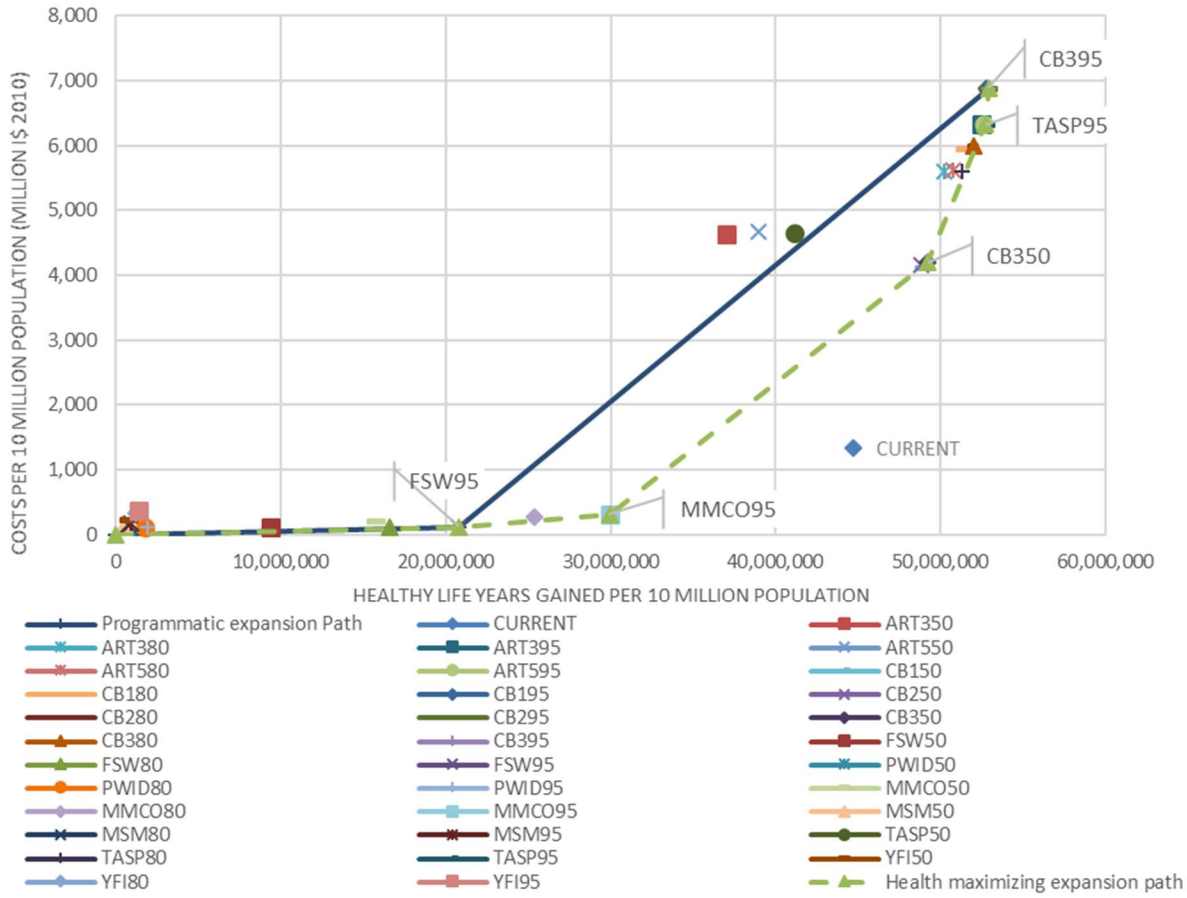
In South-East Asia, the intervention focused on female sex workers (FSW) at 95% coverage would be the most cost effective thus adopted first on the expansion path (Table 14). FSW interventions are both behavioural and biomedical. FSWs face very high risk, often the highest of any population group, and given that incidence is part of the cost-efficiency equation, FSW interventions are expected to be highly cost-effective (the more infections there are to avert, the higher the cost-effectiveness). However, it is important to note that FSWs may become hard to reach a high level of coverage given the nature of discrimination against them, and the lack of human rights-based platforms for functional intervention strategies. Voluntary male medical circumcision (VMMC) at

95% coverage would be the most cost-effective in eastern sub-Saharan Africa (Table 15). VMMC is an essential component of HIV prevention and is widely recognized as cost-effective in several African countries [66], [67], our study joins this conclusion. VMMC is biomedical and behavioural, and also incidence reducing, and in these respects is like the FSW intervention mentioned in the previous paragraph.

In both regions, the largest HLY are gained through a combination of interventions at 95% coverage including HIV testing services, antiretroviral therapy treatment as prevention for all HIV positive adults, children and PMTCT* Option B+, Mass media communication designed to increase demand and improve use of condoms, and condom provision, intervention among female sex workers, people who inject drugs community outreach and peer education, youth-focused interventions and management of Sexually Transmitted Infections (CB395) (Table 14 and 15). This shows that even in concentrated epidemic settings, HIV requires a combination approach, built around ART expansion, to achieve the overall burden reduction objectives. This means that "prevention is neither better than cure", nor "cure better than prevention"; a full suite of comprehensive approaches needs to be deployed.

Comparing the "current" intervention, at the reference time of 2010, to the expansion path: In southeast Asia, the current intervention is seen to be more cost-effective than any of the combination interventions studied in this analysis (Fig. 1). While interesting, this is mainly an artefact of our analysis, which considered interventions only in fixed combinations of 50%, 80% and 95%, and did not therefore allow for the most cost-effective combination, such as that shown in the current intervention, to be analysed (Fig. 2).

Figure 1 Cost effectiveness expansion path for HIV interventions in Southeast Asia



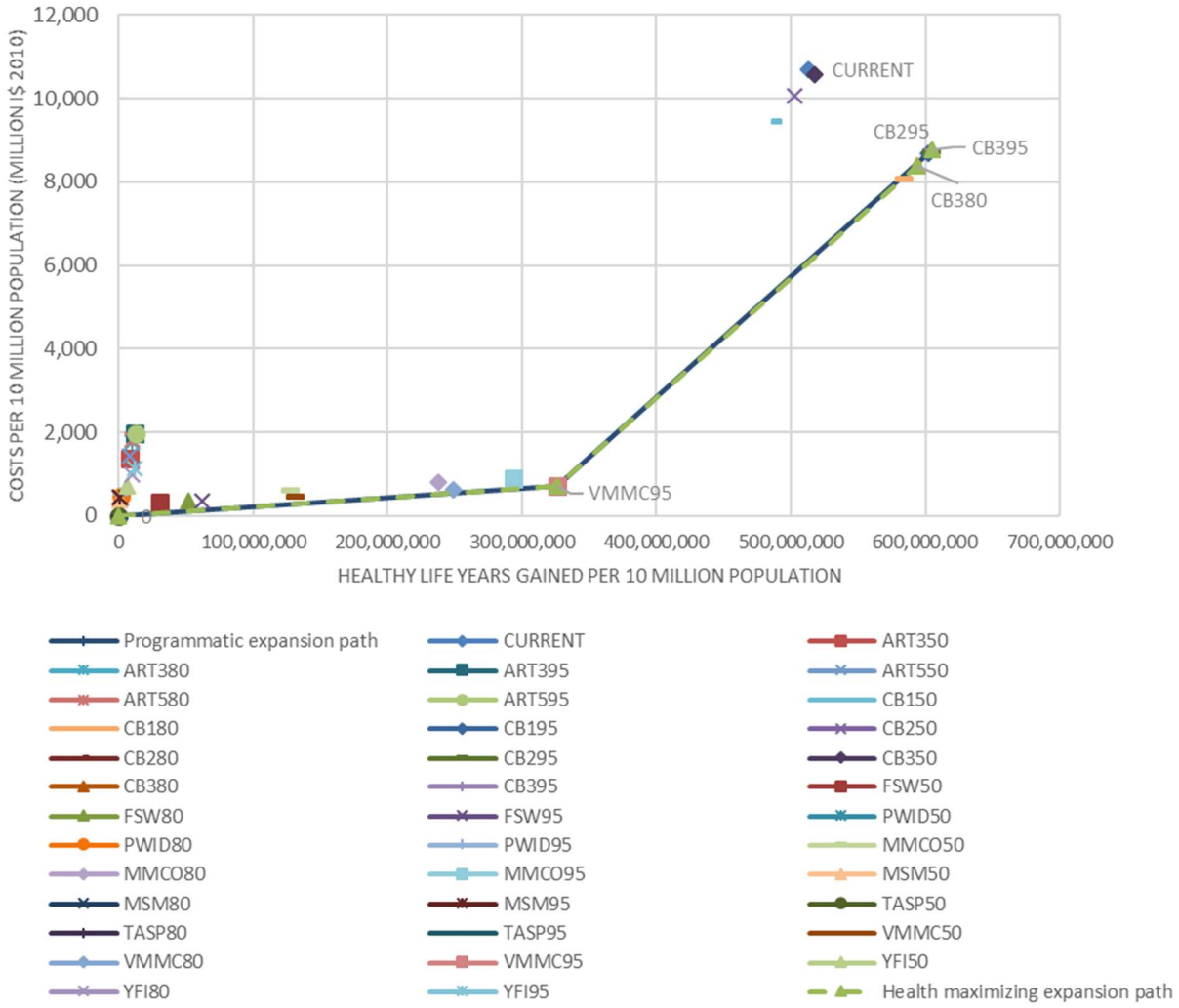
*Refer to Table 1 for interventions label *50, 80 and 95 at the end of each label refer to coverage of 50%, 80% and 95% respectively

Table 14 Costs, effects and cost effectiveness of HIV interventions in Southeast Asia over 100 years

	Intervention	Pop. coverage (%)	Total costs per 10 million population (million I$ 2010)	Healthy life years (million HLY) gained per 10 million population	ACER (I$ per HLY)	ICER (I$ per HLY) (Programmatic expansion path)	ICER (I$ per HLY) (Health maximizing expansion path)
Current	Current Scenario		1,339.1	44.7	30		
CB350	TASP + MMCO + FSW +PWID + MSM +YFI + Management of Sexually Transmitted Infections +VMMC	50	4,193.6	49.2	85	Dominated	201.1
CB395	TASP + MMCO + FSW +PWID + MSM +YFI + Management of Sexually Transmitted Infections +VMMC	95	6,887.5	53.0	130	210.3	2,781.0
FSW95	Female Sex Workers	95	124.3	20.8	6	6.0	6.0
MMCO95	Mass media communication designed to increase demand and improve use of condoms, and condom provision	95	313.4	29.9	10	Dominated	20.7
TASP95	HIV testing services + Antiretroviral therapy treatment as prevention for all	95	6,325.8	52.8	120	Dominated	602.5

	HIV positive adults, children and PMTCT* Option B+	

Figure 2 Cost effectiveness expansion path for HIV interventions in eastern sub-Saharan Africa



*Refer to Table 1 for interventions label *50, 80 and 95 at the end of each label refer to coverage of 50%, 80% and 95% respectively

Table 15 Costs, effects and cost effectiveness of HIV interventions in eastern sub-Saharan Africa over 100 years

	Intervention	Pop. coverage (%)	Total costs per 10 million population (million I$ 2010)	Healthy life years (million HLY) gained per 10 million population	ACER (I$ per HLY)	ICER (I$ per HLY) (Programmatic expansion path)	ICER (I$ per HLY) (Health maximizing expansion path)
CURRENT	Current Scenario		10,682	513	21		
CB295	ART5 + MMCO + FSW +PWID + MSM +YFI + Management of Sexually Transmitted Infections +VMMC	95	8,745	604	14	28.9	Dominated
CB380	TASP + MMCO + FSW +PWID + MSM +YFI + Management of Sexually Transmitted Infections +VMMC	80	8,386	594	14	Dominated	28.7
CB395	TASP + MMCO + FSW +PWID + MSM +YFI + Management of Sexually Transmitted Infections +VMMC	95	8,781	605	15	Dominated	34.2

VMMC95	Voluntary male medical circumcision	95	704	326	2	2.2	2.2

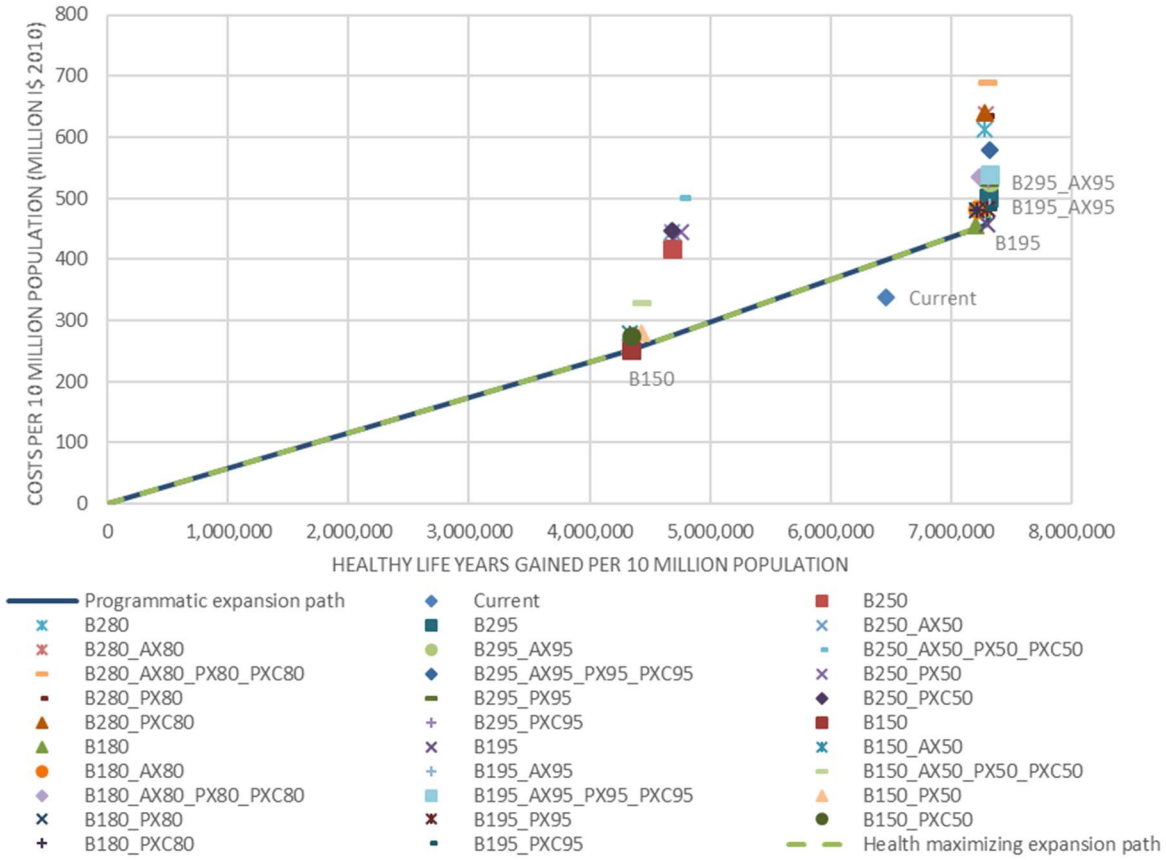
TB Results

TB treatments are known to be highly cost effective [6]. In both regions, the basic care-and-control scenario including treatment (FLD + SLD), detection (Smear + X-ray + Culture) and drug susceptibility cannot be unbundled since screening cannot be implemented separately from treatment. The expansion path shows increasing levels of coverage culminating at the highest (95%) in order to achieve maximum health gains.

Subsequently, following the programmatic expansion path and as resources become available, more interventions with lower cost-effectiveness but which are still cost effective would be added. In eastern sub-Saharan African, where the global TB/HIV burden is high, preventive therapy for HIV-positive TB cases not on ART and on ART with latent TB infection, preventive therapy for children with latent TB infection and ART prioritization for notified HIV-positive TB cases would be progressively combined to the basic care-and-control scenario. In southeast Asia, ART prioritization for notified HIV-positive TB cases would be added to the basic care-and-control scenario.

For southeast Asia we observe that an average package of current interventions for the reference time of 2010 is superior to the interventions on the programmatic expansion path (Fig.3). Similar to the HIV results discussed above, this is largely an artefact of our analysis which was performed using fixed coverage levels (50%, 80% and 95%); actual programmes can and in practice do discover coverage combinations that are more cost-effective. In eastern sub-Saharan Africa, the question is not one of fine tuning coverage levels, but rather of programmatic expansion (Fig. 4). Average current practice at the reference time of 2010 is close in efficiency terms to the programmatic expansion path but less cost effective than the health maximizing expansion path, which is focused on maximising the health gains only.

Figure 3 Cost effectiveness expansion path for TB interventions in Southeast Asia

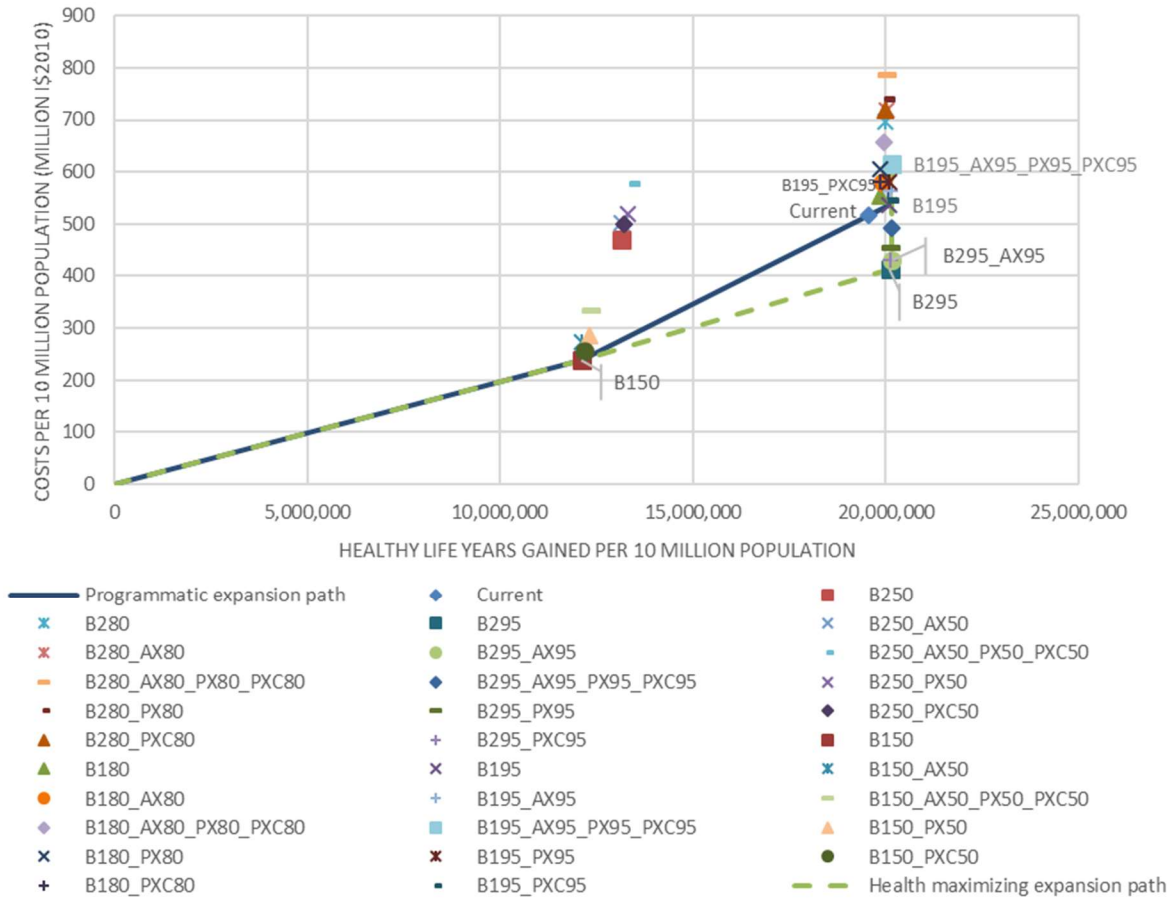


*Refer to Table 2 for interventions label *50, 80 and 95 at the end of each label refer to coverage of 50%, 80% and 95% respectively

Table 16 Costs, effects and cost effectiveness of TB interventions in Southeast Asia over 100 years

	Intervention	Pop. coverage (%)	Total costs per 10 million population (million I$ 2010)	Healthy life years (million HLY) gained per 10 million population	ACER (I$ per HLY)	ICER (I$ per HLY) (Programmatic expansion path)	ICER (I$ per HLY) (Health maximizing expansion path)
Current	Current Scenario		337.5	6.5	52		
B295_AX95	Treatment (FLD+SLD)+Detection (Xpert + X-ray +Culture) +Drug susceptibility testing + ART° prioritization for TB cases	95	525.6	7.3	72	Dominated	53,279.4
B150	Treatment (FLD +SLD) +Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing	50	251.7	4.3	58	58.0	58.0
B195	Treatment (FLD +SLD) +Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing	95	456.7	7.3	63	69.3	69.3
B195_AX95	Treatment (FLD +SLD)+Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing + ART° prioritization for TB cases	95	486.3	7.3	66	1,673.9	1,673.9

Figure 4 Cost effectiveness expansion path for TB interventions in eastern sub-Saharan Africa



*Refer to Table 2 for interventions label *50, 80 and 95 at the end of each label refer to coverage of 50%, 80% and 95% respectively

Table 17 Costs, effects and cost effectiveness of HIV interventions in eastern sub-Saharan Africa over 100 years

	Intervention	Pop. coverage (%)	Total costs per 10 million population (million I$ 2010)	Healthy life years (million HLY) gained per 10 million population	ACER (I$ per HLY)	ICER (I$ per HLY) (Programmatic expansion path)	ICER (I$ per HLY) (Health maximizing expansion path)
Current	Current Scenario		516	20	26		
B295	Treatment (FLD+SLD) +Detection (Xpert +X-ray+ Culture) +Drug susceptibility testing	95	413	20	21	Dominated	21.7
B295_AX95	Treatment (FLD+SLD)+Detection (Xpert + X-ray +Culture) +Drug susceptibility testing + ART° prioritization for TB cases	95	431	20	21	Dominated	501.2
B150	Treatment (FLD +SLD) +Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing	50	239	12	20	19.7	19.7
B195	Treatment (FLD +SLD) +Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing	95	536	20	27	37.3	Dominated
B195_AX95_PX95_PXC95	Treatment (FLD +SLD) +Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing + ART° prioritization for TB cases + Preventive therapy + Preventive therapy for children	95	614	20	30	1,306.4	15,413.7
B195_PXC95	Treatment (FLD +SLD)+Detection (Smear+ X-ray+ Culture) +Drug susceptibility testing + Preventive therapy for children	95	545	20	27	316.2	Dominated

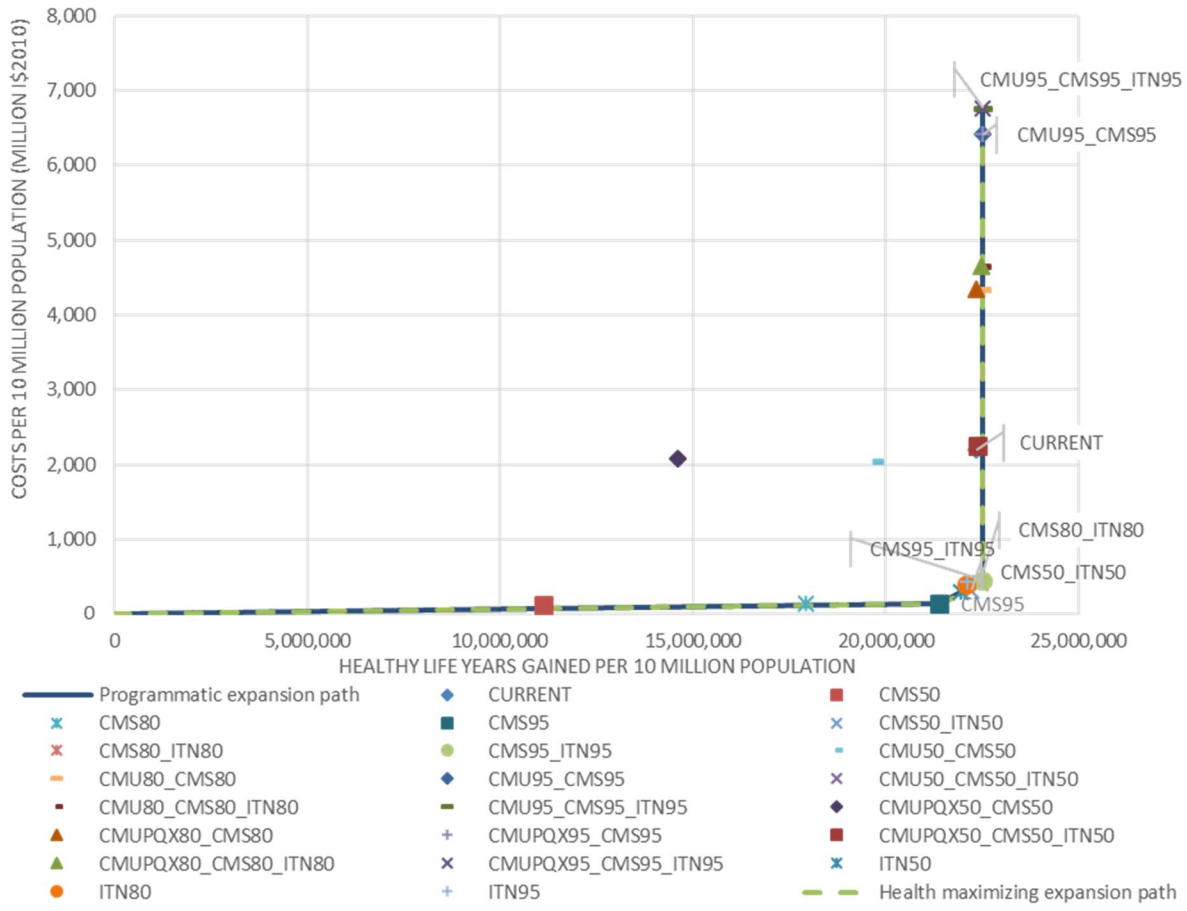
Malaria Results

P. vivax Malaria Results

In South-East Asia, management of severe cases is the most cost-effective intervention (Table 18). As severe malaria is fatal in nearly all cases without treatment, successfully treating the severe cases at reasonable cost results in important health benefits in terms of averted mortality. However, promptly treating uncomplicated malaria is necessary to avoid severe cases, as well as are preventive interventions to reduce case incidence. Prevention and case management are therefore the keys to cost-effective control of malaria.

The package of average current interventions at the reference time of 2010 is on the programmatic expansion path.

Figure 5 Cost effectiveness expansion path for P. vivax malaria interventions in Southeast Asia



*Refer to Table 3 for interventions label *50, 80 and 95 at the end of each label refer to coverage of 50%, 80% and 95% respectively

Table 18 Costs, effects and cost effectiveness of P. vivax malaria interventions in Southeast Asia over 100 years

	Intervention	Pop. coverage (%)	Total costs per 10 million population (million I$ 2010)	Healthy life years (million HLY) gained per 10 million population	ACER (I$ per HLY)	ICER (I$ per HLY) (Programmatic expansion path)	ICER (I$ per HLY) (Health maximizing expansion path)
CURRENT	Current Scenario		2201.9	22.4	98.5	_	_
CMS95	Management of severe cases	95	146.0	21.4	6.8	6.8	6.8
CMS50_ITN50	Management of severe cases + Insecticide-treated bed nets	50	319.3	22.2	14.4	Dominated	203.9
CMS80_ITN80	Management of severe cases + Insecticide-treated bed nets	80	413.9	22.4	18.4	Dominated	437.4
CMS95_ITN95	Management of severe cases + Insecticide-treated bed nets	95	453.9	22.5	20.2	273.5	671.4
CMU95_CMS95	Management of suspected uncomplicated cases + Management of severe cases	95	6412.1	22.5	284.9	Dominated	415,189.9
CMU95_CMS95_ITN95	Management of suspected uncomplicated cases + Management of severe cases + Insecticide-treated bed nets	95	6762.9	22.5	300.5	445,521.1	Dominated

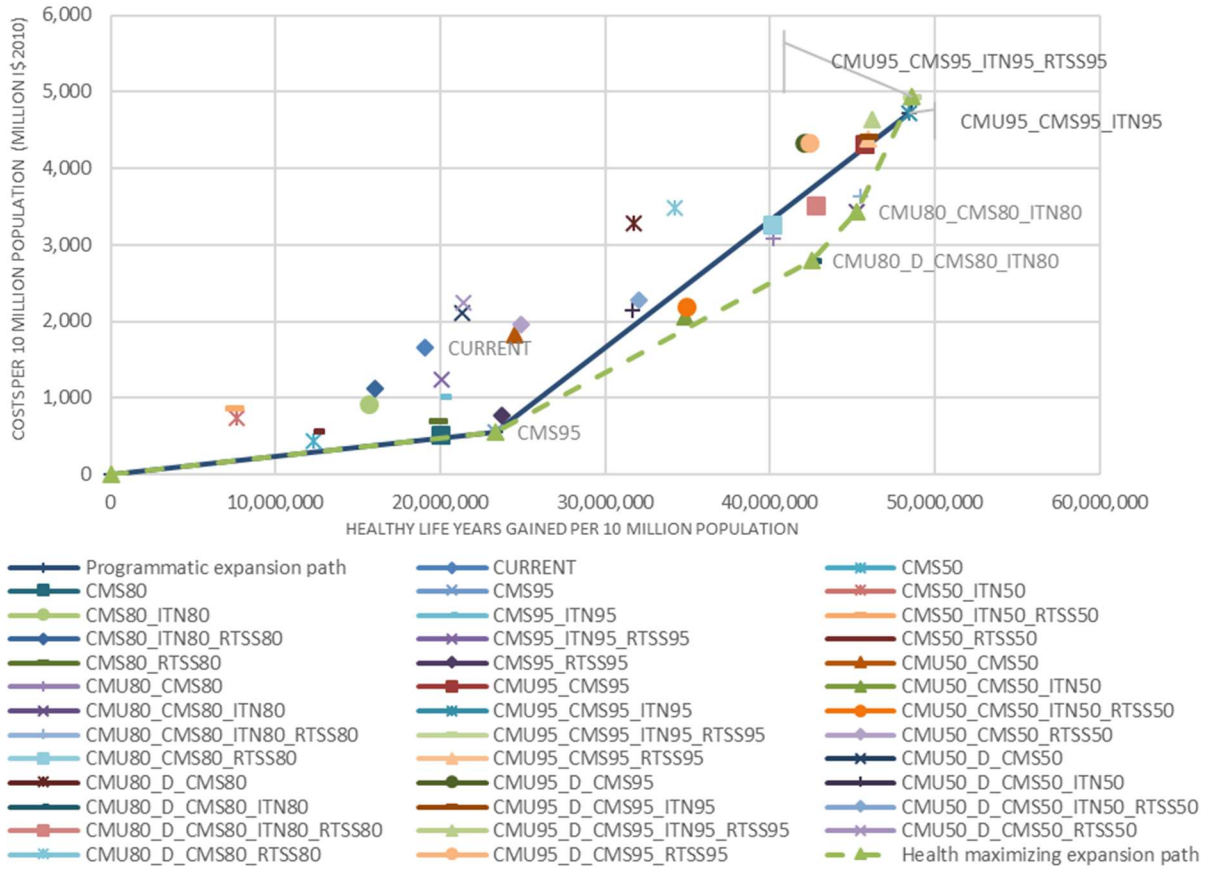
P.falciparum Malaria Results

As for the *P.vivax* malaria results, above, in eastern sub-Saharan Africa, management of severe cases is highly cost-effective. Following the programmatic expansion path, management of suspected uncomplicated cases and ITN would be added to form the treatment and incidence reducing combination, which is key to cost-effective control of malaria. Malaria vaccine with

RTS,S, at 95% coverage would complement the combination, adding to incidence reduction and maximizing the healthy life years gained (Table 19).

The package of average interventions coverage levels at the reference time of 2010 is well in the interior of the expansion path (Fig.6), highlighting the opportunity for efficiency gains without sacrificing programmatic criteria.

Figure 6 Cost effectiveness expansion path for P. falciparum malaria interventions in eastern sub-Saharan Africa



*Refer to Table 4 for interventions label *50, 80 and 95 at the end of each label refer to coverage of 50%, 80% and 95% respectively

Table 19 Costs, effects and cost effectiveness of P. falciparum malaria interventions in eastern sub-Saharan Africa

	Intervention	Pop. coverage (%)	Total costs per 10 million population (million I$ 2010)	Healthy life years (million HLY) gained per 10 million population	ACER (I$ per HLY)	ICER (I$ per HLY) (Programmatic expansion path)	ICER (I$ per HLY) (Health maximizing expansion path)
CURRENT	Current Scenario		1,657.9	19.1	87.0		
CMS95	Management of severe cases	95	556.8	23.3	23.9	23.9	23.9
CMU80_CMS80_ITN80	Management of suspected uncomplicated cases + Management of severe cases + Insecticide-treated bed nets	80	3,430.7	45.3	75.8	Dominated	232.2
CMU95_CMS95_ITN95	Management of suspected uncomplicated cases + Management of severe cases + Insecticide-treated bed nets	95	4,715.8	48.5	97.3	165.2	398.9
CMU95_CMS95_ITN95_RTSS95	Management of suspected uncomplicated cases + Management of severe cases + Insecticide treated bed nets + Malaria vaccine with RTS,S	95	4,939.3	48.6	101.6	1,792.7	1,792.7
CMU80_D_CMS80_ITN80	Management of suspected uncomplicated cases with treatment seeking fever cases RDT° tested + Management of severe cases + Insecticide-treated bed nets	80	2,791.8	42.5	65.7	Dominated	116.4

Discussion

Principal Findings

This study provides a quantitative assessment of allocative efficiency within three critical infectious-disease programme areas: HIV, TB and Malaria. By retrospectively shining a spotlight on how programme development and scale up worked during the first decade of the 21st century (2000-2010), it aims to assist policy makers in understanding what worked in obtaining value for money for HIV, TB and malaria strategy.

Over the study period, the global community has done relatively well for HIV, TB, and malaria regarding economic and programmatic criteria. The role of international assistance, financial and technical, arguably was critical to these successes. Commonly used interventions, at the reference time of 2010, for HIV, TB and malaria were cost-effective, with cost-effectiveness ratios less than I$ 100/HLY saved for virtually not only optimal interventions but for most of those included in this study. This level of cost-effectiveness would qualify interventions in the health sub-sector of HIV, TB, and malaria as "best buys" by conventional international standards **[68]**. It is essential to make this point when there is still a common perception that, for example, HIV and TB treatment regimens are prohibitively expensive compared to the health gains they offer. For South-East Asia, implemented interventions were on the programmatic expansion path or were found to be even more cost effective than the intervention combination studied in this analysis due to reasons stated above. In eastern sub-Saharan Africa, implemented interventions performed only slightly worse in cost-effectiveness terms than other combinations.

Comparison of the health-maximizing expansion path versus the programmatic expansion path shows different patterns depending on the disease and the region. However, where they differ, selection of the programmatic expansion path clearly involves important opportunity costs in health terms. These less cost-effective but programmatically superior options therefore represent real choices for policy makers: in lower- resource settings there are strong arguments in favour of the health-maximizing expansion path (since the alternative represents a very long-term future optimum), whereas in much less constrained settings it makes sense to observe the phasing of the programmatic expansion path. Actual choices in either type of setting may of course reflect the existence of asset-specific investments that have already been made.

Policy Implications

As we look across the health sector, especially in LICs and LMICs, coverage levels typically are far below what is required for optimal disease control and elimination. Although more needs to be done, high coverage levels have already been achieved in many countries. This means that populations in need of health services have, at least on average, the opportunity to receive many of the services they require. In addition, however, when we look at the mix of interventions being implemented, we can see that actual practice is highly cost effective, at least on average and at aggregate level. So, not only are coverage levels higher in HIV, TB and malaria than for other conditions in LICs and LMICs but also the mix of interventions implemented and the associated coverage levels are highly cost-effective.

It may be hard to recognize how unusual a finding this is. In almost no other area of global health is such a finding observed, at least outside of high-income countries. So, it is an interesting question to ask why this has happened? Although we cannot know the answer for sure, we discuss some hypotheses that seem likely, based on our experience working across disease areas and countries during the past two decades.

First, it seems to us that these results are not independent of the fact that HIV, TB and malaria programmes explicitly involved epidemiological and economic modelling evidence in the development of their programmes. The concept of evidence-based medicine, and evidence-based policy is arguably very strongly anchored in the control strategies of the three diseases.

Second, unprecedented levels of international donor funding and technical assistance has certainly played an important role. For example, the Global Fund has been able to provide a platform for international collective action independent from bilateral funding mechanisms and priorities and has played an important role in catalysing additional funding for the three diseases, including from domestic finance, in the worst affected countries. This suggests the extent to which sustained collective action combined with evidence-based policies can have an impact on health outcomes in the most resource constrained settings.

Major donors such as Pepfar and the Global Fund and hybrid actors such as UNITAID have likely played an important catalysing role in not only financing but also in market shaping and in ensuring the presence of high quality technical advice and the application of international normative

guidance, such as from WHO technical programmes, in the worst affected countries. While we cannot demonstrate this hypothesis scientifically, it is important to recall that the funding provided by Global Fund is, in many respects, only catalytic, as the absolute amounts provided cannot explain the overall increase in coverage witnessed since the beginning of the MDG era. Other funders have notably been important, including bilateral funders and Pepfar. But also, and quite importantly, these actors have catalysed domestic financing that has become more important as economic growth has continued in these regions.

These observations are not a cause for complacency. Coverage levels are still inadequate from the standpoint of the economic and disease burden inflicted on the regions studied. Regression to lower levels of epidemic control is not impossible and in some cases is now being witnessed. International collective action must continue to support the case for this global public good

Limitation of the Analysis

Our analysis is based on the average combination of interventions used in typical countries in the studied regions in the reference year 2010. Our results are intended to be indicative of implementation performance relative to the global knowledge of best practice at the time, rather than prescriptive packages intended for countries to implement now. Our study illustrates the economic and programmatic performance of most common interventions at the time, rather than an exhaustive cost-effectiveness analysis of all existing interventions recommended by the WHO at the time of this publication. In addition, some key population groups were missing in our analysis particularly for the HIV analysis where, for example, the target group for sex workers could have included men rather than just women. Transgender people or prisoners could also have been represented. These choices, while bringing greater realism, would have been challenging to model. Some other limitations to this paper are related to the methodological approach to cost-effectiveness analysis in general and the GCEA in particular and are discussed in more details elsewhere [69] [11]

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Chapter III: Cost-effective interventions for breast cancer, cervical cancer, and colorectal cancer: new results from WHO-CHOICE

Published in 'Cost Effectiveness and Resource Allocation' journal

Ralaidovy *et al. Cost Eff Resour Alloc (2018) 16:38*
https://doi.org/10.1186/s12962-018-0157-0

Cost-effective interventions for breast cancer, cervical cancer, and colorectal cancer: new results from WHO-CHOICE

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Abstract

Background

Following the adoption of the Global Action Plan for the Prevention and Control of NCDs 2013-2020, an update to the Appendix 3 of the action plan was requested by Member States in 2016, endorsed by the Seventieth World Health Assembly in May 2017 and provides a list of recommended NCD interventions. The main contribution of this paper is to present results of analyses identifying how decision makers can achieve maximum health gain using the cancer interventions listed in the Appendix 3. We also present methods used to calculate new WHO-CHOICE cost-effectiveness results for breast cancer, cervical cancer, and colorectal cancer in Southeast Asia and eastern sub-Saharan Africa.

Methods

We used "Generalized Cost-Effectiveness Analysis" for our analysis which uses a hypothetical null reference case, where the impacts of all current interventions are removed, in order to identify the optimal package of interventions. All health system costs, regardless of payer, were included. Health outcomes are reported as the gain in healthy life years due to a specific intervention scenario and were estimated using a deterministic state-transition cohort simulation (Markov model).

Results

Vaccination against human papillomavirus (2 doses) for 9–13-year-old girls (in eastern sub-Saharan Africa) and HPV vaccination combined with prevention of cervical cancer by screening of women aged 30–49 years through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions (in Southeast Asia) were found to be the most cost effective interventions. For breast cancer, in both regions the treatment of breast cancer, stages I and II, with surgery +/-

systemic therapy, at 95% coverage, was found to be the most cost-effective intervention. For colorectal cancer, treatment of colorectal cancer, stages I and II, with surgery +/- chemotherapy and radiotherapy, at 95% coverage, was found to be the most cost-effective intervention.

Conclusion

The results demonstrate that cancer prevention and control interventions are cost-effective and can be implemented through a step-wise approach to achieve maximum health benefits. As the global community moves toward universal health coverage, this analysis can support decision makers in identifying a core package of cancer services, ensuring treatment and palliative care for all.

Keywords

Cost-effectiveness analysis, breast cancer, cervical cancer, colorectal cancer, priority setting, resource allocation, expansion path, impact modelling, intervention costing, universal health coverage.

Background

Although not specifically mentioned in the Millennium Development Goals (MDGs), cancer is now addressed in target 3.4 of the Sustainable Development Goals (SDGs), which aims to reduce premature mortality related to non-communicable Diseases (NCDs). Cancer is one of the main causes of morbidity and mortality worldwide, with the incidence of new cases expected to rise by 70% in the next two decades [1]. Between 2000 and 2015, cancer deaths globally increased from 7 million to 8.8 million deaths each year, accounting for 1 in 6 of all deaths globally and the largest relative increase has been in low- and middle-income countries, where health systems are least prepared to manage the cancer burden [2]. While communicable disease deaths have decreased 26% between 2000 and 2015, deaths from cancer have increased 26%, with a significant increased proportion of cancer-related deaths occurring in Asia and Africa [3], [2]. Cervical cancer and breast cancer are the leading causes of cancer-related death among women in the sub-Saharan Africa region, resulting in, respectively, 23.2% and 19.3% [3] of total cancer deaths; colorectal cancer is one of the most common causes of cancer-related death for both sexes worldwide [3]. The total annual economic costs of cancer globally was estimated at approximately US$ 1.16 trillion in 2010 and has continued to rise, threatening health budgets and economies at all income levels and also causing financial catastrophe for individuals and families [3].

Following the adoption of the Global Action Plan for the Prevention and Control of NCDs 2013-2020 in 2013 [4], an update to Appendix 3 of the action plan was requested by the Member States in 2016 [5]. The update, which provides a list of recommended NCD interventions, was endorsed by the Seventieth World Health Assembly in May 2017. These priority NCD interventions, if implemented to scale, would enable countries to make significant progress to reduce by 25% the number of the NCD-related premature death by 2025 [6].

To achieve these targets and those specified in the United Nations Agenda for Sustainable Development, cancer screening programs need to become more systematic and reach a more significant proportion of their target populations in Southeast Asia and eastern sub-Saharan Africa. Data from the WHO Country Capacity Survey 2015 found that countries in WHO South-East Asia (SEAR) and Africa Regions (AFR) were the least likely among WHO Regions to have a breast screening program with 64% and 57% availability respectively. However, the majority of screening programs reached less than 10% coverage in these regions. Human papillomavirus

(HPV) vaccination was available in approximately 50% of countries in AFR and almost 20% in SEAR, similarly with the majority reaching less than 10% coverage. Cancer centres or cancer departments were available in approximately 55% of countries in SEAR and 30% in AFR. Treatment, including cancer surgery and subsidized chemotherapy, and palliative care services were also generally unavailable to the majority of countries [7]

The main contribution of this paper is to present results of analyses used to identify how decision makers can achieve maximum health gain using the cancer interventions in Appendix 3 of the global action plan. We also present methods used to calculate new WHO-CHOICE cost-effectiveness results for breast cancer, cervical cancer, and colorectal cancer. The "expansion paths" we present are a proposed sequence in which interventions could be adopted to achieve the maximum health gain. The order in which each intervention or combination of interventions appears on the line is based on the incremental costs and effectiveness of each intervention compared to the last one on the line. [8].

Methods

We used Generalized Cost-Effectiveness Analysis (GCEA) for our analysis, which is an approach recommended by WHO-CHOICE and details of which have been published previously [8], [9], [10]. In this paper, we describe the methods related to breast cancer, cervical cancer, and colorectal cancer.

We did not analyze all possible combinations of interventions for these three cancers, an approach which has been previously studied [11]. Instead, we emphasize a package of interventions relevant to a comprehensive cancer control programme. A "comprehensive cancer control approach" consists of prevention, early diagnosis and screening linked to treatment, palliative care, and survivorship care [12]. We focus moreover on those aspects of comprehensive cancer control that are generalizable to all resource settings. Furthermore, based on previous work on cancer [13] [14], the use of an approach based on comprehensive cancer control has been found to be justified on grounds of cost effectiveness.

We considered aspects of the expansion path that take into account specific programmatic concerns. This means that, if a particular technology appears on the expansion path at a certain level of coverage, then for the next step, we considered the most cost effective interventions that

included this particular technology at the same or higher coverage, since a decision maker would likely not wish to bring a particular intervention up to scale only to replace it with a competing technology when higher levels of resources are available.

Our analysis is restricted to Southeast Asia and eastern sub-Saharan Africa [15] and uses epidemiological and cost data for a base year of 2010. These two regions were selected as they are geographically and epidemiologically diverse regions which will provide differing examples of cost-effectiveness results and, we predicted, would have different findings. These regions are a WHO-CHOICE level feature across 20 diseases/risk factors. A generic approach is required for standardization. The results are intended to be indicative examples, rather than prescriptive packages for countries to implement. Health outcomes are reported as the gain in healthy life years (HLYs) and are estimated using a dynamic simulation model in the Spectrum software. HLYs are presented both undiscounted and discounted at 3% per annum [8]. Disability weights (DWs) were obtained from the Global Burden of Disease (GBD) study 2010 [16]. All health system costs required to deliver the intervention are included, regardless of payer. Costs include patient-level delivery costs as well as programme-level (i.e. overhead) costs [17]. A 3% per annum discount is applied to costs in all scenarios [8]. Programmes are considered to be implemented for 100 years. Each individual and combined intervention is evaluated at 50%, 80% and 95% coverage levels [17].

Impact modelling

Interventions

This paper analyses 14 individual and combination interventions: 9 for cervical cancer, 3 for breast cancer, and 2 for colorectal cancer.

These interventions are listed in Table 1. All interventions are first compared to the "null," a hypothetical scenario where the effects of all currently implemented interventions are removed. Following the definition of the null, the marginal effects and costs of each intervention or combination are evaluated.

Interventions are based on WHO Guidance for cervical cancer [18], for breast cancer [6], [14], [19], [20] and for colorectal cancer [14], [19], [20], [21], These guidelines emphasize comprehensive cancer control including diagnosis, staging, multi-modality treatment, survivorship care and palliative care.

Table 1: Interventions included in the analysis

Disease	Label	**Interventions** [22]
Cervical Cancer	C1a	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls
	C1b	Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions
	C1c	Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions
	C1d	Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions
	C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions
	C1f	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions
	C1g	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions
	C1h	Treatment of cervical cancer stages I and II with either surgery or radiotherapy +/- chemotherapy
	C1i	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines
Breast Cancer	C2a	Treatment of breast cancer stages I and II with surgery +/- systemic therapy
	C2b	Screening with mammography (once every 2 years for women aged 50-69 years) linked with timely diagnosis and treatment of breast cancer
	C2c	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines
Colorectal Cancer	C3a	Treatment of colorectal cancer stages I and II with surgery +/- chemotherapy and radiotherapy
	C3b	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines

Estimation of HLYs

Health outcomes were estimated using a deterministic state-transition cohort simulation (Markov model). In this type of simulation, healthy stages and disease stages, distributed by age, are modelled as the exhaustive and mutually exclusive states of a Markov model, i.e. at any cross-sectional point in time, all persons in the population belong to one and only one of the states. As persons age, they transition between states based on state-specific transition rates. They can either remain in the healthy state, or transition from healthy to the initial disease state, representing disease onset, and then transition between subsequent disease states, representing either progression to an advanced state of disease or regression to a lower disease state or back to the healthy state. Regression to healthy state is modelled only for pre-cancerous states. By representing preclinical and clinical disease stages as separate states, diagnoses are modelled through transitions from preclinical to clinical states. Persons can transition to mortality from any state, at which point they leave the model. To model the impact of disease and treatment, different rates are used for transitioning to mortality, e.g. higher rates are applied to more advanced stages of disease to represent the reduced effectiveness of treatment. A brief outline of the state transitions specific to each type of cancer are discussed below, and detailed flow diagrams are presented in Additional file 1. The model is discussed in more detail in [23].

In the absence of an intervention, transitions are based on natural rates of progression or regression. With an intervention, rates of transitions are modified, e.g. the rates from healthy to HPV state are decreased to represent the effectiveness of vaccination, or the rates from preclinical to clinical states are increased, such that more persons are diagnosed in early stages of disease to represent effective screening. The health outcomes of interventions are measured as a relative increase in healthy life years lived in an intervention scenario compared to no intervention. Healthy life years are calculated as the sum of person-time in all states (except mortality) after discounting for disability specific to each state (see Disability weights).

Cervical cancer

The vast majority of cervical cancer cases originate as human papillomavirus (HPV) infection, a sexually transmitted disease. Therefore, the cervical cancer state-transition model consisted of 3 components: HPV transmission, pre-cancerous HPV progression and regression, and cervical

cancer progression. HPV subtypes were categorized into three groups: (i) HPV 16/18 (which contributes to an estimated 70% [24] of all cervical cancers), (ii) HPV high-risk (all HPV types other than 16/18 that are at high-risk of progressing to cancer), and (iii) HPV low-risk (all other types that have a low-risk of progressing to cancer). Co-infection with multiple subtypes was not modelled.

It was assumed that women in the healthy state can become infected with one of the 3 HPV categories through sexual contact with an infected partner. Therefore, the rates of transition from healthy to HPV states were determined dynamically through a transmission model. In the pre-cancerous part of the model, persons in the HPV+ state could progress to cervical intra-epithelial neoplasia (CIN), subsequently to a low-grade dysplasia CIN-1, and then advance to CIN-2-3. Persons in CIN stages could naturally regress in disease stage and have HPV clearance, or could regress to HPV upon screening and treatment. Upon regression, there was short-term immunity to HPV before transitioning to healthy state that re-exposed persons to infection. From CIN-2-3, persons could progress to invasive cancer, first to carcinoma in-situ (CIS), and further to states I, II, III, and IV. From any of these states, persons could transition from pre-clinical to clinical states through diagnosis based on symptoms or through screening. In men, we did not model cancers related to HPV, but only modelled HPV infection, transmission and natural regression. Detailed flow diagrams of the state transitions are presented in Additional file 1.

Breast cancer

We assumed that breast cancer initiated directly as carcinoma in-situ (CIS), i.e., women could transition from healthy to CIS then progress to invasive carcinoma stages I, II, III, and IV. From any of these disease states, persons could transition from pre-clinical to clinical states through diagnosis based on symptoms or through screening.

Colorectal cancer

We assumed that about 77% of colorectal cancers originate as pre-cancerous polyps and the remaining 23% originate directly as carcinoma in-situ (CIS) [25], [26]. We have divided the pre-cancerous states into three different sizes of polyps (<= 5mm, 6-9mm, >= 10mm) because of the variation in effectiveness of treatment by polyp size [27]. Upon transition to CIS, disease progresses through invasive carcinoma stages I, II, III, and IV. From any of these states, persons

can transition from pre-clinical to clinical states through diagnosis based on symptoms or through screening.

Data sources for state-transition rates

We assumed that natural rates of transition from healthy to first stage of disease and from preclinical to clinical states, i.e., in the absence of a controlled intervention program, were specific to the population. These population-specific parameters were estimated using a newly developed Markov-process methodology that is described in elsewhere [23] and summarized in Additional file 1. We assumed that rates of natural progression and regression between disease states are specific to the cancer but do not vary by population. We extracted these parameters from the literature (see Additional file 1.)

Each major cancer group (i.e., breast, cervical and colorectal) and each stage of disease has unique values for transition parameters to account for variations in the tumor biology and progression of cancer. It is likely that there are also differences in the natural history and tumor biology between the different molecular subtypes within each of these major cancer groups. Currently, the published studies in LMIC from which parameters are generated have not generally distinguished between these molecular subtypes. However, the parameters of the model do allow for greater specificity that can be used as more data on the diagnosis and treatment of cancer subtypes becomes available – for example, the diagnostic rates and impact of trastuzumab for HER2+ breast cancer in LMIC, which does have a distinct natural history and impact of this particular treatment strategy

Intervention effect sizes

Disability weights

Disability weights (DWs) for each health state were drawn from the disability weight study of the Global Burden of Disease 2010 [16] and can be found in Additional file 2, Table 2.

GBD provides DWs for the following general cancer stages: “cancer: diagnosis and primary therapy”, “Cancer: metastatic”, “terminal phase: with medication (for cancers, end-stage kidney or liver disease)”, “terminal phase: without medication (for cancers, end-stage kidney or liver disease)”, as well as “mastectomy” and “stoma” cancer-specific stages/states.

For all three cancer types, we obtained DWs for all pre-terminal cancer phases without treatment, by inflating the “cancer: diagnosis and primary therapy” DW estimate by the ratio between the

two DW estimates provided for terminal cancer without treatment. For the terminal cancer stage of each cancer type, we used the GBD estimate directly.

For the DWs for cancer with treatment, for the terminal cancer stage of each cancer type, we used the GBD estimate directly. For the pre-terminal cancer stages we followed a disease-specific approach, as described following.

Cervical cancer

For the early stages (0 to II) we used the DW for "cancer: diagnosis and primary therapy" and applied a correction for the percentage of cases in the first year of treatment only. For stage III we did not apply a correction.

Breast cancer

For early stages (I and II) we used a weighted average DW for "cancer: diagnosis and primary therapy" and "mastectomy", and applied the DW to the percentage of cases in the first year of treatment only. For stage III we used "cancer: diagnosis and primary therapy", and we applied the DW to the percentage of cases in the first year of treatment in that stage.

Colorectal cancer

We used a weighted average DW for "cancer: diagnosis and primary therapy" and "stoma" for the estimated 5% of patients who would require a stoma, and adjusted the part corresponding to "cancer: diagnosis and primary therapy" for the percentage of cases in the first year of treatment in that stage only, except for stage III for which we did not apply this correction.

Incidence

For all 3 cancers, incidence estimates and age at diagnosis are sourced from GLOBOCAN [21].

For cervical cancer, estimates of HPV distribution by type are taken from [28], [29] and [30]. Transition rates from dysplasia (CIN) to carcinoma are taken from [31].

All effect sizes can be found in the Additional file 2.

Intervention costing

We followed a standardized framework developed for WHO-CHOICE to cost all the interventions. We used an "ingredients based" approach, whereby each input required for the intervention is identified and valued. We have included costs incurred at the point of delivery such as drugs and supplies, and health facility visits (including health workforce costs), as well as programmatic

costs such as administration, monitoring and evaluation, supervision, training [17]. Programmatic costs for cancer screening include administrative costs, quality assurance and monitoring and evaluation, estimated at approximately 20% of total costs [32]. Screening programme costs include follow-up diagnostic tests for false positive screening results. All intervention costs are calculated assuming that the health system capacity is available to support the intervention. Lists of consumables were identified from WHO Priority Medical Devices in Cancer Management 2017 [33]. Consumables required include those needed for treatment-related complications and surveillance after treatment completion. Systemic therapy treatment regimens were taken from WHO List of Essential Medicines [34]. Prices were taken from the MSH drug price database as median buyer price [35] and from the WHO-CHOICE price database [17]. Costs in all scenarios were discounted at 3% per annum. Costs are reported in 2010 International dollars. Costing assumptions can be found in Additional file 2.

Results

Costs, HLYs gained, and the cost effectiveness associated with each intervention are presented in Table 2 and Table 4. These tables present only the most cost-effective interventions on the sectoral expansion path for all three cancers. Interventions that are "dominated" i.e. are more costly or less effective, are presented in cancer-specific tables (see Additional file 2).

For cervical cancer, vaccination against human papillomavirus (2 doses) of 9–13-year-old girls combined with prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions (CVC_C1e) at 50% coverage is the most cost-effective intervention in Southeast Asia, with an incremental cost-effectiveness of I$ 87 per HLY gained. At full coverage (95%), this combination intervention produces the highest effectiveness among all cervical cancer interventions. In eastern sub-Saharan Africa, vaccination against human papillomavirus (2 doses) of 9–13-year-old girls (CVC_C1a) as an individual intervention, at 50% coverage is the most cost-effective intervention for cervical cancer, with an Incremental Cost-Effectiveness Ratio (ICER) of I$ 28 per HLY gained. For maximum health gain, this intervention then has to be progressively brought up to 95% coverage and combined with prevention of cervical cancer, by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions (CVC_C1e).

For breast cancer, for both regions, treatment of breast cancer stages I and II with surgery +/- systemic therapy (BRC_C2a) at 95 % coverage is the most cost-effective intervention with an ICER of I$ 252 per HLY gained in Southeast Asia and I$ 113 per HLY gained in eastern sub-Saharan Africa. Screening with mammography (once every 2 years for women aged 50 to 69 years) linked with timely diagnosis and treatment (BRC_C2b) is less cost-effective, since mammography is a high-resource use technology. In addition, mammography requires a robust health infrastructure for a country to be able to sustain an organized population-based screening programme [36].

For colorectal cancer, for both regions, treatment of colorectal cancer, stages I and II, with surgery +/- chemotherapy and radiotherapy (CRC_C3a) at 95% coverage is cost effective at I$ 238 per HLY gained in southeast Asia, and I$ 217 per HLY gained in eastern sub-Saharan Africa.

Overall, cervical cancer interventions are the most cost effective strategies among the studied interventions against cancer. Their favourable cost-effectiveness ratio arises from effective primary and/or secondary preventative strategies that effectively reduce the burden of disease at a low cost.

For all three cancers, basic palliative care is an essential element in cancer control that should be added at 95% coverage for optimal implementation.

Figure 1 and 2 show the expansion path a decision maker would follow to achieve the maximum health gain in respectively, Southeast Asia and eastern sub-Saharan Africa.

If, with enough resources, all the interventions on the expansion path can be implemented, the budgetary allocation at full coverage across each of the three cancers would be as follows: in Southeast Asia: breast cancer, 56%; cervical cancer, 30%; colorectal cancer, 14%; in Eastern sub-Saharan Africa: Breast Cancer, 48%; Cervical Cancer, 45%; Colorectal Cancer, 7% (Table 4).

Table 2: Costs, effects and incremental cost-effectiveness of cancer interventions in Southeast Asia

Label*	Description of the intervention	Pop° coverage (%)	Costs per 10 million population (million I$ 2010)	HLY per 10 million population (undiscounted)	Average Cost-Effectiveness Ratio (ACER)	Incremental Cost-Effectiveness Ratio (ICER)
CVC_C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	50	396	4 541 842	87	87
CRC_C3a	Treatment of colorectal cancer stages I and II with surgery +/- chemotherapy and radiotherapy	95	207	870 417	238	238
BRC_C2a	Treatment of breast cancer stages I and II with surgery +/- systemic therapy	95	206	816 200	252	252
CVC_C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–	80	549	5 106 391	108	272

	49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions					
CVC_C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	95	626	5 262 580	119	491
BRC_C2b	Screening with mammography (once every 2 years for women aged 50-69 years) linked with timely diagnosis and treatment of breast cancer	95	1,056	1 627 782	649	1 048
BRC_C2c	Basic palliative care for Breast Cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	95	193	22 877	8 434	8 434
CRC_C3b	Basic palliative care for Colorectal Cancer: home-	95	158	5 944	26 571	26 571

	based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines					
CVC_C1i	Basic palliative care for Cervical Cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	95	156	5 262	29 704	29 704

*CVC: Cervical cancer, BRC: Breast cancer, CRC: Colorectal cancer

Figure 1: Cost effectiveness expansion path for Southeast Asia. Refer to Table 1 for interventions'label

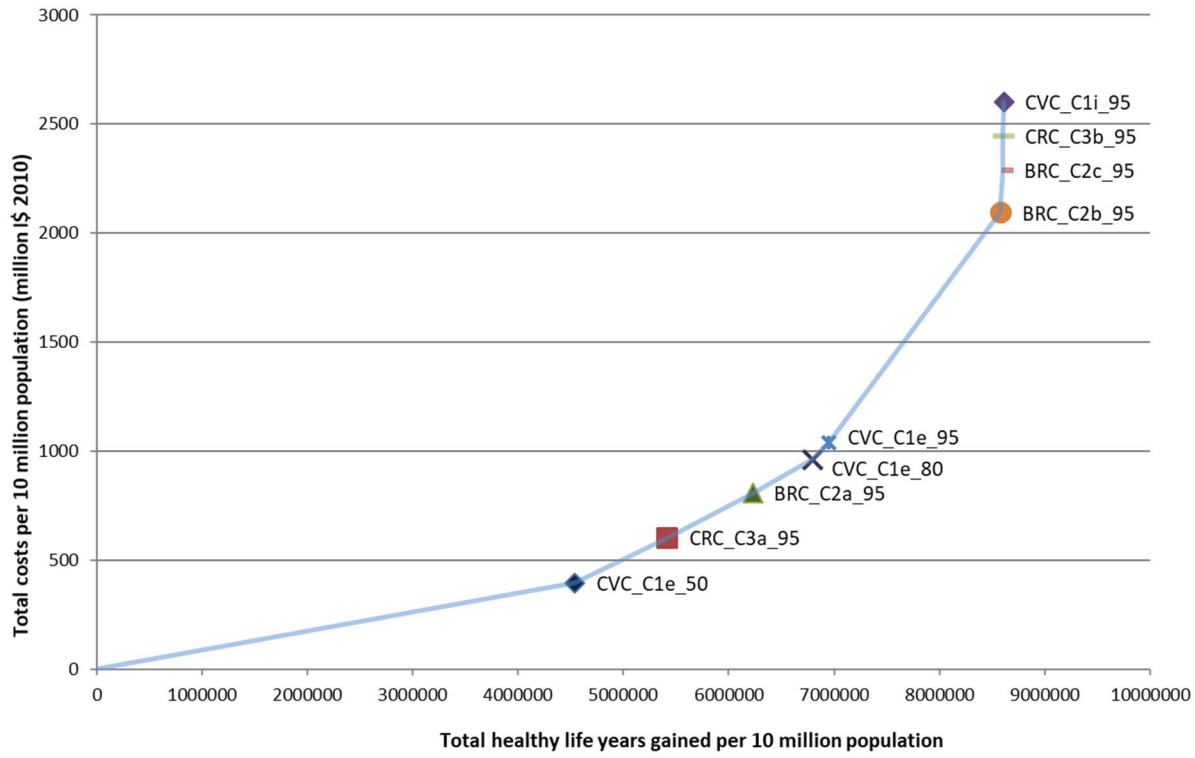

Table 3: Costs, effects and incremental cost-effectiveness of cancer interventions in Eastern sub-Saharan Africa

Label*	Description of the intervention	Pop° coverage (%)	Costs per 10 million population (I$ 2010)	HLY per 10 million population (undiscounted)	Average Cost-Effectiveness Ratio (ACER)	Incremental Cost-Effectiveness Ratio (ICER)
CVC_C1a	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls	50	146	5 215 136	28	28
CVC_C1a	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls	80	190	6 773 262	28	28
CVC_C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	80	1,163	30 421 065	38	41

BRC_C2a	Treatment of breast cancer stages I and II with surgery +/- systemic therapy	95	157	1 389 662	113	113
CVC_C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	95	1 362	31 554 286	43	175
CRC_C3a	Treatment of colorectal cancer stages I and II with surgery +/- chemotherapy and radiotherapy	95	136	626 379	217	217
BRC_C2b	Screening with mammography (once every 2 years for women aged 50-69 years) linked with	95	1 307	2 697 617	485	485

	timely diagnosis and treatment of breast cancer					
BRC_C2c	Basic palliative care for Breast cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	95	171	56 749	3 009	3 009
CVC_C1i	Basic palliative care for Cervical cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	95	161	48 488	3 316	3 316
CRC_C3b	Basic palliative care for Colorectal Cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	95	113	5 602	20 117	20 117

*CVC: Cervical cancer, BRC: Breast cancer, CRC: Colorectal cancer

Figure 2: Cost effectiveness expansion path for Eastern sub-Saharan Africa. Refer to Table 1 for interventions 'label

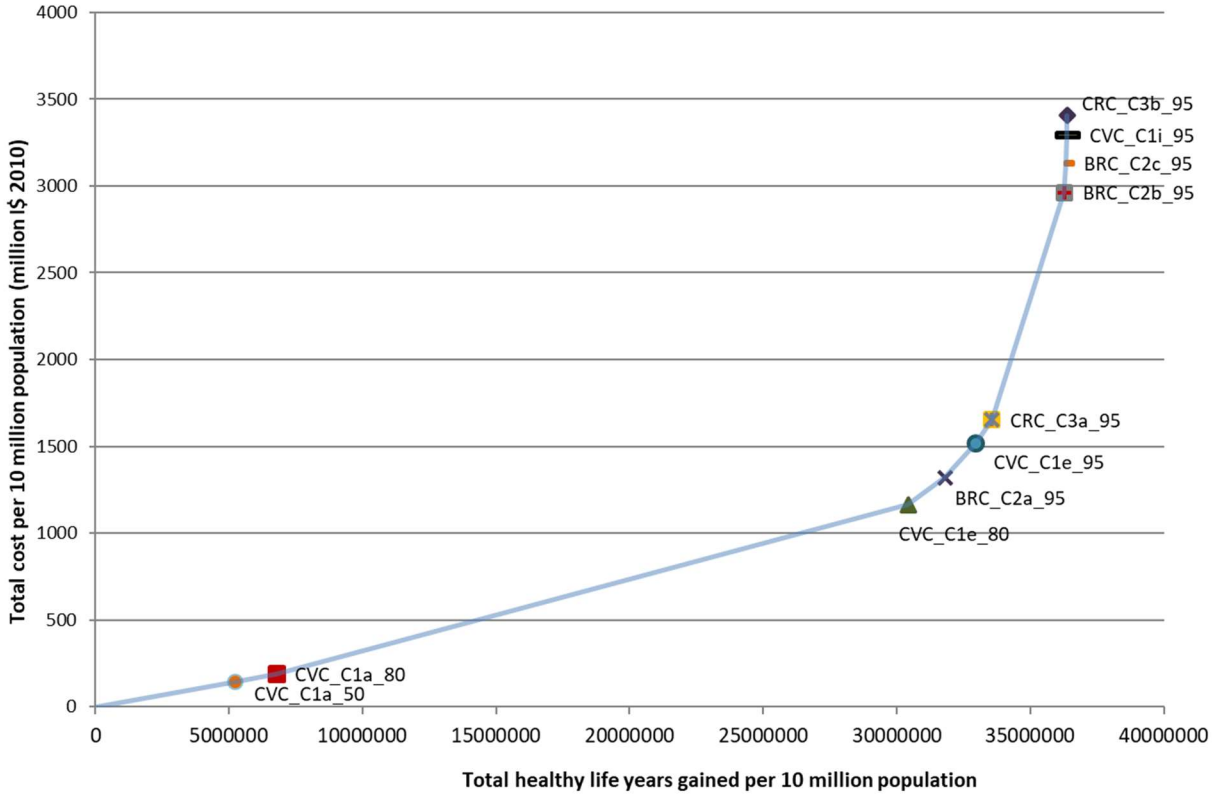

Table 4: Budgetary allocation among cancers for one country in Southeast Asia and Eastern sub-Saharan Africa for implementing the full expansion path at 95% coverage

	Total costs (Per 10 million population)		Costs (%)	
Diseases	**Southeast Asia**	**Eastern sub-Saharan Africa**	**Southeast Asia**	**Eastern sub-Saharan Africa**
CVC	781 881 006	1 522 549 019	30%	45%
BRC	1 454 645 503	1 635 269 849	56%	48%
CRC	364 949 796	248 737 875	14%	7%
Total costs (per 10 million population)	**2 601 476 305**	**3 406 556 743**		
Total undiscounted HLY(per 10 million population)	**8 611 060**	**36 378 783**		
ACER	**302.11**	**93.64**		
Total discounted HLY (per 10 million population)	**1 830 047**	**4 938 728**		

Discussion

Principal findings

The burden of disease and economic impact of cancer are significant and increasing. Effective cancer control planning requires accurate data for planning, costing and implementation. This study assists policy makers in obtaining the best value for money for breast, cervical and colorectal cancer control by identifying the impact and costs of priority cancer control interventions as part of a comprehensive programme.

There are four principle findings in this study: (i) cancer prevention and control interventions are cost-effective and can significantly reduce the burden of disease globally; (ii) a step-wise approach to implementation that considers context-specific expansion paths can be utilized; (iii) interventions for early-stage cancers are generally more cost-effective than those for late-stage cancers; and (iv) palliative care programmes, which should be prioritized since it is considered as human right to health and recommended by the World Health Assembly [37], [38], [39], can be implemented at generally low cost.

Cancer and other non-communicable diseases have received low priority, donor support and domestic resource allocation in low resource settings [40]. Contributing factors are the presumed

high costs and low health impact of cancer interventions. This study highlights that cancer interventions are cost-effective and can be implemented in a comprehensive approach, in line with other NCD interventions as well as accepted communicable disease interventions [41]. Two interventions, in particular, were found to be highly cost-effective, exceeding an Average Cost-Effectiveness Ratio (ACER) threshold of less than I$ 100 per HLY. These interventions are the prevention of cervical cancer through HPV vaccination and the screening and treatment of pre-cancerous lesions. Critically, cost-effectiveness also depends on regional incidence – cervical cancer interventions are more cost effective in eastern sub-Saharan Africa than in Southeast Asia where incidence is lower.

Decision makers are faced with selecting priority cancer control interventions unique to their setting, recognizing the heterogeneity of cancer burden according to region and the differing capacity of health systems. Context-specific expansion paths can help inform decision makers by facilitating a step-wise approach to the implementation of cancer control interventions. For example, this study demonstrates the importance in cost-effectiveness terms of ramping up treatment for the early stages of disease before progressing to systematic cancer screening programmes, an approach which is moreover consistent with existing WHO guidance, based on programmatic considerations [20]. For example, in the expansion paths for both regions, treatment of breast cancer was found to be the most cost-effective breast cancer intervention, with compared to the null, an ICER of I$ 252 per HLY in southeast Asia (screening with mammography linked to timely diagnosis and treatment has an ICER of I$ 1,048 per HLY). Thus, a step-wise approach provides additional evidence in support of the view that expanding treatment services should generally be considered before introducing population-level screening programmes.

This study also highlights the importance of diagnosing cancer early. Treatment for stage I colorectal cancer is approximately five times less expensive than treatment for stage II colorectal cancer. Furthermore, the impact of treatment is greater in stage I cancer as compared to stage II, III or IV [20], [42]. Accordingly, early diagnosis is particularly important to identify cancer at the stage when treatment is both more effective and less expensive. Cancer control strategies that facilitate early diagnosis can provide a significant return on investment [20]. In combination with the previous paragraph, this implies that treatment services need to be expanded then screening

introduced, and only when early diagnosis is achieved will the best value for money in cancer control be obtained.

Finally, it is important to note that while palliative care is not as cost-effective as other cancer control intervention, it is an essential element of treatment, critical for human dignity, and it should be integrated into the continuum of care [38]. This study demonstrates that palliative care programmes can be introduced at a relatively low cost and with minimal health system requirements. This cancer control element should be prioritized, particularly given that more than 80% of the global population live in countries with low or non-existent access to adequate pain management [43].

Strengths of the analysis

The methodology presented in this study uses a comprehensive, health systems approach to cost-effectiveness that considers diverse costs inputs including health workforce requirements, capital expenditures and consumables informed by existing WHO guidance in cancer control, programmatic monitoring and evaluation costs and service delivery costs such as false positive results associated with cancer screening. By identifying and costing all identifiable inputs, this analysis calculates total costs including the costs of health system factors required for effective implementation.

For example, breast cancer screening considers a mechanism for call and recall of the population, diagnostic tests, false positive findings including subsequent diagnosis and pathology, diagnostic tests including immunohistochemistry for hormone receptor testing, staging for select individuals found to have cancer, health workforce time for treatment, management of treatment related toxicities, inpatient and outpatient costs, surveillance after cancer treatment and monitoring and evaluation of screening. Inclusion of these elements results in a more robust and accurate model, as each of them can contribute significantly to the costs of cancer screening and treatment programmes [32], [44], [45].

Additionally, a review of effect sizes utilized in previous analysis based on the study performed by Disease Control Priority, Volume 3, Cancer was made to ensure selection of effect sizes and methodology are consistent with the best available evidence [46].

Limitation of the analysis

There are six limitations to this analysis. First, while assumptions are based on best available evidence, there are gaps in high-quality evidence for cancer prevention and control interventions. For example, because of its relatively recent introduction to the market, there is limited longitudinal data on the durability of HPV vaccination and its effect in protection against cervical cancer. Another example is to quantify the impact of surgery for stage I breast cancer compared to the null state of no treatment available. As would be expected, there is no randomized controlled trial evaluating the impact of this intervention. To mitigate the impact of this limitation, assumptions were verified using available data such as historic publications and case series of patients who refuse treatment and/or aligned with previous assumptions in cancer cost-effectiveness studies; policy implications should be minor.

Second, there are insufficient studies for region- or country-specific variables. In this study, stage distribution, health workforce costs and programmatic costs were estimated based on available data. An assumption was made that the tumour biology/natural history of cancer was similar between settings. Additionally, the effect size of the intervention was used across all settings – that is, the impact of a particular intervention (e.g. vaccination, screening, treatment) was assumed to be equal in all setting. A literature review for region- or country-specific data was performed to address this limitation. However, there are limited data in low-resourced settings. Additional research is needed to develop regional specific inputs and variables; countries cannot generalize without regional or national epidemiologic data.

Third, the data used for the model were average regional estimates, as the scope of our work was generalized analyses of the cost-effectiveness of interventions. Application of the model to individual countries should consider more country-specific data inputs as available, and conduct sensitivity analyses around the input parameters for evaluating the impact of parameter variabilities on program decisions.

Fourth, the disability weights used were from the 2010 global burden diseases study. The development of the impact models began prior to the release of more recent disability weight data. As there has been minimal change in the disability weights for cancer stages in subsequent updates, and the costing baseline year is 2010, the authors were comfortable with continuing to use the 2010 estimates which fall well within the uncertainty bounds of latter estimates.

Fifth, various models have been used for costing cancer control programmes, such as the bottom-up or top-down method. [47], [48]. Each strategy has advantages and disadvantages. In this study, the bottom-up approach was used, consistent with WHO-CHOICE methodology, allowing for comparison across diseases and settings. Furthermore, a thorough review of costing elements was considered to reduce any under-estimates. The GCEA is a standardized method for applying evidence to poor data settings where guidance is most needed. The tool has better use for priority setting than for budgeting. Results presented are intended to be indicative examples, rather than prescriptive packages or budgetary allocations for countries to implement. They must be evaluated prospectively to correlate with budgets or National Health Accounts.

Finally, regarding the health outcomes model used the transition parameters were grouped according to general cancer types. Different cancer subtypes, such as hormone receptor positive breast cancers, were not considered in this study. This model thus assumed that there is no significant heterogeneity in the cancer subtypes between different populations.

Policy implications

The 2030 Agenda for Sustainable Development ushered in the era of universal health coverage (UHC) as a global priority. In order to achieve targets related to UHC, including financial protection, and reduce premature mortality from NCDs, a basic package of cancer services must be identified. Domestic, bilateral and multilateral funding should be channeled towards evidence-based, cost-effective interventions for cancer prevention and control, thereby avoiding unnecessary expenditure on high-cost interventions, medicines and technologies that yield less health benefit for populations [49]. This study provides the foundation for region-specific data to identify the most cost-effective cancer interventions that can be considered for inclusion in a basic package of cancer services.

Conclusion

This study presents the new WHO-CHOICE cost-effectiveness results for three priority cancers, utilizing region-specific data to support decision-making based on epidemiologic profile, regional costs, and health system capacity. The results demonstrate that cancer prevention and control interventions are cost-effective and can be implemented through a step-wise approach to achieve maximum health benefits. As the global community moves toward universal health coverage, this analysis can support decision makers in identifying a core package of cancer services, ensuring

treatment and palliative care for all. Results are provided at regional level; an obvious contextualization is necessary for an individual country level implementation [50].

Abbreviations

ACER	Average Cost-Effectiveness Ratio
AFR	Africa region
CHOICE	CHOosing Interventions that are Cost-Effective
CIS	Carcinoma in-situ
DWs	Disability Weights
GBD	Global Burden of Disease
GCEA	Generalized Cost Effectiveness Analysis
HER2	Human epidermal growth factor receptor 2
HLYs	Healthy Life Years
HPV	Human papillomavirus
ICER	Incremental Cost-Effectiveness Ratio
IHME	Institute for Health Metrics and Evaluation
LMIC	Low and Middle-Income Countries
MDGs	Millennium Development Goals
MSH	Management Sciences for Health
NCDs	Noncommunicable diseases
SEAR	Southeast Asia region
SDGs	Sustainable Development Goals
UHC	Universal Health Coverage
WHO	World Health Organization

Authors' contributions

AHR performed the interventions costing, collated the databases used for the analysis, performed the cost effectiveness analysis and drafted the manuscript. CG led and performed the impact modelling. AI provided quantity assumptions, conceptual input, and quality control. CP performed the impact modelling using Spectrum and provided the health outcomes data. JAL supervised the team and provided quality control. All authors contributed to the edit of the manuscript. All authors read an approved the final manuscript.

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AHR, AI and JAL are all employees of the World Health Organization. The views expressed in this paper are those of the authors and they do not necessarily represent the views of the WHO.

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Acknowledgements

We thank Rachel Sanders and Nadia Carvalho for their inputs and assistance for the costing process.

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

The datasets that support the findings of this paper are available at http://www.who.int/choice/en.

Consent for publication

Not applicable

Ethics approval and consent to participate

Not applicable

Funding

No funding was received for this analysis.

Received: 3 April 2018. Accepted: 21 October 2018; Published online: 29 October 2018

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Additional file 1: State-transition (Markov model) cohort simulation model for estimation of health outcomes presented in the main manuscript

Overview

Health outcomes of the disease and the impact of alternative interventions for breast cancer, cervical cancer, and colorectal cancer were evaluated using a deterministic state-transition (Markov model) cohort simulation. The general structure of the model is described in the main manuscript. Here we present the mathematical structure of the simulation using breast cancer as an example. The states and transitions of the Markov model are depicted as flow diagram in Figures S1 (breast cancer), S2-S4 (cervical cancer), and S5 (colorectal cancer).

Mathematical structure of the simulation using breast cancer as an example

Let, $Z = \{\mathrm{H}, \mathrm{UC1}, \mathrm{UC2}, \mathrm{UC3}, \mathrm{UC4}, \mathrm{C1}, \mathrm{C2}, \mathrm{C3}, \mathrm{C4}\}$ be the state space, a set of mutually exclusive collectively exhaustive states, of the Markov model containing healthy (H), preclinical (UC1,UC2,UC3,U4), and clinical stages (C1,C2,C3,C4) of breast cancer (see Figure S1 for reference), and

$\mathbb{Q}$ be a matrix of transition rates (per person year) between states.

Note: empty cells =0

$\mathbb{Q} =$

	H	UC1	UC2	UC3	UC4	C1	C2	C3	C4
H	$-y - m$	y							
UC1		$-p1 - d1 - m$	$p1$			$d1$			
UC2			$-p2 - d2 - m$	$p2$			$d2$		
UC3				$-p3 - d3 - m$	$p3$			$d3$	
UC4					$-d4 - m5$				$d4$
C1						$-m1$			
C2							$-m2$		
C3								$-m3$	
C4									$-m4$

where, (see Figure S1 for reference of notations)

y are the disease onset rates

$p1, p2, p3$ are the progression rates

$d1, d2, d3, d4$ are the diagnostic rates

m are the disease-free mortalities, and

$m1, m2, m3, m4$ are the disease mortalities with treatment,

$m5$ are the disease mortality rates without treatment

To simulate the population we use a set of first-order differential equations given by

$$\rho'_{t+1} = \rho'_t + \rho_t \mathbb{Q} \Delta t$$

where,

$\rho_t = [\mathrm{H}, \mathrm{UC1}, \mathrm{UC2}, \mathrm{UC3}, \mathrm{UC4}, \mathrm{C1}, \mathrm{C2}, \mathrm{C3}, \mathrm{C4}]$, is a vector with each element equal to the number of people in that state (denoted in the vector) at time t

$\rho_t{}'$ is the transpose of the vector ρ_t

Δt is a small time-step

Simulation steps

Initialization:

- Set $t =$ base year of simulation.
- $\Delta t =$ suitably small time-step
- For each age-group in the simulation, set ρ_t as population in base year of simulation

Repeat below steps until $t =$ final year of simulation

1. For each age-group in the simulation, apply $\rho'_{t+1} = \rho'_t + \rho_t \mathbb{Q} \Delta t$, taking age-specific rates for elements of $\mathbb{Q}$ where applicable

2. For the first age-group in the simulation, increment $\rho_t(1) = \rho_t(1) + births$
3. Increment $t = t + \Delta t$

Similar structures were developed for cervical cancer and colorectal cancer. All transition rates of the Markov models were assumed static (except for HPV transmission rates), i.e., we do not model changes in cancer risk in the population due to changes in factors such as lifestyle or environment. In the case of cervical cancer simulation, we dynamically estimate HPV transmission rates over time to capture the changes in risk from interventions such as vaccination.

Dynamic estimation of HPV transmission rates in the cervical cancer simulation

The cervical cancer simulation dynamically estimates HPV transmission rates in men and women over time using

$\bar{r}_i = \alpha\bar{\partial}.(\overline{\mathbb{M}}\beta_i)(1-\bar{c}_i)$; $\quad r_i = t\partial.(\mathbb{M}\bar{\beta}_i)(1-c_i)$ where,

$\bar{r}_i$, r_i are the age-based column-vectors of HPV infection rates for HPV type i in men and women, respectively,

$\bar{r}_i = \{\bar{r}_{16-1}, \bar{r}_{high-risk}, \bar{r}_{low-risk}\} \equiv$ {r32, r33, or r34} in Figure S4,

$r_i = \{r_{16-1}, r_{high-risk}, r_{low-risk}\} \equiv$ {r1, r23, or r8} in Figure S2,

$\bar{\partial}$ and ∂ are the age-based column vectors for partner exposure-rates, which we assume are inclusive of multiple sexual parameters such as partner turn-over rate, and number of sexual exposures not 100% protected by condoms, for men and women, respectively,

$\overline{\mathbb{M}}$ and $\mathbb{M}$ are matrices representing age-mixing of sexual partnerships for men and women, respectively; each element $m_{jk} \in \overline{\mathbb{M}}$ representing the probability that a man in age j has a partnership with a woman of age k, and $m_{jk} \in \mathbb{M}$ representing the probability that a woman in age j has a partnership with a man of age k, each row adding to 1,

$\bar{\beta}_i$ and β_i are the age-based column vectors of prevalence of HPV-type i in men and women, respectively,

α is the probability of transmission per infected-susceptible contact (t $\approx$ 1 for HPV), and

$\bar{c}_i, c_i$ are the coverage of vaccination for HPV type i in men and women, respectively, which is 0 in the base case.

We assume that $\bar{\partial}, \partial, \overline{\mathbb{M}}$ and $\mathbb{M}$ are available or can be estimated through other sexual behavior data available from national surveys, here we estimated them using partnership age differences from the Demographics and Health Surveys (DHS). $\bar{\beta}_i$and β_i are estimated dynamically in the simulation using ρ_t.

Markov model transition rate estimates and data sources

The transition rates for the natural progression of cancer are presented in Tables S1-S2 (breast cancer), S3-S4 (cervical cancer), and S5-S6 (colorectal cancer). We assumed that disease onset rates, i.e., transitions from healthy to first stage of disease, and diagnostic rates, i.e., transitions from preclinical to clinical stages of cancer, vary by population, these rates are presented in Table S2, S4, S6 for 2 world regions. These rates were estimated using a newly developed methodology that is presented elsewhere [1]. We assume that progression and regression rates between cancer stages do not vary by population, these rates and data sources are presented in Tables S1, S3, S5.

Figure S1: State-transition model for breast cancer in women

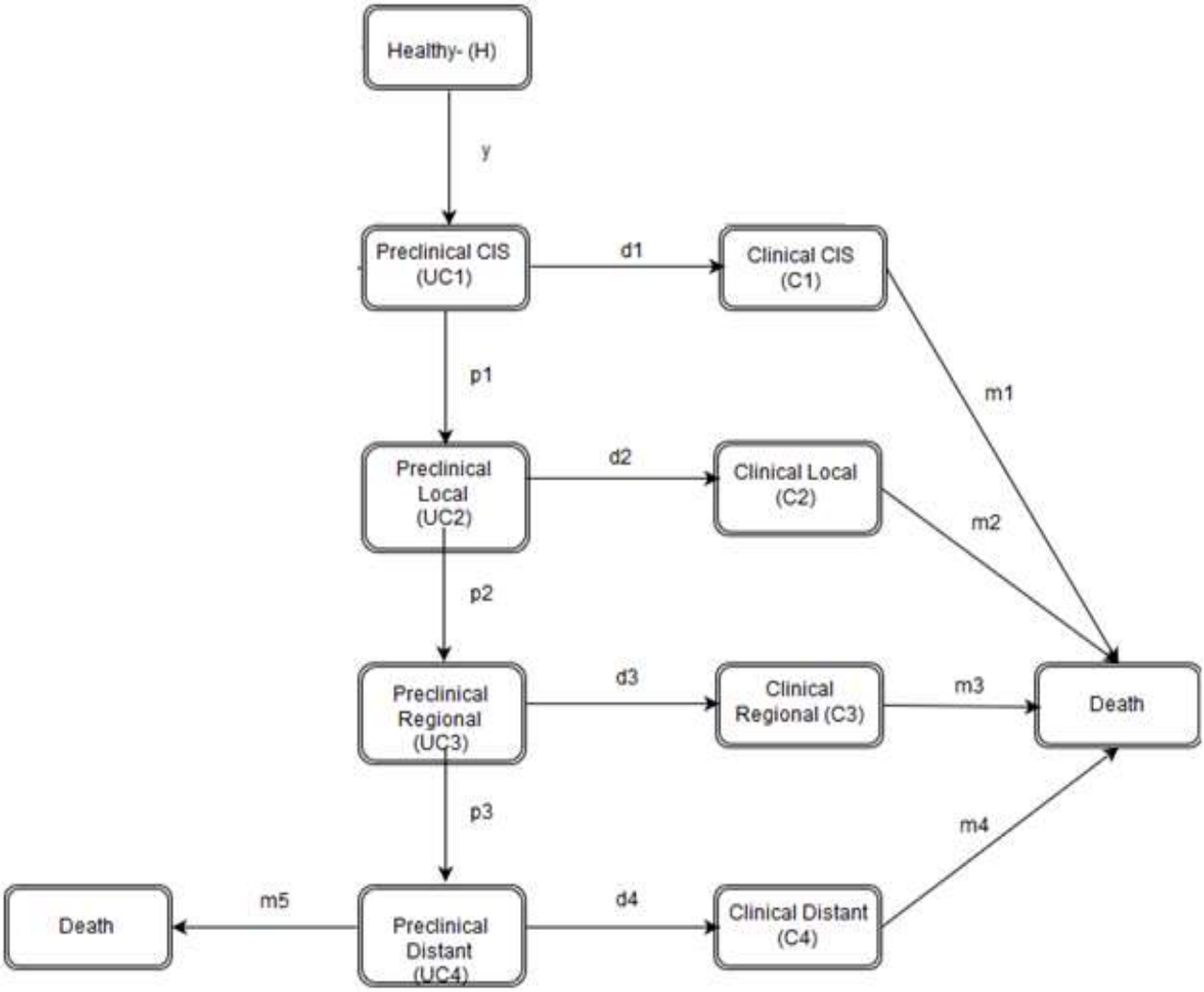

Table S1: Breast cancer- Transition rates for natural disease progression for breast cancer state-transition model in Figure S1

Parameters	Value	Source
		[2], [3], [4]
Progression rates		
In-situ to Local (p_1)	0.19	
Local to Regional (p_2)	0.33	
Regional to Distant (p_3)	0.43	
Annual mortality rate (per person year) with treatment by stage at diagnosis		
In-situ (m_1)	0.01	
Local (m_2)	0.02	
Regional (m_3)	0.08	
Distant (m_4)	0.27	

Table S2: Breast cancer- Population-specific natural disease onset rates and diagnostic rates for breast cancer state-transition model in Figure S1

Age group	Eastern Sub-Saharan Africa			Southeast Asia		
Onset rates of in-situ (y) (per 1000 persons per year)						
Age Groups	Eastern Sub-Saharan Africa			Southeast Asia		
15_19	0.07			0.07		
20_24	0.18			0.17		
25_29	0.35			0.34		
30_39	0.57			0.58		
40_49	1.45			1.67		
50_59	2.44			2.96		
60_69	3.57			3.82		
Diagnosis rates (per year)						
Age Groups	Eastern Sub-Saharan Africa			Southeast Asia		
	Local	Regional	Distant	Local	Regional	Distant
15_19	0.38	0.83	1.00	0.49	0.95	1.00
20_24	0.33	0.73	0.87	0.39	0.76	0.80
25_29	0.20	0.45	0.53	0.24	0.46	0.49
30_39	0.24	0.53	0.63	0.29	0.56	0.59
40_49	0.20	0.43	0.52	0.25	0.49	0.51
50_59	0.09	0.21	0.25	0.12	0.23	0.25
60_69	0.05	0.11	0.13	0.06	0.11	0.12

Figure S2: Overview of HPV and cervical cancer state-transition model

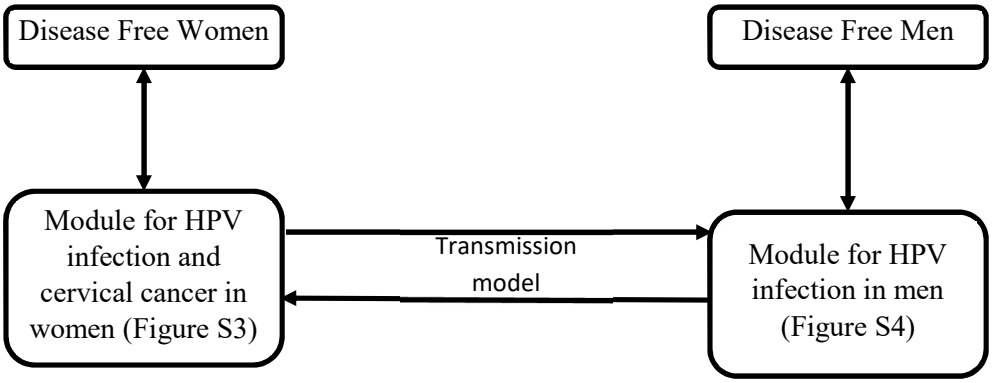

Figure S3: State transitions model for HPV infection and cervical cancer in women

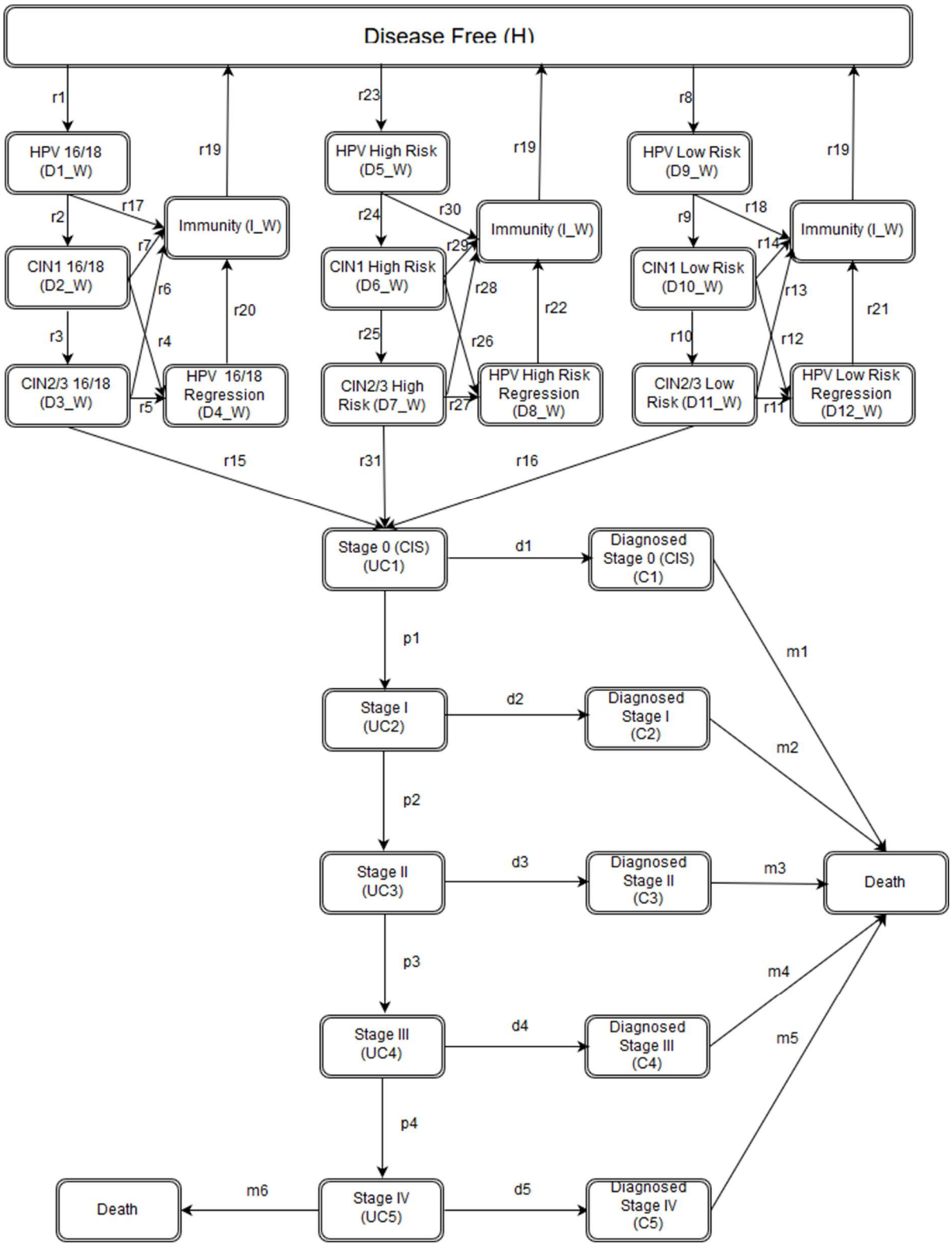

Figure S4: State-transition model for HPV infection in men

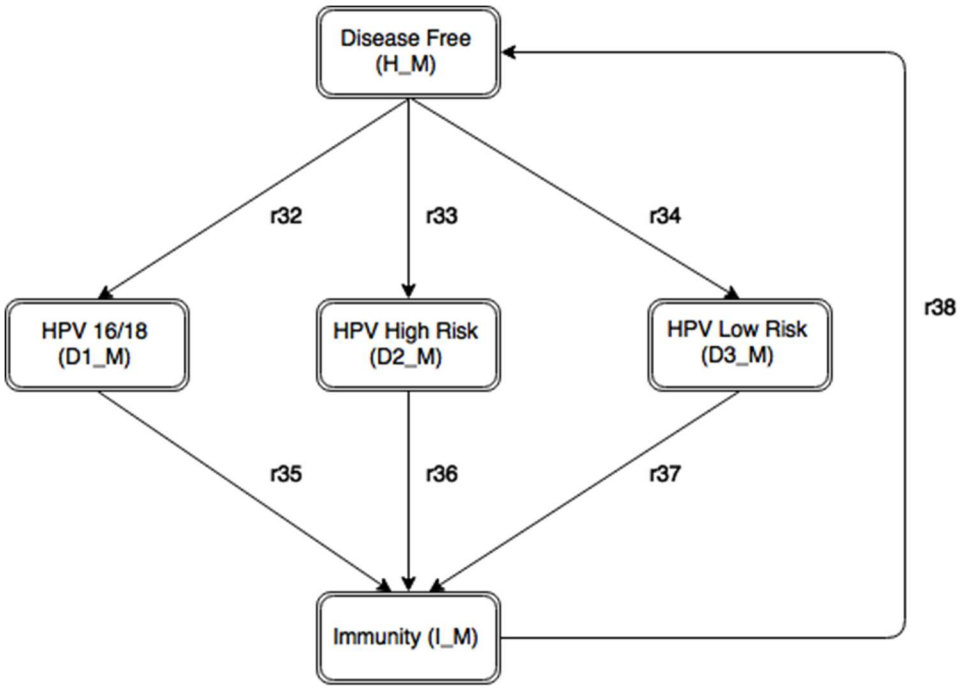

Table S3: HPV and Cervical cancer- Transition rates for natural disease progression for cervical cancer state-transition model in Figures S2- S4

Parameters	Values			Source
PARAMETERS FOR WOMEN		HPV types		[5], [6]
	16/18	High risk[9]	Low risk	
Transition rates in pre-cancer stages [2] (per person year) [2]				
HPV to CIN 1 (r_2, r_9, r_{24})	0.0931	0.0931	0.0568	
CIN 1 to CIN 2/3 (r_3, r_{10}, r_{25})	0.2107	0.2107	0.0921	
CIN 2/3 to CIS (r_{15}, r_{16}, r_{31})				
1-30 years	0.0292	0.0292	0.007	
30–39 years	0.0506	0.0506	0.014	
40–49 years	0.1344	0.1344	0.0221	
50-100 years	0.1952	0.1952	0.0445	
HPV to Immunity (r_{17}, r_{18}, r_{30})	0.0363	0.0363	0.0363	
CIN 1 to Immunity (r_7, r_{14}, r_{29})	0.1188	0.1188	0.1059	
CIN 1 to Regression (r_4, r_{12}, r_{26})	0.1188	0.1188	0.1059	
CIN 2 to Immunity (r_6, r_{13}, r_{28})	0.0171	0.0171	0.0704	
CIN 2 to Regression (r_5, r_{11}, r_{27})	0.0171	0.0171	0.0704	
Regression to Immunity (r_{20}, r_{22}, r_{21})	0.0363	0.0363	0.0363	
Immunity to Disease Free (r_{19})	0.1000	0.1000	0.1000	
Transition rates in preclinical stages (per person year)				[6]
Stage 0 (CIS) to Stage I (p_1)		All Types		
1-34 years		0.03		
35–54 years		0.273		
55–61 years		1.185		
62–100 years		5.290		
Stage I to Stage II (p_2)		0.310		
Stage II to Stage III (p_3)		0.332		
Stage III to Stage IV (p_4)		0.485		

Annual mortality rate with treatment (per person year)		[6]
Stage I (m_2)	0.027	
Stage II (m_3)	0.062	
Stage III (m_4)	0.167	
Stage IV (m_5)	0.316	

PARAMETERS FOR MEN

Transition rates in men (per person-year)	16/18	High risk	Low risk	[6]
HPV to Immunity (r_{35}, r_{36}, r_{37})	0.0363	0.0363	0.0363	
Immunity to Disease Free (r_{38})	0.1	0.1	0.1	

[1] All high-risk types of HPV other than type 16/18.

[2] 6-months probabilities from [4] have been converted to annual rates using $-[ln(1-p)]/t$ where p is the probability and t is the time in years.

Table S4: Cervical cancer- Population-specific natural disease onset rates and diagnostic rates for HPV and cervical cancer state-transition model in Figures S2-S4)

Age group	Eastern Sub-Saharan Africa			Southeast Asia		
PARAMETERS FOR WOMEN						
Onset rates of HPV (per 1000 women per year)						
Age Groups	Eastern Sub-Saharan Africa			Southeast Asia		
	16/18	High risk	Low risk	16/18	High risk	Low risk
15-19	8.20E-03	1.80E-03	6.82E-03	7.20E-03	2.80E-03	4.63E-03
20-24	130.14	28.57	11.66	47.11	18.32	4.69
25-29	46.57	10.22	7.01	16.02	6.23	2.1
30-39	49.27	10.81	6.54	14.11	5.49	1.68
40-49	39.38	8.64	3.13	8.01	3.12	0.58
50-59	38.5	8.45	2.71	7.95	3.09	0.49
60-69	47.68	10.47	3.15	9.04	3.51	0.54

Diagnosis rates of cervical cancer (per 1000 person years among women in pre-clinical stages)

Age Groups	Eastern Sub-Saharan Africa				Southeast Asia			
	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV
15-19	171.15	375.31	838.63	1000	193.28	554.62	949.58	1000
20-24	171.15	375.31	838.63	1000	193.28	554.62	949.58	1000
25-29	161.68	354.54	792.23	944.67	188.91	542.09	928.12	977.4
30-39	44.5	97.58	218.05	260	42.29	121.35	207.76	218.8
40-49	30.06	65.91	147.29	175.63	26.69	76.6	131.15	138.11
50-59	11.94	26.19	58.52	69.78	8.97	25.74	44.06	46.4
60-69	9.06	19.87	44.41	52.95	6.89	19.76	33.84	35.63

PARAMETERS FOR MEN

Onset rates of HPV (per 1000 person years)

	Eastern Sub-Saharan Africa			Southeast Asia		
Age group	16/18	High risk	Low risk	16/18	High risk	Low risk
15-19	0	0	0	0	0	0
20-24	22.53	4.95	2.26	22.34	8.69	2.32
25-29	30.37	6.67	3.14	9.63	3.75	1.01
30-39	49.85	10.94	5.48	3.57	1.39	0.38
40-49	39.73	8.72	4.27	0.27	0.1	0.03
50-59	30.21	6.63	2.8	1.83E-02	7.12E-03	1.62E-03
60-69	24.5	5.38	1.99	1.39E-03	5.40E-04	1.10E-04

Figure S5: State-transition model for colorectal pre-cancerous polyps and cancer

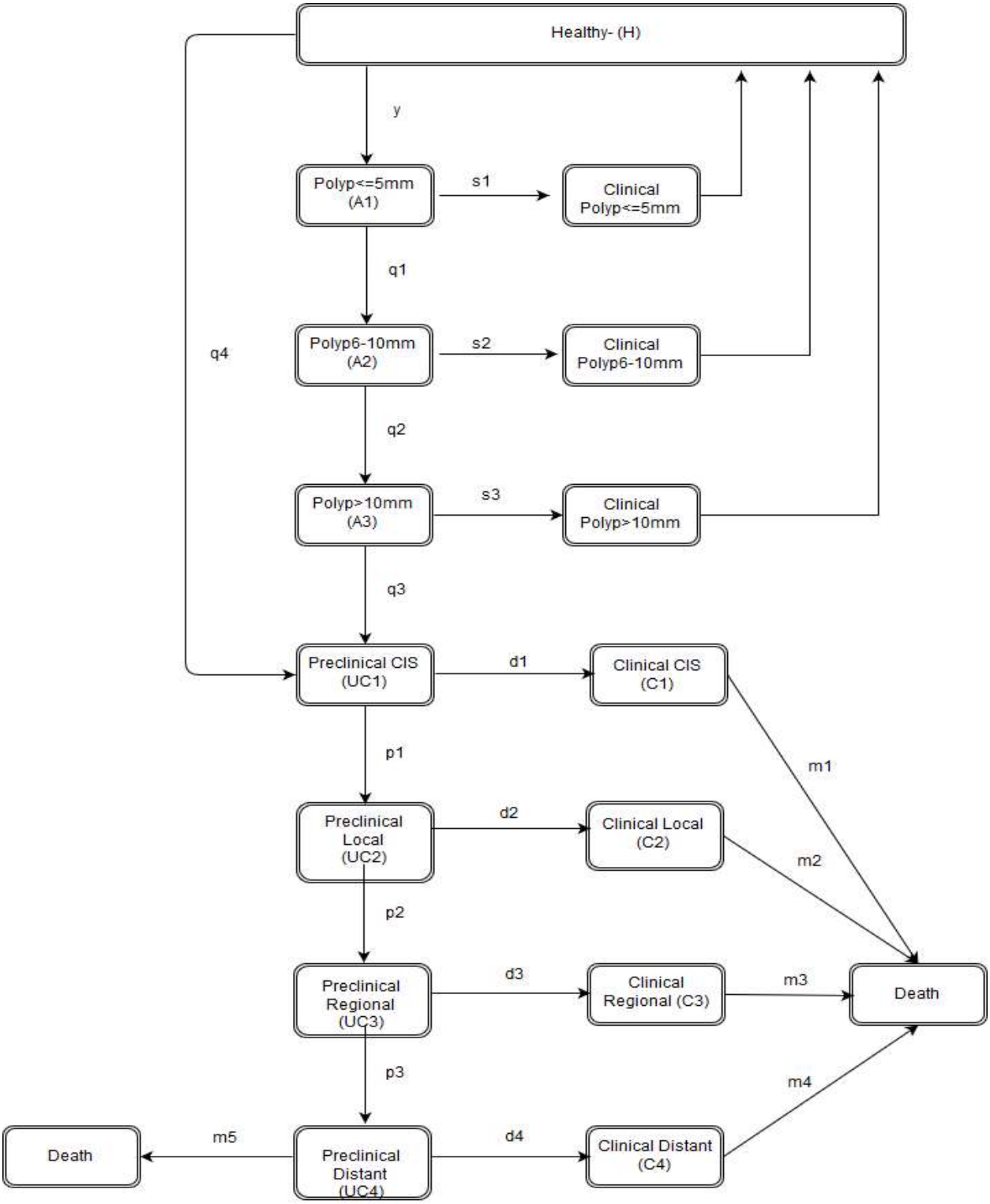

Table S5: Colorectal cancer- Transition rates for natural disease progression for colorectal cancer state-transition model in Figure S5

Parameters	Value	Source
Progression rates (per person year)		
PolypLT5mm to Polyp6to10mm (q_1)	0.021	[7], [8], [9]
PolypLT10mm to PolypGT10mm (q_2)	0.057	
PolypLT10mm to Preclinical 0 (q_3)	0.063	
In-situ to Local (p_1)	0.29	[9], [10], [11], [12], [13], [14]
Local to Regional (p_2)	0.34	
Regional to Distant (p_3)	0.64	
Proportion of cancers from de novo carcinoma (q4)	23%	[7], [15]
Annual mortality rate (per person year) with treatment		[9], [10], [11], [12], [13], [14]
In-situ (m_1)	0.01	
Local (m_2)	0.01	
Regional (m_3)	0.05	
Distant (m_4)	0.57	

Table S6: Colorectal cancer- Population-specific natural disease onset rates and diagnostic rates for colorectal cancer state-transition model in Figure S5

Age groups	Eastern Sub-Saharan Africa	Southeast Asia

Rate of adenoma polyp onset (y)(per 1000 person-years)

Age Groups	Eastern Sub-Saharan Africa	Southeast Asia
20_24	1.6	3.4
25_29	2.1	4.4
30_39	2.1	4.5
40_49	2.1	4.7
50_59	2.2	4.9
60_69	2.2	5.2
70_79	2.2	5.4

Diagnostic rates (per person year) (rates for in-situ (d1) are zero)

Age Groups	Eastern Sub-Saharan Africa			Southeast Asia		
	Local(d2)	Regional(d3)	Distant(d4)	Local(d2)	Regional(d3)	Distant(d4)
15_19	0.01	0.06	0.10	0.01	0.06	0.10
20_24	0.01	0.12	0.19	0.01	0.07	0.11
25_29	0.03	0.39	0.60	0.01	0.14	0.22
30_39	0.04	0.47	0.72	0.03	0.31	0.48
40_49	0.05	0.62	0.96	0.05	0.56	0.86
50_59	0.06	0.64	1.00	0.06	0.64	1.00
60_69	0.05	0.63	0.98	0.06	0.64	1.00
70_79	0.04	0.43	0.67	0.05	0.58	0.90

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Additional file 2: Effect sizes, costing assumptions and detailed results per region

Table 1: Effect sizes for "Prevention" interventions

Diseases	Procedures	Sensitivity	Specificity	Frequency (per year)	Reduction in incidence	References
Cervical Cancer						
HPV vaccination for types 16 and 18					90%[10]	WHO position paper, Oct 2014 [1]; WHO position paper, Sept 2014 [2] PRIME [3][
Screening with visual Inspection with acetic acid (VIA)		0.66	0.77	1/3		IARC, 2005 [4], Goldie et al.2001 [5], WHO, 2014 [6]
Screening with Papanicolaou ("Pap") smear		0.62	0.95	1/3		IARC, 2005 [4], Goldie et al., 2001 [5], WHO, 2014 [6]
Screening with HPV DNA test		0.88	0.75	1/5		WHO,2014 [6]; IARC, 2005 [4]; Goldie et al., 2001 [5]
Breast Cancer						
Screening with Mammography		0.76	0.93	1/2		IARC, 2016 [7], WHO, 2014 [8]

[10] 90% effectiveness for types 16 and 18 as used in WHO PRIME tool [3]. Estimated Incidence of HPV types 16 and 18 taken from [47], [48], [49]

Table 2: Effect sizes for "Treatment" interventions

Diseases	Variables	Stage I	Stage II	Stage III	Stage IV	References
Cervical Cancer						
Annual mortality rate	without treatment	0.120	0.196	0.4766	1.266	Goldie et al.,2003 [9], NCCN, 2016 [10], Chuang, 2016 [11]
	with treatment	0.027	0.062	0.167	0.316	
Impact of treatment (% reduction of mortality)		78%	68%	65%	75%	
Disability weight	without treatment	0.3	0.3	0.3	0.57	Calculated using IHME_GBD_Disability Weight [12]
	with treatment	0.007	0.014	0.045	0.54	
Breast Cancer						
Annual mortality rate	without treatment	0.14	0.18	0.23	0.5	Groot et al. 2006 [13]; Zelle et al. 2012 [14], Perez et al. 2014 [15]; Davies et al., 2013, [16]; Feng et al., 2014 [17]
	with treatment	0.006	0.039	0.093	0.27	
Impact of treatment (% reduction of mortality)		96%	78%	60%	46%	
Disability weight	without treatment	0.3	0.3	0.3	0.57	Calculated using IHME_GBD_Disability Weight [12]
	with treatment	0.008	0.008	0.029	0.54	
Colorectal Cancer						
Annual mortality rate	without treatment	0.18	0.18	0.58	0.9	Liu et al., 2014 [18], NCCN, 2017; Frazier et al., 2000 [19]; Wu et al., 2006 [20]; Chadder et al., 2016 [21]; NCIN, 2009 [22]; Seinfeld [23]
	with treatment	0.01	0.01	0.05	0.57	
Impact of treatment (% reduction of mortality)		94%	94%	91%	37%	
Disability weight	without treatment	0.3	0.3	0.3	0.57	Calculated using IHME_GBD_Disability Weight [12]
	with treatment	0.012	0.012	0.048	0.54	

Table 3: Stage distribution at diagnosis

Diseases	Region	Stage I	Stage II	Stage III	Stage IV	References
Cervical cancer						
	Eastern sub-Saharan Africa	17.12%	20.42%	46.33%	16.14%	Quinn et al.,2006 [24]
	Southeast Asia	19.33%	36.13%	39.50%	5.04%	
Breast cancer						
	Eastern sub-Saharan Africa	13%	31%	39%	17%	IARC registry data [25]; Sant et al.,2004 [26]; Mandelblatt et al. 2011 [27]; Schwartsmann, 2001 [28]; Chopra, 2001 [29]; Vorobiof et al., 2001 [30]; Groot et al., 2006 [13]; Brinton et al, 2014 [31]; Laurens et al., 2014 [32]; Zelle et al., 2013 [33]; Zelle et al., 2012 [14]; Okonkwo et al., 2008 [34]
	Southeast Asia	17%	38%	40%	5%	
Colorectal cancer						
	Eastern sub-Saharan Africa	12.30%	21.90%	41.90%	23.90%	Seinfeld [23]; Graham et al., 2012 [35]; Brenner et al. 2016 [36] ; Alsanea et al.,2015 [37]; Zorzi et al., 2015 [38]; Hsu et al., 2015 [39]; IARC registry data [25]; Benitez-Majano et al., 2016 [40]
	Southeast Asia	12.30%	21.90%	41.90%	23.90%	

Table 4: Intervention costing assumptions for Cervical Cancer

Interventions	Costing components	Cost of Drugs and supplies per person identified/treated (I$ 2010)	Outpatient visits[11]	Inpatient days
Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls	HPV vaccine price estimated from WHO Prime Tool [3]	8.52	2	0
Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	Screening with visual inspection with acetic acid (VIA) performed by trained provider[12]	2.79	1	0
	Same-day treatment of pre-cancerous lesions with cryotherapy for individuals with positive findings on VIA	10.98		
	Programme monitoring and evaluation, call and recall mechanism [41]			
Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions	Screening with Papanicolaou ("Pap") smear performed by trained provider with subsequent review by cytopathologist	2.64	2	0
	Treatment of pre-cancerous lesions (cryotherapy/ loop electrosurgical excision procedure (LEEP)) for individuals with positive findings on colposcopy	33.47		
	Programme monitoring and evaluation, call and recall mechanism [41]			
Prevention of cervical cancer by screening women aged 30–49	Screening with HPV DNA test performed by trained provider [42]	10.34	2	0

[11] Costing includes health workforce time and outpatient facility visit.
[12] Referral for subsequent colposcopy and/or biopsy for suspicious lesions

through Human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions	Recall for positive HPV test with subsequent visual inspection with acetic acid	21.03		
	Same-day treatment of pre-cancerous lesions with cryotherapy for those with positive findings on VIA	10.98		
	Programme monitoring and evaluation, call and recall mechanism [41]			
Treatment of cervical cancer stages I and II with either surgery or radiotherapy +/- chemotherapy	*Diagnosis and staging*:	18.05		
	Diagnostic evaluation with biopsy, specimen fixative, and staining			
	Pre-treatment tests and staging studies when indicated including cross-sectional imaging and ultrasound			
	Treatment [6], [10], [11]:	274.93, 1874.65[15]		
	Cone biopsy or simple hysterectomy for microinvasive disease		7, 10[13]	6, 2[14]
	Radical hysterectomy for early invasive surgery			
	Concurrent chemoradiotherapy with cisplatin and stage IB2 or stage II [43]			
	Management of chemotherapy-associated nausea including ondansetron			
	Surveillance with imaging as indicated for 5 years			
Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and	Symptom management including amitriptyline, stool softener, morphine (slow release, immediate release), urinary catheter, as needed	219.75	2	2

[13] 7 visits for stage I, 10 visits for stage II
[14] 6 days for stage I, 2 days for stage II
[15] 274.93 I$ for stage I, 1874.65 I$ for stage II

essential supportive medicines				

Table 5: Intervention costing assumptions for Breast Cancer

Interventions	Costing components	Cost of Drugs and supplies per person identified/treated (I$ 2010)	Outpatient visits[16]	Inpatient days
Treatment of breast cancer stages I and II with surgery +/- systemic therapy	*Diagnosis and staging*:	116.63	8, 10[17]	2
	Diagnostic evaluation with biopsy, specimen fixative, and staining			
	Biopsy equipment, specimen fixative, and staining			
	Pre-treatment tests and staging studies when indicated including x-ray and ultrasound.			
	Treatment:	218.01, 464.58[18]		
	Modified radical mastectomy including pre-operative antibiotics, wound drainage kit			
	Adjuvant[19] (or neoadjuvant) systemic therapy including doxorubicin, cyclophosphamide, and paclitaxel [44]			
	Hormone therapy with tamoxifen[20]			
	Management of neutropenia and chemotherapy-associated nausea including filgrastim, ondansetron, and dexamethasone			
	Surveillance with mammogram and clinical exam one visit for 5 years			
Screening with mammography (once every 2 years for women aged 50-69 years) linked with	*Screening*:		8, 10[21]	2
	Screening mammogram	2.45		
	Programme monitoring and evaluation, call and recall mechanism [41]			

[16] Costing includes health workforce time and outpatient facility visit.
[17] 8 days for stage I, 10 days for stage II
[18] 218.01 for Stage I, 464.58 for Stage II
[19] Given to 5% of stage I patients and 30% of stage II patients
[20] Needed for patients with hormone receptor positive cancers (estimated at 40%)
[21] 8 days for stage I, 10 days for stage II

timely diagnosis and treatment of breast cancer	Management of screen-positive mammograms with subsequent diagnostic studies including mammogram			
	Diagnosis and staging:	551.36[22]		
	Biopsy equipment, specimen fixative and staining			
	Pre-treatment tests and staging studies when indicated including x-ray and ultrasound			
	Treatment:	218.01, 464.58,684.84[23]		
	Modified radical mastectomy including pre-operative antibiotics, wound drainage kit			
	Adjuvant systemic therapy including doxorubicin, cyclophosphamide, and paclitaxel[24]			
	Hormone therapy with tamoxifen[25]			
	Surveillance with mammogram and clinical exam one visit for 5 years			
Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	Symptom management including amitriptyline, stool softener, morphine (slow release, immediate release), bisphosphonates [45]	219.75	2	2

[22] Diagnostic costs include false positive findings requiring subsequent diagnostic mammography with or without biopsy

[23] 218.01 for Stage I, 464.58 for Stage II, 684.84 for Stage III

[24] Adjuvant therapy is given to 5% of stage I patients, 30% of stage II patients, and 60% of stage III

[25] Needed for patients with hormone receptor positive cancers (estimated at 40%)

Table 6: Intervention costing assumptions for Colorectal Cancer

Interventions	Costing components	Cost of Drugs and supplies per person identified/treated (I$ 2010)	Outpatient visits[26]	Inpatient days
Treatment of colorectal cancer stages I and II with surgery +/- chemotherapy and radiotherapy	*Diagnosis and staging*:	24.12	8, 14[27]	7
	Diagnosis with colonoscopy, biopsy, specimen fixative and staining			
	Pre-treatment tests and staging studies when indicated including cross-axial imaging			
	Treatment:	95.34, 459.88,[28]		
	Colectomy including pre-operative antibiotics			
	Adjuvant systemic therapy for colon cancer such as capecitabine and oxaliplatin for select patients with Stage II colon cancer [46] and [44][29]			
	Neoadjuvant systemic therapy for rectal cancer such as capecitabine and radiotherapy for select patients with Stage II rectal cancer [46] and [44][30]			
	Adjuvant chemotherapy with 5-FU, oxaliplatin, and leucovorin for select patients with Stage II rectal cancer [46] and [44][31]			
	Management of complications and toxicities including surgical infection, neutropenia and chemotherapy-associated nausea that includes antibiotics, filgrastim, and ondansetron			
	Surveillance includes laboratory test, cross-axial imaging, and endoscopy			
Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and	Symptom management including amitriptyline, stool softener, morphine (slow release, immediate release), bisphosphonates [45]	219.75	2	2

[26] Costing includes health workforce time and outpatient facility visit.
[27] 8 for stage I, 14 for stage II
[28] 95.34 for Stage I, 459.88 for Stage II
[29] Estimated at 10% of stage II colon cancer patients require systemic therapy.
[30] Estimated at 50% of stage II rectal cancer patients require neoadjuvant systemic therapy
[31] Estimated at 10% of stage II rectal cancer patients require adjuvant systemic therapy.

access to opiates and essential supportive medicines	

*Refer to Table 1 for interventions label

Table 7: Costs, effects and incremental cost-effectiveness of cervical cancer interventions in Southeast Asia

Label*	Description of the intervention	Pop° coverage (%)	Costs per 10 million population (million I$ 2010)	HLY per 10 million population (undiscounted)	ACER	ICER
CVC_C1h	Treatment of cervical cancer stages I and II with either surgery or radiotherapy +/- chemotherapy	50	170	171,314	993	Dominated
CVC_C1h	Treatment of cervical cancer stages I and II with either surgery or radiotherapy +/- chemotherapy	80	189	335,061	565	Dominated
CVC_C1h	Treatment of cervical cancer stages I and II with either surgery or radiotherapy +/- chemotherapy	95	199	445,670	447	Dominated
CVC_C1a	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls	50	141	1,112,285	127	Dominated
CVC_C1a	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls	80	159	1,499,743	106	Dominated
CVC_C1a	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls	95	169	1,630,353	103	Dominated
CVC_C1g	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions	50	363	4,284,936	85	Dominated
CVC_C1g	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening	80	487	4,927,198	99	Dominated

	women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions					
CVC_C1g	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions	95	549	5,109,215	108	Dominated
CVC_C1f	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions	50	520	4,472,666	116	Dominated
CVC_C1f	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions	80	738	5,059,125	146	Dominated
CVC_C1f	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions	95	847	5,222,303	162	Dominated
CVC_C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid	50	396	4,541,842	87	87

	linked with timely treatment of pre-cancerous lesions					
CVC_C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	80	549	5,106,391	108	272
CVC_C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	95	626	5,262,580	119	491
CVC_C1d	Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions	50	336	3,776,827	89	Dominated
CVC_C1d	Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions	80	452	4,384,869	103	Dominated
CVC_C1d	Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions	95	510	4,565,750	112	Dominated
CVC_C1c	Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions	50	493	4,002,315	123	Dominated
CVC_C1c	Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked	80	703	4,554,619	154	Dominated

	with timely treatment of pre-cancerous lesions					
CVC_C1c	Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions	95	807	4,714,860	171	Dominated
CVC_C1b	Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	50	368	4,085,368	90	Dominated
CVC_C1b	Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	80	513	4,615,409	111	Dominated
CVC_C1b	Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	95	585	4,767,951	123	Dominated
CVC_C1i	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	50	135	2,769	48,612	Dominated
CVC_C1i	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	80	149	4,431	33,643	Dominated
CVC_C1i	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	95	156	5,262	29,704	Dominated

*CVC: Cervical cancer

Table 8: Costs, effects and incremental cost-effectiveness of breast cancer interventions in Southeast Asia

Label*	Description of the intervention	Pop° coverage (%)	Costs per 10 million population (million I$ 2010)	HLY per 10 million population (undiscounted)	ACER	ICER
BRC_C2a	Treatment of breast cancer stages I and II with surgery +/- systemic therapy	50	174	335,651	517	Dominated
BRC_C2a	Treatment of breast cancer stages I and II with surgery +/- systemic therapy	80	195	629,010	310	Dominated
BRC_C2a	Treatment of breast cancer stages I and II with surgery +/- systemic therapy	95	206	816,200	252	252
BRC_C2b	Screening with mammography (once every 2 years for women aged 50-69 years) linked with timely diagnosis and treatment of breast cancer	50	618	745,528	829	Dominated
BRC_C2b	Screening with mammography (once every 2 years for women aged 50-69 years) linked with timely diagnosis and treatment of breast cancer	80	909	1,298,852	700	Dominated
BRC_C2b	Screening with mammography (once every 2 years for women aged 50-69 years) linked with timely diagnosis and treatment of breast cancer	95	1,056	1,627,782	649	1,048
BRC_C2c	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	50	154	12,041	12,783	Dominated
BRC_C2c	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	80	180	19,265	9,340	Dominated
BRC_C2c	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	95	193	22,877	8,434	Dominated

*BRC: Breast cancer

Table 9: Costs, effects and incremental cost-effectiveness of colorectal cancer interventions in Southeast Asia

Label*	Description of the intervention	Pop° coverage (%)	Costs per 10 million population (million I$ 2010)	HLY per 10 million population (undiscounted)	ACER	ICER
CRC_C3a	Treatment of colorectal cancer stages I and II with surgery +/- chemotherapy and radiotherapy	50	174	310,289	562	Dominated
CRC_C3a	Treatment of colorectal cancer stages I and II with surgery +/- chemotherapy and radiotherapy	80	196	633,637	310	Dominated
CRC_C3a	Treatment of colorectal cancer stages I and II with surgery +/- chemotherapy and radiotherapy	95	207	870,417	238	238
CRC_C3b	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	50	135	3,128	43,307	Dominated
CRC_C3b	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	80	150	5,006	30,058	Dominated
CRC_C3b	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	95	158	5,944	26,571	Dominated

*CRC: Colorectal cancer

Table 10: Costs, effects and incremental cost-effectiveness of cervical cancer interventions in Eastern sub-Saharan Africa

Label*	Description of the intervention	Pop° coverage (%)	Costs per 10 million population (million I$ 2010)	HLY per 10 million population (undiscounted)	ACER	ICER
CVC_C1h	Treatment of cervical cancer stages I and II with either surgery or radiotherapy +/- chemotherapy	50	164	918,353	179	Dominated
CVC_C1h	Treatment of cervical cancer stages I and II with either surgery or radiotherapy +/- chemotherapy	80	211	1,777,983	119	Dominated
CVC_C1h	Treatment of cervical cancer stages I and II with either surgery or radiotherapy +/- chemotherapy	95	235	2,355,450	100	Dominated
CVC_C1a	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls	50	146	5,215,136	28	28
CVC_C1a	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls	80	190	6,773,262	28	28
CVC_C1a	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls	95	213	7,297,912	29	Dominated
CVC_C1g	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions	50	697	24,649,274	28	Dominated
CVC_C1g	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5	80	1,043	29,121,530	36	Dominated

	years linked with timely treatment of pre-cancerous lesions					
CVC_C1g	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions	95	1,213	30,413,350	40	Dominated
CVC_C1f	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions	50	1,071	25,894,136	41	Dominated
CVC_C1f	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions	80	1,639	30,073,810	55	Dominated
CVC_C1f	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions	95	1,920	31,251,433	61	Dominated
CVC_C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer	50	764	26,362,292	29	Dominated

	by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions					
CVC_C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	80	1,163	30,421,065	38	41
CVC_C1e	Vaccination against human papillomavirus (2 doses) of 9–13-year-old girls & Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	95	1,362	31,554,286	43	175
CVC_C1d	Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions	50	621	21,058,982	29	Dominated
CVC_C1d	Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions	80	919	25,096,943	37	Dominated
CVC_C1d	Prevention of cervical cancer by screening women aged 30–49 through human papillomavirus test every 5 years linked with timely treatment of pre-cancerous lesions	95	1,064	26,370,394	40	Dominated
CVC_C1c	Prevention of cervical cancer by screening women aged 30–49 through Pap smear	50	995	22,516,816	44	Dominated

	(cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions					
CVC_C1c	Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions	80	1,514	26,290,979	58	Dominated
CVC_C1c	Prevention of cervical cancer by screening women aged 30–49 through Pap smear (cervical cytology) every 3–5 years linked with timely treatment of pre-cancerous lesions	95	1,769	27,447,414	64	Dominated
CVC_C1b	Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	50	687	23,064,846	30	Dominated
CVC_C1b	Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	80	1,038	26,726,375	39	Dominated
CVC_C1b	Prevention of cervical cancer by screening women aged 30–49 through visual inspection with acetic acid linked with timely treatment of pre-cancerous lesions	95	1,210	27,836,622	43	Dominated
CVC_C1i	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	50	119	25,520	4,654	Dominated
CVC_C1i	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access	80	147	40,832	3,595	Dominated

	to opiates and essential supportive medicines					
CVC_C1i	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	95	161	48,488	3,316	Dominated

*CVC: Cervical cancer

Table 11: Costs, effects and incremental cost-effectiveness of breast cancer interventions in Eastern sub-Saharan Africa

Label*	Description of the intervention	Pop° coverage (%)	Costs per 10 million population (million I$ 2010)	HLY per 10 million population (undiscounted)	ACER	ICER
BRC_C2a	Treatment of breast cancer stages I and II with surgery +/- systemic therapy	50	123	584,274	211	Dominated
BRC_C2a	Treatment of breast cancer stages I and II with surgery +/- systemic therapy	80	146	1,080,913	135	Dominated
BRC_C2a	Treatment of breast cancer stages I and II with surgery +/- systemic therapy	95	157	1,389,662	113	113
BRC_C2b	Screening with mammography (once every 2 years for women aged 50-69 years) linked with timely diagnosis and treatment of breast cancer	50	721	1,237,705	582	Dominated
BRC_C2b	Screening with mammography (once every 2 years for women aged 50-69 years) linked with timely diagnosis and treatment of breast cancer	80	1,110	2,159,801	514	Dominated
BRC_C2b	Screening with mammography (once every 2 years for women aged 50-69 years) linked with timely diagnosis and treatment of breast cancer	95	1,307	2,697,617	485	879

BRC_C2c	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	50	124	29,868	4,152	Dominated
BRC_C2c	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	80	155	47,789	3,247	Dominated
BRC_C2c	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	95	171	56,749	3,009	Dominated

*BRC: Breast cancer

Table 12: Costs, effects and incremental cost-effectiveness of colorectal cancer interventions in Eastern sub-Saharan Africa

Label*	Description of the intervention	Pop° coverage (%)	Costs per 10 million population (million I$ 2010)	HLY per 10 million population (undiscounted)	ACER	ICER
CRC_C3a	Treatment of colorectal cancer stages I and II with surgery +/- chemotherapy and radiotherapy	50	112	233,095	480	Dominated
CRC_C3a	Treatment of colorectal cancer stages I and II with surgery +/- chemotherapy and radiotherapy	80	128	464,692	275	Dominated
CRC_C3a	Treatment of colorectal cancer stages I and II with surgery +/- chemotherapy and radiotherapy	95	136	626,379	217	217
CRC_C3b	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	50	93	2,949	31,699	Dominated
CRC_C3b	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	80	106	4,718	22,530	Dominated
CRC_C3b	Basic palliative care for cancer: home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicines	95	113	5,602	20,117	Dominated

*CRC: Colorectal cancer

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Chapter IV: Cost-effectiveness of strategies to prevent road traffic injuries in eastern sub-Saharan Africa and Southeast Asia: new results from WHO-CHOICE

Published in 'Cost Effectiveness and Resource Allocation' journal

Ralaidovy *et al. Cost Eff Resour Alloc (2018) 16:59*
https://doi.org/10.1186/s12962-018-0161-4

Cost-effectiveness of strategies to prevent road traffic injuries in eastern sub-Saharan Africa and Southeast Asia: new results from WHO-CHOICE

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Abstract

Background

Road safety has been receiving increased attention through the United Nations Decade of Action on Road Safety, and is also now specifically addressed in the Sustainable Development Goals (SDGs) 3.6 and 11.2. In an effort to enhance the response to Road Traffic Injuries (RTIs), this paper aims to examine the cost effectiveness of proven preventive interventions and forms part of an update of the WHO-CHOICE programme.

Methods

Generalized cost-effectiveness analysis (GCEA) approach was used for our analysis. GCEA applies a null reference case, in which the effects of currently implemented interventions are subtracted from current rates of burden, in order to identify the most efficient package of interventions. A population model was used to arrive at estimates of intervention effectiveness. All heath system costs required to deliver the intervention, regardless of payer, were included. Interventions are considered to be implemented for 100 years. The analysis was undertaken for eastern sub-Saharan Africa and Southeast Asia.

Results

In Southeast Asia, among individual interventions, drink driving legislation and its enforcement via random breath testing of drivers at roadside checkpoints, at 80% coverage, was found to be the

most cost-effective intervention. Moreover, the combination of “speed limits + random breath testing + motorcycle helmet use”, at 90% coverage, was found to be the most cost-effective package. In eastern sub-Saharan Africa, enforcement of speed limits via mobile/handheld cameras, at 80% coverage, was found to be the most cost-effective single intervention. The combination of “seatbelt use + motorcycle helmet use + speed limits + random breath testing” at 90% coverage was found to be the most cost-effective intervention package.

Conclusion

This study presents updated estimates on cost-effectiveness of practical, evidence-based strategies that countries can use to address the burden of RTIs. The combination of individual interventions that enforces simultaneously multiple road safety measures are proving to be the most cost-effective scenarios. It is important to note, however, that, in addition to enacting and enforcing legislation on the risk factors highlighted as part of this paper, countries need to have a coordinated, multi-faceted strategy to improve road safety.

Keywords

Cost-effectiveness analysis, road traffic injury, road safety, priority setting, resource allocation, expansion path, WHO-CHOICE, abdulgafoor m. bachani, dan chisholm.

Background

Annually, 1.25 million people die in road crashes worldwide [1]. Road traffic injuries (RTIs) represent the tenth leading cause of death among all age groups [2], and are predicted to be the seventh leading cause of death by 2030 [1]. RTIs are the leading cause of death among persons aged 15 to 29 years [1], and pedestrians, bicyclists, and motorcyclists represent 49% of all road traffic deaths [1]. The African region has the highest rates of road traffic deaths. RTIs are not only a public health problem, but also a development issue. As a result of RTIs, it has been estimated that low and middle-income countries (LMICs) lose approximately 3% of their gross domestic product (GDP) each year [1]. In recognition of the scale of the problem, road safety has been receiving increased attention through the United Nations Decade of Action on Road Safety, and it is also now specifically addressed in two of the Sustainable Development Goals (SDGs). SDG target 3.6 calls for halving the number of global deaths and injuries from road traffic accidents by 2020 [3].

In an effort to enhance the response to RTIs, this paper aims to examine the cost effectiveness of proven interventions. This work forms part of an update of the WHO-CHOICE programme. Generalized cost-effectiveness analysis (GCEA) is used, which enables the efficiency of current interventions to be assessed alongside that of new interventions [4]. All currently recommended interventions are included in the analysis individually, and then as packages of care, based on combining the most cost-effective interventions.

For the purposes of consistency and comparability, this paper largely adopts the framework of an earlier WHO-CHOICE analysis [5] [6]. That analysis concluded that combined enforcement strategies represent the most efficient way to reduce the burden of RTIs, since combinations benefit from synergies on the cost side while producing greater overall health gain. This new analysis builds on that earlier work by using updated attributable fractions of RTIs associated with the different road users groups (pedestrians, bicyclists, car occupants, etc.) for our regions of interest, also by extending the time horizon of implementation from 10 years to 100 years. The following were also updated: the prevalence and distribution of RTIs (both fatal and non-fatal), the population sizes and mortality rates, the health-state valuations for long-term sequelae of RTIs, as well as the prices of the resources used in interventions.

Methods

Detailed descriptions of the methods employed in WHO-CHOICE have been published previously [4] [7]. The goal of WHO-CHOICE is to compare both current and new interventions in terms of cost effectiveness. In this paper, we describe specific methods related to RTIs. The base year of 2010 was selected to be in line with the 2010 Global Burden of Disease study [8], whose data form the base of many of the disease models used in WHO-CHOICE. The analysis was undertaken for the eastern sub-Saharan Africa and Southeast Asia regions [9].

To allow for comparison of results in a sector-wide analysis, the WHO-CHOICE project evaluates interventions across a range of diseases and risk factors, using common methods. Health outcomes are measured as the gain in healthy life years (HLYs) due to an intervention. The use of HLYs allows for priority setting across the health sector since it facilitates comparison across different diseases. HLYs are reported both discounted at 3% per annum and undiscounted. WHO-CHOICE adopts the costing perspective of "the health system", by which is meant the ensemble of actions and actors whose primary intent is to improve human health. The analysis, therefore, contains all direct, market-valued costs, whether public or private, that are required to deliver the intervention, regardless of payer. All costs are discounted at 3% per annum. Interventions are considered to be implemented for 100 years.

Identification of risk factors and interventions for road traffic injuries

As for the previous WHO-CHOICE analysis, a dynamic system modelled with a Haddon matrix [10] was used as a reference framework for identifying factors that have an impact on RTI. Each cell of the matrix allows opportunities for an intervention to reduce road traffic injuries. Factors in bold are those included in the analysis (see Table 1).

This analysis evaluates 13 individual and combination interventions. They are drawn from recommendations in the the World report on road traffic injury prevention [10] and are mainly focused on pre-event road safety measures, targeting change in human behaviour, due to the availability of robust evidence on their effectiveness and feasibility (see Table 2).

Key parameters in this analysis were the prevalence and distribution of RTIs, both fatal and non-fatal, the prevalence and distribution of risk factors for RTIs, the prevalence, distribution and effectiveness of interventions to reduce RTIs, the population size and mortality rates, and the health state valuations for the long-term sequelae of RTIs.

Table 1: The Haddon Matrix

Phase		**Factors**		
		Human	*Vehicle*	*Environment*
Pre-crash	Crash prevention	Information Attitudes **Impairment** **Police enforcement**	Roadworthiness Lighting Braking Handling	Road design Road layout **Speed limits** Pedestrian facilities
Crash	Injury prevention during the crash	**Use of restraints** **Impairment**	Occupant restraints Other safety devices Crash-protective design	Forgiving roadside
Post-crash	Life sustaining	First-aid skill Access to hospital	Ease of access Fire risk	Rescue facilities Congestion

Source: World report on road traffic injury prevention, Fig 1.3; factors in bold are those included in the analysis

Table 2: Interventions included in the analysis

#	Scenario Name	Intervention	Description
1	RBT	Random breath testing	Drink driving legislations and its enforcement via random breath testing of drivers at roadside checkpoints
2	ESL	Enforcement of speed limits	Sustained effort by traffic enforcement teams to raise the perceived risk of drivers being caught via the use of mobile/hand held speed cameras at randomly chosen checkpoint sites
3	HUB	Bicycle helmet use	Legislation and enforcement of helmet use by bicyclists aged 15 years or less
4	HUM	Motorcycle helmet use	Legislation and enforcement of helmet use among riders of moped and motorcycles

5	SBU	Seatbelt use	Legislation and enforcement of seat belt use in cars (drivers and passengers)
6	SBU_HUM	Seatbelt use + Motorcycle helmet use	
7	SBU_HUM_RBT	Seatbelt use + Motorcycle helmet use + Random breath testing	
8	SBU_HUM_ESL	Seatbelt use + Motorcycle helmet use + Speed limits	
9	SBU_HUM_ESL_RBT	Seatbelt use + Motorcycle helmet use + Speed limits + Random breath testing	
10	SBU_HUM_ESL_RBT_HUB	Seatbelt use + Motorcycle helmet use + Speed limits + Random breath testing + Bicycle helmet use	
11	ESL_RBT	Speed limits + Random breath testing	
12	ESL_RBT_HUM	Speed limits + Random breath testing + Motorcycle helmet use	
13	ESL_RBT_SBU	Speed limits + Random breath testing + Seatbelt use	

Attribution of RTIs by road user group

A literature review to give an overview of published data between 2006-2014 on fatal and non-fatal road traffic injuries, their risk factors and sequelae was conducted (see Additional file 1). The attributable fractions are calculated separately for all risk factors at the regional level based on the epidemiological evidence (e.g. exposure rates) from the countries in the region, weighted by population size. Key data on fatal and non-fatal injuries by road user type, sex and age group was provided by the International Injury Research Unit of the Johns Hopkins Bloomberg School of Public Health, which maintains and develops a global database of RTIs. Information collected with the literature review was used in triangulation of the attribution of the RTIs by road user group in combination of the data provided by the Johns Hopkins Bloomberg School of Public Health and the findings of the original literature review that informed the original model creation along with its attribution distribution.

Figure 1: Distribution of road traffic fatalities by road user type calculated based on data provided by the International Injury Research Units of Johns Hopkins Bloomberg School of Public Health

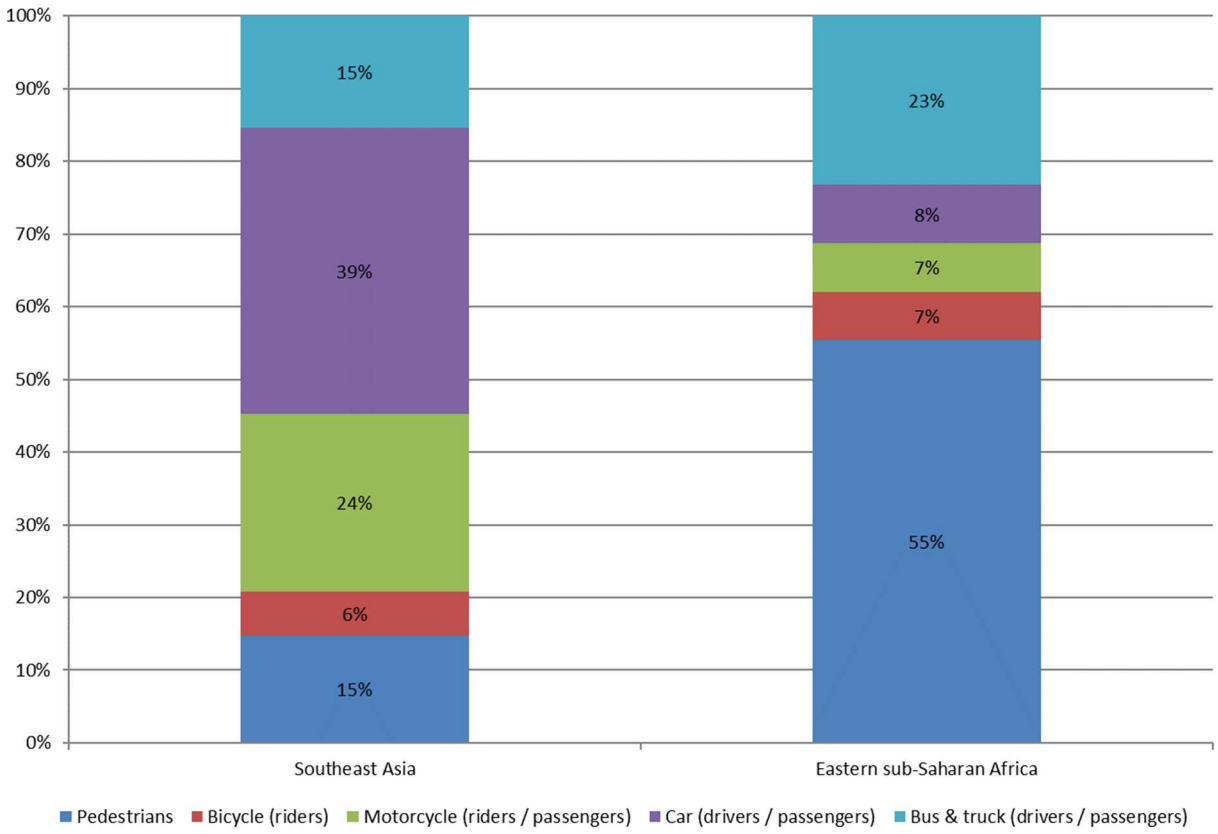


Figure 2: Age distribution of fatalities by road user type in Southeast Asia. Calculated based on data provided by the International Injury Research Unit of Johns Hopkins Bloomberg School of Public Health

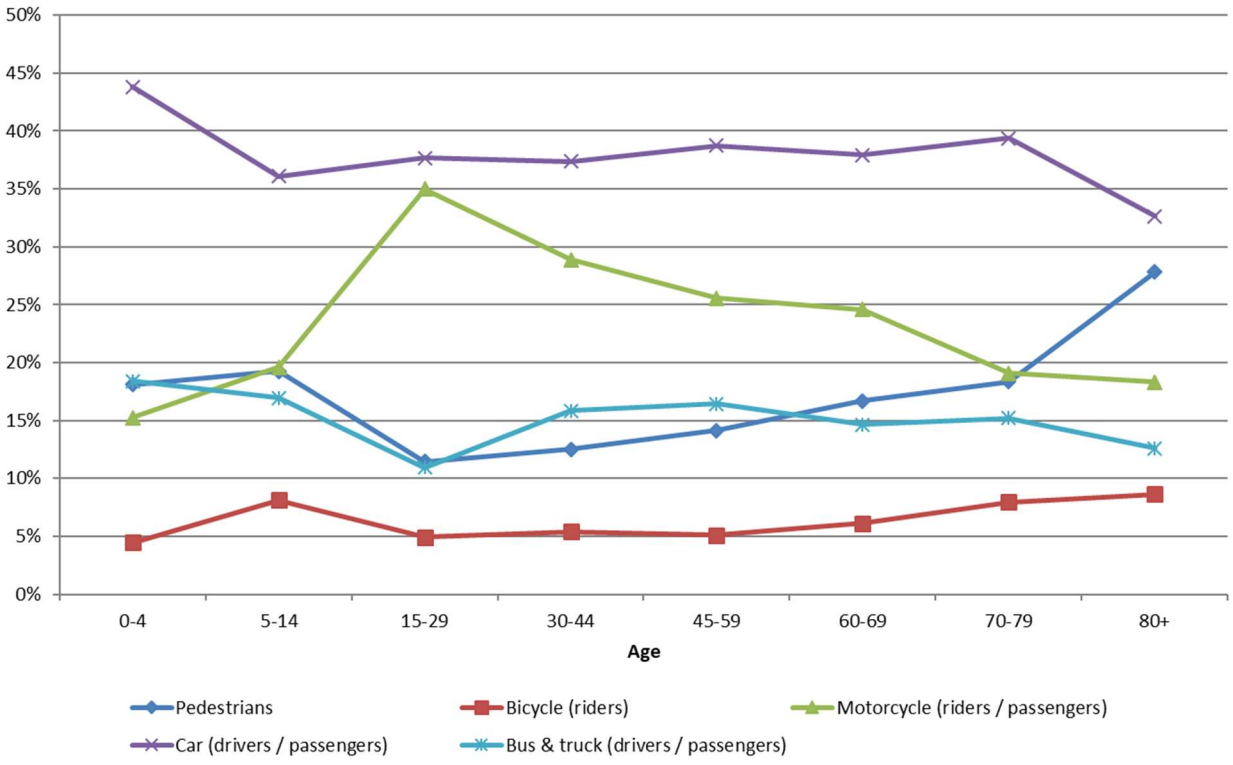
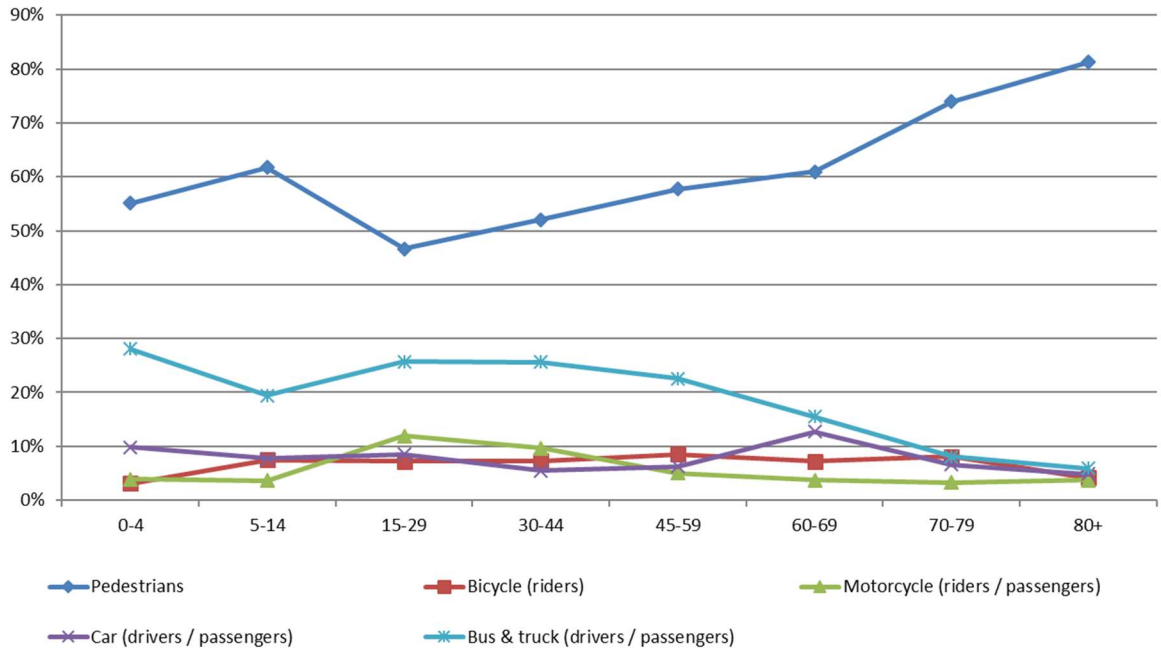


Figure 3: Age distribution of fatalities by road user type in Eastern sub-Saharan Africa. Calculated based on data provided by the International Injury Research Unit of Johns Hopkins Bloomberg School of Public Health



Attribution of RTIs by risk factor

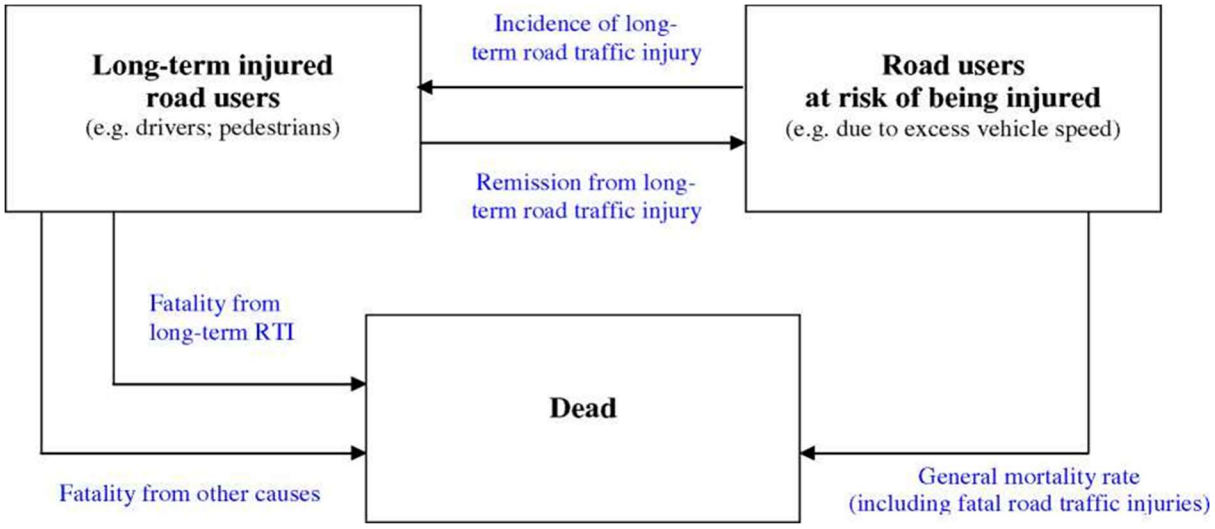
To measure the independent contribution of different risk factors to overall rates of RTIs in the population, we used the population attributable fraction (PAF), which can be defined as the fraction of incident cases attributable to the risk exposure:

$$PAF = \frac{\text{(Incidence of injury in all road users) - (Injury in road users without the exposure)}}{\text{Incidence of injury in all road users}}$$

Estimation of intervention effectiveness

Interventions are at first compared to a hypothetical scenario where the known effects of implemented interventions are removed, referred to as the null scenario. Then the marginal impacts of interventions are evaluated with reference to the null scenario. A multi-state population model [11] was used to estimate scenarios (see Figure 4). Further details on the methods can be found in [5]. Non-fatal acute injuries of short term duration (e.g. bruises, cuts) were not considered in the analysis.

Figure 4: Population model for estimating health impact of road safety measures. (Source: Road traffic injury prevention: an assessment of risk exposure and intervention cost effectiveness in different world regions , 2008 [5], Fig.8)



The same estimates of the effects of interventions as in the previous WHO analysis [5] were used. (see Additional file 2). This is due to the fact that during initial literature scoping on the intervention effects in the regions modelled, no papers of suitable focus and/or quality were found to enable updating of the sub-model of the intervention effect estimates in the targeted countries. The estimates used in this analysis of the incidence, prevalence and case fatality rates of RTIs, as well as their associated levels of disability are also shown in Additional file 2. The impact of the selected interventions on population health were evaluated individually, and then as a combination by multiplying the effects of each individual intervention.

Intervention costing

Costs of interventions were estimated at the health system level, and include the costs of all market-valued inputs required to deliver the intervention. For example, costs include those of the passage of legislation, the enforcement of legislation and programme management [12]. For "bicycle helmet use" and "motorcycle helmet use" interventions, the costs of equipping bicyclists and motorcyclists with helmets were included, since these costs represent an integral component of those interventions. For the "seatbelt use" intervention, the costs of installing driver and passengers' seatbelts in cars not already so equipped were included. Costs are discounted at 3% per annum, assuming a 100-year implementation period. Capital costs are annualized over the lifetime of the asset. All prices are in 2010 International Dollars. 2010 was chosen as the baseline

year in line with the 2010 Global Burden of Disease epidemiological data which forms the base of many of the disease models used in WHO-CHOICE. The main costing assumptions are shown in Additional file 2.

Results

The results for each intervention individually, and then as a package, are presented in Table 3 and 4.

Table 3: Costs, effects and cost effectiveness of road safety measures in Southeast Asia over 100 years

Intervention (Legislation and enforcement)	Pop° coverage (%)	Total costs per 10 million population (I$ 2010)	Healthy life Years (HLY) gained per 10 Million population	ACER (I$ per HLY)	ICER (I$ per HLY)
Random breath testing	80	117 632 481	52 288	2 250	Dominated
Speed limits	80	120 598 909	44 216	2 727	Dominated
Bicycle helmet use	80	111 809 164	1 068	104 648	Dominated
Motorcycle helmet use	90	169 026 306	51 497	3 282	Dominated
Seatbelt use	50	102 206 381	12 058	8 476	Dominated
Seatbelt use + Motorcycle helmet use	90	185 043 479	63 644	2 907	Dominated
Seatbelt use + Motorcycle helmet use + Random breath testing	90	204 664 782	116 168	1 762	Dominated
Seatbelt use + Motorcycle helmet use + Speed limits	80	202 251 594	108 096	1 871	Dominated
Seatbelt use + Motorcycle helmet use + Speed limits + Random breath testing	90	224 072 895	160 738	1 394	1 552
Seatbelt use + Motorcycle helmet use + Speed limits + Random breath testing + Bicycle helmet use	90	249 482 034	161 811	1 542	23 692
Speed limits + Random breath testing	80	139 450 546	96 620	1 443	Dominated

Speed limits + Random breath testing + Motorcycle helmet use	90	205 065 577	148 493	1 381	1,381
Speed limits + Random breath testing + Seatbelt use	80	158 109 184	108 774	1 454	Dominated

Table 4: Costs, effects and cost effectiveness of road safety measures in Eastern sub-Saharan Africa over 100 years

Intervention (Legislation and enforcement)	**Pop° coverage (%)**	**Total costs per 10 million population (I$ 2010)**	**Healthy life Years (HLY) gained per 10 Million population**	**ACER (I$ per HLY)**	**ICER (I$ per HLY)**
Random breath testing	80	371 264 947	8 242	45 048	Dominated
Speed limits	80	372 557 382	14 576	25 559	Dominated
Bicycle helmet use	80	367 527 956	243	1 514 136	Dominated
Motorcycle helmet use	90	385 934 475	6 191	62 343	Dominated
Seatbelt use	50	336 588 617	3 480	96 715	Dominated
Seatbelt use + Motorcycle helmet use	90	439 366 375	9 688	45 353	Dominated
Seatbelt use + Motorcycle helmet use + Random breath testing	90	495 706 294	17 972	27 583	Dominated
Seatbelt use + Motorcycle helmet use + Speed limits	80	485 490 048	24 335	19 950	Dominated
Seatbelt use + Motorcycle helmet use + Speed limits + Random breath testing	90	551 981 331	32 649	16 907	16 907
Seatbelt use + Motorcycle helmet use + Speed limits + Random breath testing + Bicycle helmet use	90	612 222 569	32 892	18 613	247 240
Speed limits + Random breath testing	80	427 607 093	22 846	18 717	Dominated
Speed limits + Random breath testing + Motorcycle helmet use	90	496 182 560	29 060	17 074	Dominated
Speed limits + Random breath testing + Seatbelt use	80	482 432 030	26 417	18 262	Dominated

Population-level effects of interventions

The effectiveness of interventions are reported in healthy life years (HLYs) gained due to the specific intervention (Tables 3 and 4).

Because the highest road fatalities are among car drivers and passengers in Southeast Asia (39% of all fatalities, Fig. 1), drink driving legislation and its enforcement via "random breath testing" at roadside checkpoints was found to be the most effective single intervention in this region. The legislation "motorcycle helmet use", and its enforcement, was found to be the second most effective single intervention; this is consistent with the high proportion of motorcycles in this region and the percentage of road fatalities among this road user group (24%, Fig. 1).

In eastern sub-Saharan Africa, the enforcement of "speed limits" via mobile/handheld cameras at 80% coverage was found to be the most effective single intervention, probably reflecting the fact that pedestrians account for more than 50% of road fatalities among all road user groups in this region (see Fig.1).

The legislation and enforcement of "bicycle helmet use", at 80% coverage, was found to be the least effective single intervention in both regions.

Among the combination of interventions, a scenario that combined all 5 individual interventions was found to be the most effective in both regions.

Population level costs of interventions

The total costs estimated for motorcycle helmet use include not only the costs of the passage of legislation and its enforcement but also the costs to the household of purchasing safety equipment, which may explain why this intervention represents the most costly single intervention in both sub-regions. The household cost component is also added to the costs of "seatbelt use" and "bicycle helmet use"; the costs of "seatbelt use" is applied to cars that are not already equipped (assumed to be at 50% in low-income sub-regions); and "bicycle helmet use" targets only children aged 15 years or less (Tables 3 and 4).

Economies of scope are realised by combining individual interventions due to the synergies that exists between different enforcement strategies.

Cost effectiveness of interventions

The cost effectiveness of individual interventions and their combinations are presented in Tables 3 and 4. Cost-effectiveness ratios are reported as costs (in international dollars) per HLY gained.

Among single interventions, “random breath testing”, at 80% coverage, was found to be the most cost-effective intervention in Southeast Asia, whereas in eastern sub-Saharan Africa, it was “speed limits”, at 80% coverage.

Combinations of individual interventions were found to be the most cost-effective: “speed limits + random breath testing + motorcycle helmet use”, at 90% coverage, in Southeast Asia and “seatbelt use + motorcycle helmet use + speed limits + random breath testing”, at 90% coverage, in eastern sub-Saharan Africa.

Figures 5 and 6 show the expansion path a decision maker could follow to achieve the maximum health gain for a given level of expenditure. The expansion path shows the order in which each intervention would be adopted based on its incremental cost-effectiveness ratio, compared to the previously adopted intervention, until no more health gain is possible [4].

Figure 5: Cost-effectiveness expansion path for Southeast Asia. Refer to Table 2 for interventions 'labels

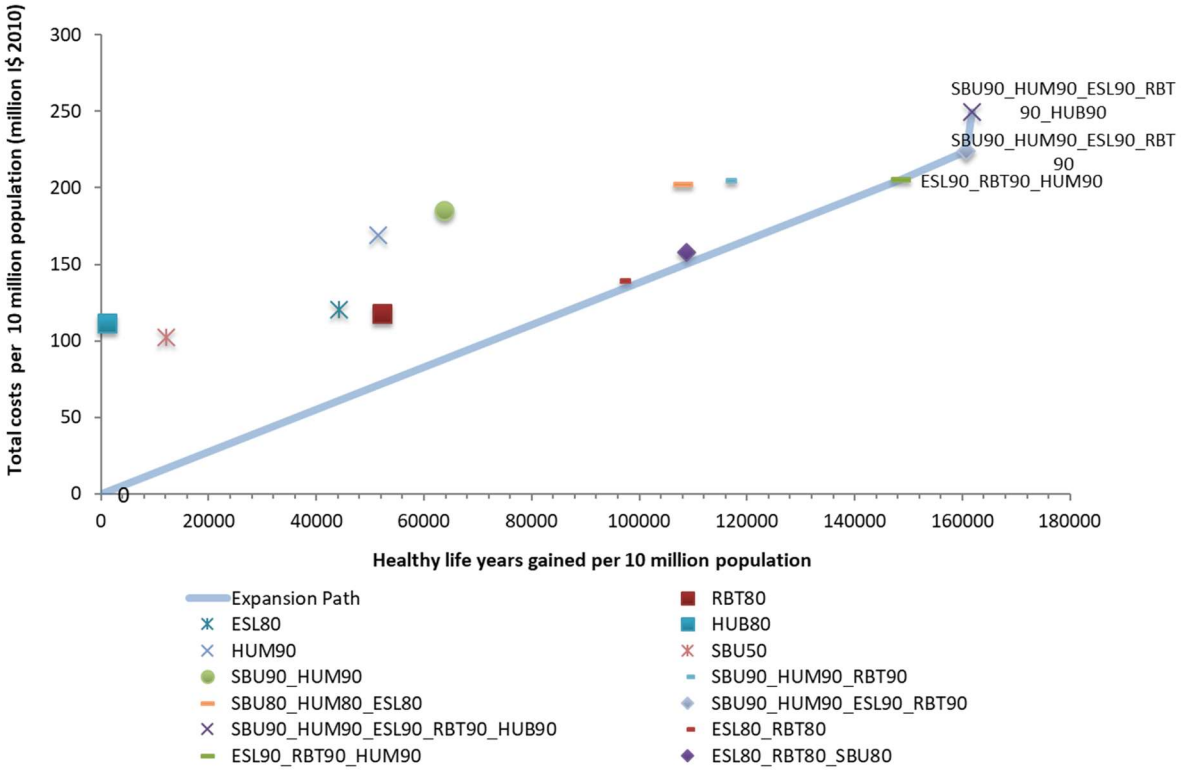
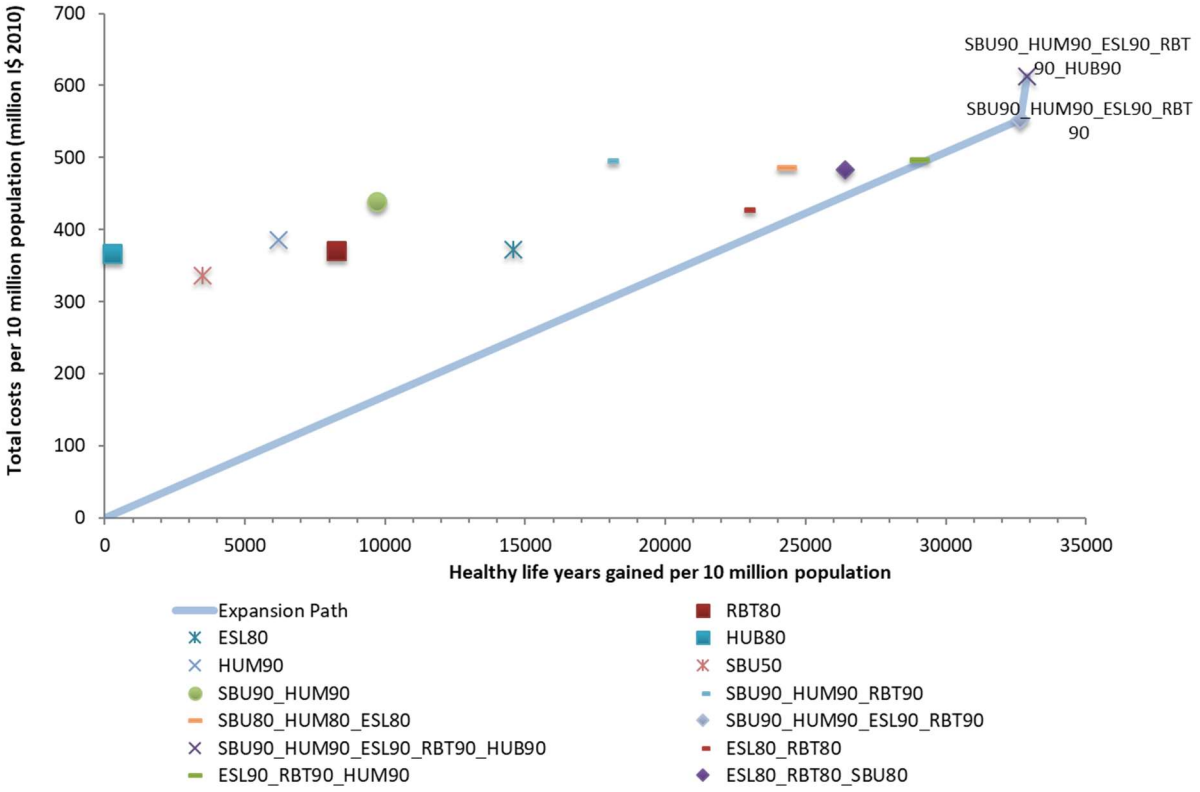


Figure 1: Cost-effectiveness expansion path for Eastern sub-Saharan Africa. Refer to Table 2 for interventions 'labels



Following the expansion path in Figure 5, in Southeast Asia policymakers would first implement "speed limits + random breath testing + motorcycle helmet use", at 90% coverage, and when additional resources become available, add "seatbelt use", at 90% coverage, followed by "bicycle helmet use", also at 90% coverage.

In eastern sub-Saharan Africa, after "seatbelt use + motorcycle helmet use + speed limits + random breath testing", at 90 % coverage, a policymaker could add "bicycle helmet use", also at 90% coverage, to maximize health gain (see Fig.6).

Discussion

This paper adopts the framework of the 2012 study and is showing that the most cost effective interventions are essentially unchanged. However, the ranking of interventions is slightly different. Bicycle helmet use, while being on the expansion path (as a single intervention) in the previous analysis for countries in sub-Saharan Africa, is now shown to be less cost effective in this update

unless combined with other interventions. The combination of speed limits, random breath testing and motorcycle helmet use at 90% coverage also appears on the expansion path in this update, and is the most cost effective combination of interventions in Southeast Asia, while it was dominated in the previous analysis. Nevertheless, these findings corroborate the conclusion of the previous analysis stating that combined enforcement strategies represent the most efficient way to reduce the burden of RTIs.

The analysis presented in this paper underscores the cost-effective nature of interventions to prevent road traffic injuries in low-income and lower middle-income countries. As previous studies have demonstrated, compared to other public health measures, strategies to improve road safety are cost-effective interventions [6], [13], [14], [15]. Our analysis shows that interventions aimed at enforcing legislation for road safety are especially effective, as they improve cost efficiencies while also enhancing gains in effectiveness.

The interventions included in our analysis are in line with the recently proposed Save-LIVES technical package published by WHO [16]. This package was developed to provide a comprehensive, evidence-based set of tools to address the growing burden of RTIs globally. Based on the recommendations included in this package, legislation and its enforcement are the cornerstones of an effective road safety programme. Our findings, which show significant potential gains as a result of enacting and enforcing legislation targeting the leading risk factors for road traffic injuries, support this recommendation.

As the United Nations Decade of Action for Road Safety reaches its final years, and with the goal of halving the world's road traffic deaths by the year 2020 (SDG 3.6) upon us, there is an increased sense of urgency to address the burden of RTIs globally [17], [3]. Action needs to be taken at national levels, and countries should identify and implement strategies to improve road safety within their borders. In recognition of the fact that policy-makers work under resource-constrained conditions, and have to make decisions about competing programs, our analysis presents a practical approach that identifies the most cost-effective individual interventions that countries could implement first, followed by an expansion strategy that can be employed as more resources become available. Such a phased approach is more likely to be more feasible than an all-or-nothing option.

A limitation of our analysis is that we take a regional perspective, rather than a country specific one, and that we present analysis for only two regions in the world. These are, however, regions that have high burdens of RTIs and related fatalities. It is also expected that the findings would hold true at country level.

Conclusion

This study presents updated estimates on cost-effectiveness of practical, evidence-based strategies that countries can use to address the burden of RTIs. It is important to note, however, that, in addition to enacting and enforcing legislation on the risk factors highlighted as part of this paper, countries need to have a coordinated, multi-faceted strategy to improve road safety that includes leadership and coordination of activities around road safety; efficient and reliable mechanisms to gather data that would aid in understanding the burden as well as evaluating the effectiveness and efficiency of programs; infrastructural improvements; a focus on vehicle safety standards; and a coordinated post-crash care system that is aimed at minimizing the impact of a road accident on the individual.

Abbreviations

ACER	Average Cost-Effectiveness Ratio
CHOICE	CHOosing Interventions that are Cost-Effective
GCEA	Generalized Cost-Effectiveness Analysis
GDP	Gross Domestic Product
HLY	Healthy Life Years
ICER	Incremental Cost-Effectiveness Ratio
PAF	Population Attributable Fraction
RTI	Road Traffic Injuries
SDGs	Sustainable Development Goals
WHO	World Health Organization

Authors' contributions

AHR run the multi-state population model to estimate each scenario, performed the costing and the cost-effectiveness analysis, and drafted the manuscript. AMB provided conceptual input and contributes to the discussion part. JAL provided conceptual input, quality control and supervised the analysis. TL did the literature review and updated the model accordingly. DC as the lead author of the previous analysis, provided quality control. All authors contributed to the edit of the manuscript. All authors read an approved the final manuscript.

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Acknowledgements

We thank Adnan Hyder for his careful review and comments on the paper.

Competing interests

Not applicable

Availability of data and materials

The datasets that support the findings of this paper are available at http://www.who.int/choice/en

Consent for publication

Not applicable

Ethics approval and consent to participate

Not applicable

Funding

No funding was received for this analysis

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institution affiliations

Received : 11 April 2018 Accepted: 8 November 2018; Published online: 20 November 2018

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Additional file 1: Detailed results of the literature review (2006-2014)

Introduction

The aim of this literature review is to give an overview of recently published data on fatal and non-fatal road traffic injuries, their risk factors and sequelae in Sub-Saharan Africa and South-East Asia for renewing the model of cost-effectiveness of road traffic safety interventions.

Published studies and unpublished reports on country-specific road traffic injuries, their sequelae and road user distribution from 2006 and later (that were not used in the previous report) were sought by:

- An online keyword search using search engines such as EBSCO (incl. Medline), Google Scholar, Google, PubMed
- Relevant references cited in articles identified by the electronic search and relevant articles referring to identified articles were selected

The number of peer-reviewed articles reporting population-based distributions of road traffic injuries by road user category was limited; the majority of the data sources were mostly urban, hospital-based studies. More than one data source was identified for a number of countries.

Some articles are cited under more than one topic, if they include data on both.

1. Age- and sex-specific road traffic fatality rates

For attributing total injury estimates across different age groups, we tried to find a sub-set of countries that provided this detailed level of information (data were found for South Africa, Tanzania, India, Thailand). Last (2008) report by Chisholm & Naci found that the overall age distribution for fatalities and non-fatal injuries by road user type does not differ greatly among countries, although South Africa is at variance with the other countries due to a much lower life expectancy in age groups over 60.

Data on fatal road traffic injuries were more widespread than for non-fatal injuries. Very few studies provided a detailed distribution of road traffic fatalities or injuries by sex and age group, and more detailed age groups were available in very few studies.

1.1 Age- and sex specific RTI fatality rates in Sub-Saharan Africa

For Sub-Saharan Africa region an age distribution of RTI fatalities was detected for 4 countries, a total of 10 articles. These studies are outlined in Table 1. Of these, data for Republic of South

Africa, Tanzania, and Kenya provided a detailed distribution of RTI by age that was close to the distribution used in the previous study.

Most comprehensive statistics on RTI fatalities are available for South Africa where a mortality surveillance system is in place. For Kenya one hospital-based study was found, as well as one report based on data from the police, and one survey study. For Tanzania and Ethiopia survey data and a few hospital-based studies were found. In most of these studies road traffic fatality data were reported by age groups and by sex separately, so that a detailed age/sex distribution has to be imputed.

Table 1. Data sources for age- and sex-specific road traffic fatality rates in Sub-Saharan Africa

Reference	Country	Region	Type of data	Data period	n	Age groups reported	Findings
Norman, R., Matzopoulos, R., Groenewald, P., & Bradshawa, D. (2007). The high burden of injuries in South Africa. *Bulletin of the World Health Organization 2007*(85), 695–702.	South Africa	-	surveillance	2000	59 935 injury deaths	0-4, 5-14, 15-29, 30-44, >60	Rate per 100 000 by sex & age group
A profile of fatal injuries in South Africa - 7th Annual Report of the NATIONAL INJURY MORTALITY SURVEILLANCE SYSTEM 2005	South Africa	-	surveillance	2005	29 596 injury deaths, 5675 traffic deaths	<1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65+	Absolute numbers by age group
Statistics South Africa (2009). *Road Traffic Accident Deaths in South Africa, 2001–2006: Evidence from death notification.* Report No. 03-09-07 (2001–2006).	South Africa	-	death notifications	2001-2006	28 890 road traffic deaths	0-14, 15-24, 25-34, 35-49, 50-64, 65+	Deaths per 100 000 by sex & year, deaths per 100 000 by age & year, deaths per 100 000 by sex and age
Bachani, A. M., Koradia, P., Herbert, H. K., Mogere, S., Akungah, D., Nyamari, J., Osoro, E., Maina, W., & Stevens, K. A. (2012) Road Traffic Injuries in Kenya: The Health Burden and Risk Factors in Two Districts,	Kenya	Thika, Naivasha, urban + rural	traffic police, vital registration, observations	2004-2009	n/a	<1, 1-4, 5-14, 15-24, 25-34, 35-44, 45-54, 55-74, >74	% of RTI fatalities by sex & age

Traffic Injury Prevention, 13(sup1), 24-30.							
Gichuhi , K. (2007). Injury Pattern Among Non-fatal Road Traffic Crash Victims. *East African Orthopaedic Journal 1. 23-25.*	Kenya	Nairobi, urban?	hospital-based study	2004	1424 RTI victims treated in hospital	0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70+	Number of RTIs by age group
Macharia , W. M., Njeru, E. K., Muli-Musiime, F., & Nantulya, V. (2009). Severe road traffic injuries in Kenya, quality of care and access. *African Health Sciences 9*(2), 118-124.	Kenya	n/a	survey	1998-1999	310 RTI casualties	<15, 15-24, 25-49, >49	Number of RTIs by age group, number of RTIs by sex
Komba, D. D. (2006). *Risk Factors and Road Traffic Accidents in Tanzania: A Case Study of Kibaha District.* Master Thesis in Development Studies, Norwegian University of Science and Technology (NTNU)	Tan-zania	Kibaha	hospital data	2001-2004	246 fatal, 591 non-fatal	0-17, 18-24, 25-34, 35-44, 45+	Number of fatal & non-fatal RTIs by sex & age group
Masaoe, E. N. (2007). Study on Road Accidents in Mainland Tanzania. Final Report submitted to Surface and Marine Transport Regulatory Authority (SUMATRA). http://www.sumatra.or.tz/index.php/component/docman/doc_view/49-study-on-road-accidents-in-mainland-tanzania?Itemid=317 (Accessed on 24.07.2014)	Tan-zania	Dar es Salaam, Coast, Arusha, Kilimanjaro	post-accident survey	1994-2007	102 accident victims	<7, 8-12, 13-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, >55	Distribution of RTIs by age group & sex (approximate), fatal & nonfatal injuries by age group (total + percentage)
Zimmerman, K., Mzige, A. A., Kibatala, P. L., Museru, L. M., Guerrero, A. (2012). Road traffic injury incidence and crash characteristics in Dar es Salaam: A population based study. *Accident Analysis and Prevention 45*, 204– 210.	Tan-zania	Dar es Salaam	household survey	?	196 non-fatal RTI victims	0–4, 5–14, 15–44, >45	Number of RTIs by age group

Woldemichael, K., & Berhanu, N. (2011). Magnitude and pattern of injury in Jimma University specialized hospital, South-West Ethiopia. *Ethiopian Journal of Health Sciences 21*(3). 155-165.	Ethiopia	Jimma, South-West Ethiopia	hospital-based study	2010-2011	334 RTA victims	0-4, 5-14, 15-49, 50-64, >64	Number of RTIs by age group, number of RTIs by sex

1.2 Age- and sex specific RTI fatality rates in South-East Asia

For South-East Asia data for 4 countries were detected, a total of 12 articles with available data for India, Thailand, Vietnam and Nepal (see Table 2). Of these, some data for India and Thailand provided a detailed distribution of RTI by age, and couple of studies (e.g. Hsiao et al. 2013; Ditsuwan et al. 2011) attempted to correct for underreporting of RTIs and to fill in the data gaps with data from various sources.

For India, mostly hospital-based and autopsy studies were available, but one large mortality survey/verbal autopsy study (Hsiao et al. 2013) is probably the most comprehensive data source for RTI-related mortality in India, and provides good estimates.

For Thailand a comprehensive Burden of Disease study was found (Ditsuwan et al. 2011) and for Vietnam some quite comprehensive preliminary surveillance data (Ngo et al. 2012) representing 3% of the population was found. For Nepal only one hospital-based study was available, and for other countries in the region no recent data were found.

Table 2. Data sources for age- and sex-specific road traffic fatality rates in South-East Asia

Reference	Country	Region	Type of data	Data period	n	Age groups reported	Findings
Dandona, R., Kumar, A., Ameer, A., Ahmed, M., & Dandona, L. (2008). Incidence and Burden of Road Traffic Injuries in Urban India. *Injury Prevention 14*(6), 354–359.	India	Hyderabad city	survey data	2005-2009	536 non-fatal RTIs by 520 participants	5-9, 10-14, 15-19, 20-29, 30-39, 40-49	Estimated annual non-fatal RTI incidence rate per 100 persons in population aged 5-49 years
Honnungar, R. S., Aramani, S. C., Vijay Kumar, A. G., Ajay Kumar, T. S, Jirli, P. S. (2011). An Epidemiological Survey of Fatal Road Traffic Accidents and their Relationship with Head Injuries. *Journal of Indian Academic Forensic Medicine 33*(2), 135-137.	India	Karnataka	autopsy study	2004-2009	506 vehicle accident fatalities	<10, 11-20, 21-30, 31-40, 41-50, 51-60, >60	Fatal RTIs by age group & sex
Hsiao, M., Malhotra, A., Thakur, J.S., et al. (2013). Road traffic injury mortality and its mechanisms in India: nationally representative mortality survey of 1.1 million homes. *BMJ Open 2013(3)*:e002621.	India		large mortality survey, verbal autopsy	2001-2005	11543 injury deaths	0-4, 5-14, 15-29, 30-44, 45-59, 60-69, >70	Number of RTIs by sex and age group, estimated totals for 2005
Kakeri, S. R., Bagali, M.A., Goudar, E.S., & Qadri, S. Y. (2014). Pattern of injuries and death sustained by the occupants of the two-wheeler during road traffic accidents. *Al Ameen Journal of Medical Science 7*(2), 118-124.	India	Bijapur	hospital-based study	2005-2007	150 RTA victims	<10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, >70	Fatal RTIs by age group
Khajuria, B., Sharma, R., & Verma, A. (2008). A profile of the autopsies of road traffic accident victims in Jammu. *Journal of Clinical and Diagnostic Research 2*, 639-642	India	Jammu	autopsy study	2000-2005	249 RTA victims	<20, 20-40, 41-60, >60	Fatal RTIs by age group, fatal RTIs by sex

Mohan Kumar, T.S., Tanuj Kanchan, Yoganarasimha, K., Pradeep Kumar, G. (2006). Profile of unnatural deaths in Manipal, Southern India 1994–2004. *Journal of Clinical Forensic Medicine 13*(3), 117-120.	India	Manipal, Southern India	autopsy study	1994-2004	653 RTA victims	0–9, 10–19, 20–29, 30–39, 40–49, 50–59, >60	Fatal RTIs by age group & sex
Sharma, B.R., Sharma, A.K., Sharma, S. & Singh, H. (2007). Fatal Road Traffic Injuries in Northern India: Can They Be Prevented? *Trends in Medical Research 2*(3), 142-148.	India	Northern India	autopsy study	1996-2005	1109 RTA victims	0-10, 11-15, 16-20, 21-25, 26-30, 31-40, 41-50, 51-60, >61	Fatal RTIs by age group & sex
Manish, K, Jyothi, N. S, Pawar, G. S., Jatti, V. B. (2012). Fatal Head Injuries in Road Traffic Accidents in and around Davangere: A Prospective Study. Indian Journal of Forensic Medicine and Pathology 5(2).	India	Davangere	hospital-based study	2005-2007	408 RTI deaths	0-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80	Fatal RTIs by age group
Ditsuwan, V., Veerman, L. J., Barendregt, J. J., Bertram, M., & Vos, T. (2011). The national burden of road traffic injuries in Thailand. *Population Health Metrics 9*(2)	Thailand		estimate of fatal RTIs from SPICE cause of death study, hospital data, injury surveillance data, emergency department data	2004	567000 RTI victims	0-4, 5-14, 15-29, 30-44, 45-59, 60-69, 70-79, 80+	Fatal & nonfatal RTIs: deaths, admissions and RTI victims at emergency departments by age group & sex
Nakahara, S., Chadbunchachai, W., Ichikawa, M., *Tipsuntornsak* N., Wakai, S. (2005). Temporal distribution of motorcyclist injuries and risk of fatalities in relation to age, helmet use, and riding while intoxicated in Khon Kaen, Thailand. *Accident Analysis and Prevention 37*, 833–842.	Thailand	Khon Khaen	hospital-based study	1998-2002	9948 injured motorcyclists	10-19, 20-29, 30-39, 40+	Motorcycle RTIs by age group, motorcycle RTIs by sex

Ngo, A.D., Rao, C., Phuong Hoa, N., Hoy, D. G., Quynh Trang, K. T., & Hill, P. S. (2012). Road traffic related mortality in Vietnam: Evidence for policy from a national sample mortality surveillance system. *BMC Public Health 12*, 561.	Vietnam	Sample of 192 communes in 16 provinces, representing six socioeconomic regions in Vietnam (3% of pop)	surveillance data, verbal autopsy	2008-2009	1061 RTA victims	<15, 15-19, 20-29, 30-39, 40-49, 50-59, 60+	Number of RTI deaths by age group, number of RTI victims by sex
Mishra, B., Sinha, N. D., Suhkla, S. K., & Sinha, A. K. (2010). Epidemiological Study of Road Traffic Accident Cases from Western Nepal. *Indian Journal of Community Medicine 35*(1), 115–121.	Nepal	Western Nepal	hospital-based study		360 RTA victims	0-15, 16-30, 31-45, 46-60, >60	RTA victims by age, RTA victims by sex

2. Road users: age distribution, risk factors & injuries by road users

A standardized online keyword search was carried out to obtain country specific risk factor information, using online search engines such as Google, Google Scholar, and EBSCO. Keywords used were country name+road traffic injuries+road user, country name+ road traffic injuries+pedestrians, country name+road traffic injuries+motorcycle riders, country name+road traffic injuries+bicyclists, country name+road traffic injuries+car occupants, vehicle occupants.

Very few studies provided information on the distribution of non-fatal injuries by road user category. Additionally, very few studies provided age breakdowns or compared deaths in different road user groups by sex. Classification of casualties by category of road-users was not uniform and in many instances such aggregated groupings did not allow for accurate identification of road-user categories.

2.1 Age distribution of road users

As to age distribution of road users, the only available estimations were for South Africa. They originated from 2004, and provided an expected distribution of road users, based on calculations and data from 1997-1998 (Table 3).

Table 3. Data sources for age distribution of road users

Reference	Country	Region	Type of data	Data period	n	Age groups reported	Findings
De Beer, E.J.H., & van Niekerk, E.C. (2004). *The estimation of unit costs of road traffic accidents in South Africa*. National Department of Transport Contract Report CR-2004/6	South Africa		calculations	1997-1998	n/a	0-1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-59, 80+	expected distribution of road users, based on calculations

2.2 Distribution of risk factors by road users

Search keywords used were country name+seat belt, country name+helmet, country name+speeding, country name+drink-driving, driving under influence, alcohol-impaired driving.

The aim was to locate country-specific risk-factor information, not only relating to direct assessment of the contribution of specific risk factors to overall road traffic injury rates, but also relating to levels of risk factor exposure (e.g. not wearing seatbelts). Concerning direct measures, only a limited number of country specific references were found, mostly from journal articles based on police or hospital data.

Distributing road users into five distinct categories was problematic, because local classification systems included local means of transportation which have an arbitrary number of wheels and could be motorized or not, or powered by draft animals.

In some cases no distinction was made between motorized and non-motorized two-wheelers, in some cases bus & truck occupants were grouped together as motorized four-wheeler occupants. In some cases data for drivers and pillions were reported separately.

2.2.1 Distribution of risk factors by road users in Sub-Saharan Africa

Data on risk factor distribution by road users were available for 6 countries from Sub-Saharan Africa, a total of 7 articles (Table 4). Risk factor data are notably fragmented, and distribution of risk factors by age groups was not reported in any study. Blood alcohol concentration is not routinely measured, and not using safety equipment is often not recorded in hospital data.

Table 4. Data sources on distribution of risk factors by road users in Sub-Saharan Africa

Reference	Country	Region	Type of data	Data period	n	Road user groups reported	Findings
Bachani, A. M., Koradia, P., Herbert, H. K., Mogere, S., Akungah, D., Nyamari, J., Osoro, E., Maina, W., & Stevens, K. A. (2012) Road Traffic Injuries in Kenya: The Health Burden and Risk Factors in Two Districts, *Traffic Injury Prevention, 13*(sup1), 24-30.	Kenya	Thika, Naivasha, urban + rural	traffic police, vital registration, observations	2010	6218	all road users	Motorcycle drivers wearing a helmet - 30,37%, passengers 4,06
Masaoe, E. N. (2007). Study on Road Accidents in Mainland Tanzania. Final Report submitted to Surface and Marine Transport Regulatory Authority (SUMATRA). http://www.sumatra.or.tz/index.php/component/docman/doc_view/49-study-on-road-accidents-in-mainland-tanzania?Itemid=317 (Accessed on 24.07.2014)	Tanzania	Dar es Salaam, Coast, Arusha, Kilimanjaro	traffic police statistics	2000-2005	85434	all road users	Excessive speed 3,7%, reckless driving 54,5%, intoxication 0,8% of RTIs
Chalya, P. L., Mabula, J. B., Dass, R. M., Mbelenge, N., Ngayomela, I. H., Chandika, A. B., & Gilyoma, J. M. (2012). Injury characteristics and outcome of road traffic crash victims at Bugando Medical Centre in Northwestern Tanzania. *Journal of Trauma Management & Outcomes 6*(1).	Tanzania	Northwestern Tanzania	hospital-based study	2010-2011	1678 road traffic crash victims	all road users	road traffic crash victims, helmet use by motorcyclists 24.7%, seat belt use by car occupants 13.5%, alcohol use prior to crash 17.2%
Abegaz, T., Berhane, Y., Worku, A., Assrat, A., & Assefa, A. (2014). Effects of excessive speeding and falling asleep while driving on crash injury severity in Ethiopia: A	Ethiopia	Addis Ababa-Hawassa highway	police data	2012-2013	819 road crashes	all road users	Alcohol use 9,8%, speeding 52,6% of total injuries, not using seatbelt

generalized ordered logit model analysis. *Accident Analysis and Prevention 71*, 15-21.							20,6%; distribution of types of vehicles involved in accidents
Damsere-Derry, J. Ebel, B. E., Mock, C. N., Afukaar, F., & Donkor, P. (2010). Pedestrians' injury patterns in Ghana. *Accident Analysis and Prevention 42*, 1080–1088.	Ghana	Kumasi–Accra highway	police data	2002-2006	812 fatal & nonfatal RTIs	pedestrians	27,9% of pedestrian total injuries speeding is a factor; probability that a pedestrian fatality occurring in Ghana attributable to excessive speeding is 65%
A profile of fatal injuries in South Africa - 7th Annual Report of the NATIONAL INJURY MORTALITY SURVEILLANCE SYSTEM 2005	South Africa		mortuary data	2005	5675 transport deaths	all road users	Pedestrian & vehicle driver & passenger deaths by age. Car drivers 53,5% BAC positive, passengers 39,7% BAC positive, pedestrians 58,7% BAC positive, cyclists 44,9% BAC positive.
TRANSPORT STATISTICS: 2007. STATS BRIEF Released by the Central Statistics Office. Republic of Botswana	Botswana		police data/official statistics	2007	37463 casualties	all road users	Deaths: alcohol/drugs 15 (3%) Injuries: alcohol/drugs 201 (2,8%)

2.2.2 Distribution of risk factors by road users in South-East Asia

Some data on risk factor distribution by road users were found for 4 countries from South-East Asia, a total of 7 articles (Table 5). For India, one comprehensive report for 2011 outlines deaths attributable to intake of alcohol and speeding; other studies are limited to certain road user groups (e.g. two-wheelers).

Table 5. Data sources for distribution of risk factors by road users in South-East Asia

Reference	Country	Region	Type of data	Data period	n	Road user groups reported	Findings
Road accidents in India 2011. Government of India, Ministry of Road Transport and Highways, Transport research wing, New Delhi.	India		police data	2011	497 686 accidents, 653 879 victims	all road users	accidents caused due to intake of alcohol/drugs 6,4% of accidents, 10,3% of deaths; speeding 59% of accidents, 58,4% of deaths
Kakeri, S. R., Bagali, M. A., Goudar, E.S., & Qadri, S. Y. (2014). Pattern of injuries and death sustained by the occupants of the two-wheeler during road traffic accidents. *Al Ameen Journal of Medical Science 7*(2) , 118-124.	India	Bijapur	hospital-based study	2005-2007	150 RTA victims	two-wheelers	74% two-wheeler road traffic accident victims did not wear helmets
Fitzharris, M., Dandona, R., Kumar, R., & Dandona, L. (2009). Crash characteristics and patterns of injury among hospitalizedmotorised two-wheeled vehicle users in urban India. *BMC Public Health 9(*11).	India	Hyderabad city, urban	multiple hospital study	2005-2006	378 motorized two-wheeler users	motorized two-wheelers	19.6% of injured and deaths wore a helmet correctly; 80,4% of injured and deaths did not wear a helmet
Waseela M, & Laosee O. (2014). Determinants of Road Traffic Injury Among Adult Motorcyclists in Malé, Maldives. A*sian Pacific Journal of Public Health. 2014 Jun 23*. [Epub ahead of print]	Maldives	Malé	survey data	2012-2013	294 motorcycle riders	motorcyclists	Excessive speed 14,5% as the primary cause for motorcycle RTIs
Weerawardena, W. A. K., Illanagasingha, T. D. B, Piyadasa, I. J., Rathnayaka, S.M., Subaweera, W.T.D.U.P.L., & Niroshana, G.A.L. (2013). Analysis of patients admitted with history of Road Traffic Accidents to surgical unit B Teaching Hospital Anuradhapura, Sri Lanka. *Anuradhapura Medical Journal 7*(1), 2-5.	Sri Lanka	Anuradhapura	hospital-based study	2012-2013	214 patients	all road users, admitted patients	distribution of injuries by vehicle types & road users, 32% alcohol use, 39% not wearing a helmet.

Nakahara, S., Chadbunchachai, W., Ichikawa, M., Tipsuntornsak, N., & Wakai, S. (2005). Temporal distribution of motorcyclist injuries and risk of fatalities in relation to age, helmet use, and riding while intoxicated in Khon Kaen, Thailand. *Accident Analysis and Prevention 37*, 833–842.	Thailand	Khon Khaen	hospital-based study	1998-2002	9948 injured motorcyclists	motorcyclists	fatal & nonfatal cases of motorcyclist injuries, 74,9% not wearing a helmet, 36,5% drink-driving.

2.3. Fatal and non-fatal injuries by road users

2.3.1 Fatal and non-fatal injuries by road users, Sub-Saharan Africa

Report by WHO, "Global Status Report on Road Safety 2013" provides data for fatal road traffic injures by country and road user type. Other than that, data for multiple Sub-Saharan Africa countries were found (a total of 11 data sources). Also some regional data were reported on WHO factsheets, and a review from 2009 by Naci, Chisholm & Baker. Usually most RTI studies provide some distribution by road users, although the categories may not correspond to those used previously, and an age distribution of these road users is usually missing. Table 6 shows data sources for RTI distribution by road users in Sub-Saharan Africa region. Most studies find pedestrians the most vulnerable road user group, accounting for 19-60% of RTIs, followed by car occupants and motorcycle riders. The share of car occupants in RTI casualties in Sub-Saharan Africa has increased when compared to previous analysis.

Table 6. Data sources for fatal and non-fatal injuries by road users, Sub-Saharan Africa

Reference	Country	Region	Type of data	Data period	n	Road user groups / fatality	Findings
ROAD SAFETY IN THE WHO AFRICAN REGION. THE FACTS 2013 (WHO factsheet)	African region	-	WHO data	2013	-	all road users, fatal injuries	Deaths: 43% vehicle occupants, 38% pedestrians, 7% cyclists, 7% 2- & 3-wheeler occupants, 5% other
Naci, H., Chisholm, D., Baker, T. D. (2009). Distribution of road traffic deaths by road user group: a global comparison. *Injury Prevention 15,* 55–59	African region, South-East Asia Region	-	literature review	1991-2006	-	all road users, fatal injuries	Deaths: AFRO-E motorized four-wheelers 29%, motorcyclists 5%, bicyclists 11%, pedestrians 55%; SEAR-D motorized four-wheelers 19%, motorcyclists 43%, bicyclists 8%, pedestrians 30%
Macharia, W. M., Njeru, E. K., Muli-Musiime, F., & Nantulya, V. (2009). Severe road traffic injuries in Kenya, quality of care and access. *African Health Sciences 9*(2), 118-124.	Kenya	-	hospital-based/survey study (sample: 50 hospitals)	1997-1998	310 RTI casualties	all road users, nonfatal injuries	**Of RTI victims:** owner 2%, employee driver 4,2%, passenger 47,2%, pedestrian 32,9%, unspecified 13,7%. **Of crash vehicles:** private cars 20,3%, buses 30%, commuter mini-buses 43,6%, lorries 12,9%, pedal/motorc

							ycles 3,9%, unspecified 9,5%
Ogendi, J., Odero, W., Mitullah, W., & Khayesi, M. (2013). Pattern of pedestrian injuries in the city of Nairobi: implications for urban safety planning. *Journal of Urban Health 90*(5).	Kenya	City of Nairobi	hospital-based study	2011	176 persons with RTIs	all road users, fatality not known	Pedestrians comprised the highest (59.1 %) proportion of road traffic injury admissions, followed by motor vehicle passengers (24.4 %) and motor cyclists (9.7 %). Bicyclists and drivers accounted for 5.1 and 1.7 %, respectively
Damsere-Derry, J. Ebel, B. E., Mock, C. N., Afukaar, F., & Donkor, P. (2010). Pedestrians' injury patterns in Ghana. *Accident Analysis and Prevention 42*, 1080–1088.	Ghana	-	surveillance/police data	2002-2006	812 pedestrian casualties	pedestrians	distribution of fatal & non-fatal injuries by vehicle type, sex and injury severity / bus occupants 15,4% non-fatal, 11,0% fatal; motorcycle 2,9% non-fatal, 0,4% fatal; bicycle 0,5% non-fatal, 0% fatal
Whiteside, L.K., Oteng, R., Carter, P., Amuasi, J., Abban, E., Rominski, S., Nypaver, M., & Cunningham, R.M. (2012) Non-fatal injuries among pediatric patients seeking care in an urban Ghanaian emergency department. *International Journal Of Emergency Medicine 5* (1), 36.	Ghana	Kumasi	hospital-based study	2009	50 RTI patients	children only	pediatric road traffic injuries by road user type: 58% (29) car crash, 26% (13) pedestrian injury, 14% (7), bicycle crash 2%(1)

http://www.arrivealive.co.za/documents/FATAL%20CRASHES%20PER%20MONTH_Nov_2011-March_2012.pdf	South Africa	All provinces	surveillance data	2011-2012	5514 fatalities	drivers, passengers, pedestrians	Drivers (1681) 30,5%, passengers (1890) 34,3%, pedestrians (1944) 35,3%
Abegaz, T., Berhane, Y., Worku, A., & Assrat, A. (2014). Effectiveness of an improved road safety policy in Ethiopia: an interrupted time series study. *BMC Public Health 14*(539).	Ethiopia	Addis Ababa - Adama/Hawassa main road	police data/crash records	2002-2011	4,053 crashes, of those 1193 fatal & 980 non-fatal injury crashes (1392 fatalities, 1749 injuries)	all road users	From 1,193 fatal crashes 1,392 people were dying, on average 1.2 deaths per fatal crashes. Of these deaths, more than half 7.5% (800) were pedestrian, 32% (445) vehicle occupants and 10.5% (147) drivers. During the 980 injury crashes 1,749 people were injured, on average, 1.8 injuries per crash, over half, 55.2% (965) were vehicle occupants, followed by pedestrian 35.1% (614) and the rest 9.7% (170) were drivers.
TRANSPORT STATISTICS: 2007. STATS BRIEF Released by the Central Statistics Office. Republic of Botswana	Botswana		police data/official statistics	2003-2007	37463 casualties	all road users	Casualities by road user: 19,6% pedestrians, 1,1% cyclists, 1,1% motorcyclists, 30% car occupants (excl. taxi, 4WD, pickup), 24,7% pickup user, 8,1% bus

							or minibus user.
Chalya, P. L., Mabula, J. B., Dass, R. M., Mbelenge, N., Ngayomela, I. H., Chandika, A. B., & Gilyoma, J. M. (2012). Injury characteristics and outcome of road traffic crash victims at Bugando Medical Centre in Northwestern Tanzania. *Journal of Trauma Management & Outcomes 6*(1).	Tanzania	Northwestern Tanzania	hospital-based study	2010-2011	1678 road traffic crash victims	all road users	Motorcycle (986, 58.8%) was responsible for the majority of road traffic crashes, followed by motor-vehicles (650, 38.7%), bicycle (36, 2.1%) and other means of transport (e.g. donkey, trolley etc) in 4 (0.2%) of cases. Pedestrians (930, 55.4%) accounted for the majority of victims, followed by passengers (457, 27.2%), drivers/riders (287, 17.2%) and others (4, 0.2%).
Masaoe, E.N. (2007). Study on Road Accidents in Mainland Tanzania. Final Report submitted to Surface and Marine Transport Regulatory Authority (SUMATRA).	Tanzania		police data	2000-2005	12538 fatalities & 92123 injured in 2000-2005	all road users	fatal & non-fatal road traffic injuries by road user type & vehicle type - **fatal:** car occupants (drivers 11,6% + passengers 42,8%) 54,4%; motorcyclists 3,9%; pedal cyclists 8,9%; pedestrians 32,9%. **Non-fatal:** car

							occupants 59,6%; motorcyclists 2,8%; pedal cyclists 7,0%; pedestrians 30,6%.
Komba, D. D. (2006). *Risk Factors and Road Traffic Accidents in Tanzania: A Case Study of Kibaha District.* Master Thesis in Development Studies, Specialising In Geography Department of Geography Norwegian University of Science and Technology (NTNU).	Tanzania	Kibaha / Tumbi hospital	hospital data	2001-2004	764	Age groups 0-17, 18-24, 25-34, 35-44, 45+	age distribution of injuries by road user type: car occupants 75,8%, pedestrians 21%, motorcyclists 1,7% & cyclists 1,6% of all injured persons

2.3.2 Fatal and non-fatal injuries by road users, South-East Asia

In addition to already aggregated regional data for South-East Asia (Naci et al. 2009; Road Safety Status in the… 2013), data were found for 4 South-East Asia countries: India, Sri Lanka, Vietnam and Malawi (a total of 13 articles) (Table 7). Numerous data sources were found for India (although mainly small hospital-based and autopsy studies). The share of motorcyclists' and other motorized light vehicle occupants among all RTI deaths and injured is typically high; although in some regions pedestrians appear to be the most endangered road user group (Malawi, Northern India). Compared to previous report the share of motorized light vehicles appears to be even higher during recent years.

Table 7. Data sources for datal and non-fatal injuries by road users in South-East Asia

Reference	Country	Region	Type of data	Data period	n	Road user groups / fatality	Findings
Naci, H., Chisholm, D., Baker, T. D. (2009). Distribution of road traffic deaths by road user group: a global comparison. *Injury Prevention 15,* 55–59	South-East Asia Region	-	literature review	1991-2006	-	all road users, fatal injuries	Deaths: SEAR-D motorized four-wheelers 19%, motorcyclists 43%, bicyclists 8%, pedestrians 30%
Road safety status in the WHO South-East Asia Region, 2013 (WHO factsheet)	South-East Asia Region	-	WHO data	2009-2010	-	all road users, fatal injuries	Deaths: 33% motorized two- or three-wheelers, 12% pedestrians, 4% cyclists, 15% car occupants, 36% unspecified
Hsiao, M., Malhotra, A., Thakur, J.S., et al. (2013). Road traffic injury mortality and its mechanisms in India: nationally representative mortality survey of 1.1 million homes. *BMJ Open 2013(3*):e002621.	India	-	large mortality survey, verbal autopsy	2001-2003	2299 RTI deaths in the survey correspond to an estimated 183 600 RTI deaths or about 2% of all deaths in 2005 nationally	all road users	estimated road traffic deaths by road user type: pedestrians 37%, motorcyclists 20%, car occupants 16%, bicyclists 8% (+three-wheelers 3%).
Road accidents in India 2011. Government of India, Ministry of Road Transport and Highways, Transport Research Wing, New Delhi 2012. I	India	-	official statistics	2011	142 485 killed; 511 394 injured (in 497686 accidents)	all road users	**% of killed:** 19,2% two-wheelers; 17,6% cars, 36,6% buses/trucks; **of injured:** 22,5% two-wheelers; 20,4% cars, 32,6 buses/trucks
Patil, S. S., Kakade, R. V., Durgawale, P. M., & Kakade, S. V. (2008). Pattern of Road Traffic Injuries: A Study from Western Maharashtra. Indian Journal of Community Medicine 33(1), 56-57.	India	Western Maharashtra	hospital-based study	2003-2004	350 RTIs	all road users	road traffic injuries by road user type, drivers & passengers separately reported. Of casualities: 82,3% male, 17,7% female, highest number (29,4%) between 20-29

							years of age. Pedestrians 13,4%, bicyclists 21,7% of drivers.
Manish, K, Jyothi, N. S, Pawar, G. S., Jatti, V. B. (2012). Fatal Head Injuries in Road Traffic Accidents in and around Davangere: A Prospective Study. Indian Journal of Forensic Medicine and Pathology 5(2).	India	Davangere	hospital-based study	2005-2007	408 RTI deaths	all road users	of fatalities: 46,3% motorcyclists, 31,7% pedestrians, 4,8% cyclists, 3,6% car occupants, 4,8% bus or truck occupants
Das, R. K., Chakraborty, P. N., Das, P. (2014). A Study of the pattern of Cranio-Facial Injuries in Fatal Road Traffic Accidents in Tripura. *Journal of Evolution of Medical and Dental Sciences 3*(24), 6726-6735.	India	Tripura	autopsy study	2011-2013	196 victims of fatal RTIs, craniofacial injuries	RTI victims with cranio-facial injuries	fatal RTI victims w/ craniofacial injuries: pedestrians 42,9%; car occupants 16,3; bicyclists 5,1%.
Khajuria, B., Sharma, R., Verma, A. (2008). A Profile of the Autopsies of Road Traffic Accident Victims in Jammu. *Journal of Clinical and Diagnostic Research 2*, 639-642.	India	Jammu	autopsy study	2000-2005	249 RTA victims	all road users	fatal RTI victims: pedestrians 55,32%, vehicle occupants 34,68
Sharma, B. R., Sharma, A. K., Sharma, S. & Singh, H. (2007). Fatal Road Traffic Injuries in Northern India: Can They Be Prevented? *Trends in Medical Research 2*(3), 142-148.	India	Northern India	hospital-based study, autopsies	1996-2005	1109 RTA victims	all road users	Fatal RTIs: pedestrians 38,7%, motorized two-wheelers 34,1%, cyclists 5,9%, light motor vehicles 10,4%, bus occupants 2,9%.
Jain, A., Menezes, R. G., Kanchan, T., Gagan, S., & Jain, R. (2009). Two wheeler accidents on Indian roads – a study from Mangalore, India. *Journal of Forensic and Legal Medicine 16*, 130–133.	India	Mangalore	police data	2000-2004	1231 two-wheeler accidents	two-wheelers only	age distribution of two-wheeler accident victims / age groups <18, 18-24, 25-34, 35-44, 45-54, >55
Road Safety in India: A Framework for Action. (2011). National Institute of Mental Health & Neuro Sciences, WHO Collaborating Centre for Injury Prevention & Safety Promotion, Department of Epidemiology.	India	-	official statistics	2009-2010	160000 estimated RTI deaths	all road users	approximate distribution of fatal & non-fatal road crashes by urban/rural & by road user type. Fatal: ~40% pedestrians, 40% two-wheeler riders & pillions. Non-

							fatal: 25% pedestrians, 50% two-wheeler riders & pillions
Honnungar, R. S., Aramani, S. C., Vijay Kumar, A. G., Ajay Kumar, T. S, Jirli, P. S. (2011). An Epidemiological Survey of Fatal Road Traffic Accidents and their Relationship with Head Injuries. *Journal of Indian Academic Forensic Medicine 33*(2), 135-137.	India	Karnataka	autopsy study	2004-2009	506 vehicle accident fatalities	all road users	Fatal injuries: pedestrians 16,4%, pedal-cyclists 13,1%, motorcyclists 28,3%, drivers 42,2%
Somasundaraswaran, A. K. (2006). Accident Statistics in Sri Lanka. *IATSS Research 30*(1).	Sri Lanka	-	police data	1989-2005	All reported accidents during the period (43171 in 2005)	all road users	fatalities & casualties by road user type. Fatalities in 2005: 32,4% pedestrians, 26,3% car occupants, 14,1% bicyclists. Non-fatal in 2001: 30,8% pedestrians, 12,2% bicyclists, car occupants 40,7%
Weerawardena, W. A. K, Illanagasingha, T. D. B., Piyadasa, I.J., Rathnayaka, S. M., Subaweera, W. T. D. U. P. L., Niroshana, G. A. L. (2013). Analysis of patients admitted with history of Road Traffic Accidents to surgical unit B Teaching Hospital Anuradhapura, Sri Lanka. *Anuradhapura Medical Journal 7*(1), 2-5.	Sri Lanka	Anuradhapura	hospital-based study	2012-2013	214 RTI patients	all road users	fatal & nonfatal injuries. Vehicle type involved with the injury: motorcycle 138(65%), bicycles 23(11%), three wheelers 23(11%), tractors 11(5%), buses 5(2%), lorries 6(3%), cars 2(1%) and other 3(1%). There were 135(64%) drivers/riders, 59(28%) passengers and 17(8%)pedestrians.
Ngo, A.D., Rao, C., Phuong Hoa, N., Hoy, D. G., Quynh Trang, K. T., & Hill, P. S. (2012). Road traffic related mortality in Vietnam: Evidence for policy from a national sample mortality surveillance system. *BMC Public Health 12*, 561.	Vietnam		statistics from surveillance system	2008-2009	1,061 deaths attributable to road crashes	all road users	Of deaths: 11,2% pedestrians, 3,2% cyclists, 57,9% motorcyclists, 2,45% car occupants

Samuel, J. C., Sankhulani, E., Qureshi, J. S., Baloyi, P., Thupi, C., et al. (2012). Under-Reporting of Road Traffic Mortality in Developing Countries: Application of a Capture-Recapture Statistical Model to Refine Mortality Estimates. *PLoS ONE 7*(2): e31091.	Malawi		hospital data, police data, estimated number	2008-2009	380 estimated RTI deaths	all road users	road traffic deaths: 42,4% pedestrians, 10,3% bicyclists, 36,3% car occupants.

3. Road safety interventions

Search keywords used were country name+road safety, country name+speed bumps, country name+drink-driving, country name+speed cameras, country name+helmet use.

No data were found on coverage of speed humps/bumps, drink-driving law & enforcement nor coverage of speed cameras in Sub-Saharan Africa or South-East Asia countries.

Some data were found on seat belt, motorcycle and bicycle helmet use. Road safety intervention statistics are based mainly on surveillance data, and some survey data.

3.1. Seat belts, Sub-Saharan Africa

The percentage of vehicle occupants wearing a seatbelt was only available for South Africa (Table 8).

Table 8. Data sources for seat belt use in Sub-Saharan Africa

Reference	Country	Region	Type of data	Data period	n	Road user groups reported	Findings
van Hoving, D. J., Sinclair, M., Wallis, L. A. (2013). Patterns of seatbelt use in different socioeconomic communities in the Cape Town Metropole, South Africa. *African Medical Journal 103*(9).	South Africa	Cape Town Metropole	surveillance data	2010	4 651 vehicles with 6 848 occupants were surveyed	vehicle occupants	vehicle occupants, 45.1% wearing a seatbelt

3.2 Seat belts, South-East Asia

WHO factsheets on South-East Asia Region provide numbers for seat belt use in India & Sri Lanka, also two studies for India report some estimates for seat belt use among car occupants (Table 9). The estimates differ, although the study reporting the highest percentages of seat belt use (Mohan, 2009) is the only one that describes the methods how the estimates were calculated.

Table 9. Data on seat belt use in South-East Asia

Reference	Country	Region	Type of data	Data period	n	Road user groups reported	Findings
Road safety status in the WHO South-East Asia Region, 2013 (WHO factsheet)	India, Sri Lanka		unknown	n/a	n/a		seat belt use: 27% in India; 79% in Sri Lanka
Mohan, D. (2009). Seat Belt Law and Road Traffic Injuries in Delhi, India. Proceedings of the Eastern Asia Society for Transportation Studies 7.	India	urban	surveillance data	2002-2005	5,315 cars, average of 2.2 persons per car	vehicle occupants	Front seat passengers: male drivers – 82%; female drivers – 80%; male passengers – 58%; female passengers – 61%
Gururaj G. (2011). Road safety in India: a framework for action. National Institute of Mental Health and Neuro Sciences, Publication no 83, 1–40.	India	Bangalore city, urban	official statistics?	n/a	n/a	car drivers	only 27% of car drivers wear seat belts

3.3. Motorcycle helmet use, Sub-Saharan Africa

WHO factsheet on African Region provides numbers for motorcycle helmet wearing rates for Congo, South Africa, Seychelles, Botswana. Data from other sources: some motorcycle helmet use statistics were available for Kenya (Table 10).

Table 10. Data on motorcycle helmet use in Sub-Saharan Africa

Reference	Country	Region	Type of data	Data period	n	Road user groups reported	Findings
ROAD SAFETY IN THE WHO AFRICAN REGION. THE FACTS 2013 (WHO factsheet)	-	-	official statistics	2013?	n/a	motorcyclists	motorcycle helmet wearing rates for: 3% in Congo to 95% in both South Africa and Seychelles, and 100% in Botswana.
Bachani, A. M., Koradia, P., Herbert, H. K., Mogere, S., Akungah, D., Nyamari, J., Osoro, E., Maina, W., & Stevens, K. A. (2012) Road Traffic Injuries in Kenya: The Health Burden and Risk Factors in Two Districts, *Traffic Injury Prevention, 13*(sup1), 24-30.	Kenya	Thika, Naivasha	surveillance data	2010	3075 (Thika), 3143 (Naivasha)	motorcyclists	Thika: 30,37% of drivers, 4,06% of passengers / Naivasha 21,29% of drivers, 2,61% of passengers

3.4. Motorcycle helmet use, South-East Asia

Motorcycle helmet use in South-East Asia is better documented in Vietnam, where after compulsory helmet use legislation and enforcement in 2007 helmet wearing rates increased from 27% to 99% in drivers; and 21% to 99% in passengers. For India we have two self-reported estimates from surveys, the more clear one marks motorcycle helmet use at 64% in India (Table 11).

Table 11. Data on motorcycle helmet use in South-East Asia

Reference	Country	Region	Type of data	Data period	n	Road user groups reported	Findings
Mirkazemi, R., Kar, A. (2009). Injury-related unsafe behavior among households from different socioeconomic strata in Pune city. Indian Journal of Community Medicine 34(4), 301-305.	India	Pune city	survey data	2007-2008	200 house-holds	two-wheeled vehicle riders	Two-wheeled vehicle riders: 35,6% did not have a helmet and 57,7% of those who had one, did not use it regularly
Gururaj G. (2011). Bangalore road safety and injury prevention program - results and learning 2007-2010. National Institute of Mental Health and Neuro Sciences. Publication No 81	India	Bangalore	survey data	2011	145789 two wheeler riders	motorcyclists	The use of helmets was only 64%. 49% of urban and 80% of rural injured motorcyclists had not worn helmets at the time of crash.
Passmore, J. W., Nguyen, L. H., Nguyen, N. P., & Olivé, J-M. (2010). The formulation and implementation of a national helmet law: a case study from Viet Nam. Bulletin of the World Health Organization 88(10), 783-787.	Vietnam		surveillance data	2007-2008	n/a	motorcyclists	approximate % of motorcycle riders wearing a helmet before and after legislation on compulsory helmet use. In Da Nang, helmet wearing increased from 27% to 99% in drivers; and 21% to 99% in passengers

3.5. Bicycle helmet use, South-East Asia

Bicycle helmet use was documented in one study from Singapore, and this study only evaluated the helmet use of bicycle-related trauma patients, and placed the estimate at 10,6% (Table 12).

Table 12. Data on bicycle helmet use, South-East Asia

Reference	Country	Region	Type of data	Data period	n	Road user groups reported	Findings
Heng, K. W., Lee, A. H., Zhu, S., Tham, K. Y., & Seow, E. (2006). Helmet use and bicycle-related trauma in patients presenting to an acute hospital in Singapore. *Singapore Medical Journal 47*(5), 367-372.	Singapore	-	survey data	2004-2005	160 bicyclists	bicyclists, trauma patients	% of bicycle-related trauma patients wearing a helmet: helmets were worn by 10.6 percent of the patients

4. Sequelae of road traffic accidents

A standardized online keyword search was carried out to obtain country specific risk factor information, using online search engines such as Google, Google Scholar, and EBSCO. We tried to find information on sequelae by injury categories used in the previous report: fractured skull, intracranial injuries, fractured femur, injured spinal chord, injury to eyes. Keywords used were country name+road traffic+skull fracture, country name+road traffic+intracranial injuries, country name+road traffic+femur fracture, country name+road traffic+spine injury, country name+road traffic+eye injury

No studies provided the exact distribution of sequelae used in the previous report (fractured skull, intracranial injuries, fractured femur, injured spinal cord and injury to eyes). Some studies differentiated between soft-tissue injuries and fractures, some divided injuries into categories by body part injured. If the study distinguished between fatal & non-fatal injuries, the distinction between long-term and acute injuries was impossible to make.

4.1 Sequelae of road traffic accidents, Sub-Saharan Africa

Some hospital-based and survey data for Tanzania and Kenya were found. There was a lot of variation in estimates for fractured skull as a percentage from all road traffic injuries. Some studies did not differentiate between different head injuries. The results of the studies seem to indicate that head injury is present in at least 10% of fatal and non-fatal RTIs, but more likely is the rate of 25% and higher (Table 13).

Table 13. Data on sequelae of road traffic accidents, Sub-Saharan Africa

Reference	Country	Region	Type of data	Data period	n	Road user groups reported	Findings
Akama, M. K., Chindia, M. L., Macigo, F. G., & Guthua, S. W. (2007). Pattern of maxillofacial and associated injuries in road traffic accidents. *East African Medical Journal 84*(6, 287-95.	Kenya	Nairobi	hospital-based study	n/a	482	all road users	skull fractures, % of all fatal & non-fatal injuries / head injury 37,7%, ~5% skull fractures
Gichuhi , K. (2007). Injury Pattern Among Non-fatal Road Traffic Crash Victims. *East African Orthopaedic Journal 1*. 23-25.	Kenya	Nairobi	hospital-based study	2004	1424 victims of road traffic crashes	all road users	head injury 25,6%, femoral fracture 12,4%, spine injury 1,1%, ruptured eye 0,2%, % of all fatal & non-fatal injuries
Masaoe, E. N. (2007). Study on Road Accidents in Mainland Tanzania. Final Report submitted to Surface and Marine Transport Regulatory Authority (SUMATRA). http://www.sumatra.or.tz/index.php/component/docman/doc_view/49-study-on-road-accidents-in-mainland-tanzania?Itemid=317 (Accessed on 24.07.2014)	Tanzania		survey of RTI survivors & relatives	1994-2007	102 RTI victims /relatives	all road users	Head injuries 11%, back injuries 10%, sight problems 2% of all fatal & non-fatal injuries
Chalya, P. L., Mabula, J. B., Dass, R. M., Mbelenge, N., Ngayomela, I. H., Chandika, A. B., & Gilyoma, J. M. (2012). Injury characteristics and outcome of road traffic crash victims at Bugando Medical Centre in Northwestern Tanzania. *Journal of Trauma Management & Outcomes 6*(1).	Tanzania	Northwestern Tanzania	hospital-based survey	2010-2011	1678 road traffic crash victims	all road users	all head injuries 52.1%, spinal fractures 1,4%, skull/maxillofacial fractures 19,7%, pelvic fractures 3,6%, % of all fatal & non-fatal injuries

4.2 Sequelae of road traffic accidents, South-East Asia

As for South-East Asia region, only available data on sequelae of RTAs originated from India (8 studies, 5 of them autopsy studies, the rest hospital-based or surveillance data, see Table 14). The data seem to indicate that head injuries, including skull fracture, are present at up to 70% of fatal

RTIs; the prevalence of the rest of the sequelae vary depending on the road user status of accident victims and other circumstances of the injury.

Table 14. Data on sequelae of road traffic accidents, South-East Asia

Reference	Country	Region	Type of data	Data period	n	Road user groups reported	Findings
Manish, K, Jyothi, N. S, Pawar, G. S., Jatti, V. B. (2012). Fatal Head Injuries in Road Traffic Accidents in and around Davangere: A Prospective Study. Indian Journal of Forensic Medicine and Pathology 5(2).	India	Davangere	autopsy study	2005-2007	408 RTI deaths	all road users	fractured skull, 40,1% of all fatal injuries
Sharma, B.R., Sharma, A.K., Sharma, S. & Singh, H. (2007). Fatal Road Traffic Injuries in Northern India: Can They Be Prevented? *Trends in Medical Research 2*(3), 142-148.	India	Northern India	autopsy study	1996-2005	1109 autopsies	all road users	head injury w/ skull fracture 52,4%, head injury w/o skull fracture 8,6%, % of all fatal injuries
Patil, S. S., Kakade, R. V., Durgawale, P. M., & Kakade, S. V. (2008). Pattern of Road Traffic Injuries: A Study from Western Maharashtra. Indian Journal of Community Medicine 33(1), 56-57.	India	Western Maharashtra	hospital-based study	2003-2004	350 RTIs	all road users	13,2% skull fracture
Kumar, A., Lalwani, S., Deepak, A., Rautji. R., & Dogra, T. D. (2008). Fatal road traffic accidents and their relationship with head injuries: An epidemiological survey of five years. *Indian Journal of Neurotrauma 5*(2), 63-67.	India		autopsy study	2001-2005	2472 autopsies of vehicular accidents	all road users	68,7 head injury, 69,6% skull fracture, intracranial hemorrhage ~89%, spine fracture 6,4%; % of all fatal injuries
Khajuria, B., Sharma, R., & Verma, A. (2008). A profile of the autopsies of road traffic accident victims in Jammu. *Journal of Clinical and Diagnostic Research 2*, 639-642	India		autopsy study	2000-2005	249 RTA victims	all road users	of deaths: head injury 69,48%; spine injury 0,8% / of injuries: head injury 28,62%; spine injury 0,82%
Honnungar, R. S., Aramani, S. C., Vijay Kumar, A. G., Ajay Kumar, T. S, Jirli, P. S. (2011). An Epidemiological Survey of Fatal Road Traffic Accidents and their Relationship with Head Injuries. *Journal of Indian*	India	Karnataka	autopsy study	2005-2009	506 vehicle accident fatalities	all road users, medico legal cases autopsied	skull fracture 77,7%; subdural hemorrhage 73,9%; % of all fatal injuries

Academic Forensic Medicine 33(2), 135-137.							
Fitzharris, M., Dandona, R., Kumar, R., & Dandona, L. (2009). Crash characteristics and patterns of injury among hospitalized motorised two-wheeled vehicle users in urban India. *BMC Public Health 9*(11).	India	Hyderabad, Urban	hospital-based study	2005-2006	378	motorized two-wheelers only	head fracture 10,3%; intracranial injuries 11,1-11,5%; % of all non-fatal & fatal injuries in two-wheeler riders & pillions
Bengaluru Injury / Road Traffic Injury Surveillance Programme: A feasibility study. (2008). National Institute of Mental Health & Neuro Sciences	India	Bengaluru	surveillance data / official statistics	2001	2542 fatal and 48775 non-fatal injuries	car occupants only	fatal: head 77%, spine 5% / non-fatal: head 43%, spine 2%

Additional file 2: Effect sizes and costing assumptions

Table 1: Intervention effect sizes used in the analysis

Intervention	Effect on RTI	Size of effect (by type of road user)					
		Pedestrian	Bicyclist	Motorcyclist	Cars / vans	Buses	Other
Enforcement of speed limits (via mobile speed cameras)	Incidence of L-T RTI (non-fatal)	-6%	-6%	-6%	-6%	-6%	-6%
	Crash mortality rate (fatal)	-14%	-14%	-14%	-14%	-14%	-14%
Drink-drive legislation & enforcement (via breath-testing campaigns)	Incidence of L-T RTI (non-fatal)	-15%	-15%	-15%	-15%	-15%	-15%
	Crash mortality rate (fatal)	-25%	-25%	-25%	-25%	-25%	-25%
Legislation & enforcement of seat belt use in cars (drivers and passengers)	Incidence of L-T RTI (non-fatal)	-	-	-	-18%	-	-
	Crash mortality rate (fatal)	-	-	-	-11%	-	-
Legislation & enforcement of helmet use by motorcyclists (all riders)	Incidence of L-T RTI (non-fatal)	-	-	-18 to -29%	-	-	-
	Crash mortality rate (fatal)	-	-	-36%	-	-	-
Legislation & enforcement of helmet use by bicyclists aged below 15 years	Incidence of L-T RTI (non-fatal)	-	-17 to -28%	-	-	-	-
	Crash mortality rate (fatal)	-	-69%	-	-	-	-

Source: Road traffic injury prevention: an assessment of risk exposure and intervention cost effectiveness in different world region, 2008 [5], Table 2

Table 2: Long-term non-fatal road traffic injury: mortality risk and disability level

	% of incident episodes with long-term effects		% of non-fatal RTI burden (% of long-term burden)*		Relative risk of mortality	Disability weight
	Southeast Asia	Eastern sub-Saharan Africa	Southeast Asia	Eastern sub-Saharan Africa		
Fractured skull	15%	15%	6% (1%)	5% (2%)		
Intracranial injuries	13%	5%	20% (82%)	16%(64%)		
Fractured femur	5%	5%	14% (1%)	21% (2%)		
Injured spinal chord	100%	100%	38% (11%)	22% (21%)		
Injury to eyes	10%	10%	7% (6%)	13% (10%)		
Weighted average(Southeast Asia)					4.0	0.524
Weighted average(Eastern sub-Saharan Africa)					4.3	0.455

Calculated based on data provided by the International Injury Research Unit at the Johns Hopkins University

Table 3: Coverage per intervention

Intervention	Coverage\Region	Southeast Asia	Eastern sub-Saharan Africa
Enforcement of speed limits (via mobile speed cameras)	Baseline coverage	10%	5%
	Target coverage	80%	80%
Drink-drive legislation & enforcement (via breath-testing campaigns)	Baseline coverage	10%	10%
	Target coverage	80%	80%
Legislation & enforcement of seat belt use in cars (drivers and passengers)	Baseline coverage	0%	0%
	Target coverage	50%	50%
Legislation & enforcement of helmet use by motorcyclists (all riders)	Baseline coverage	30%	30%
	Target coverage	90%	90%
Legislation & Enforcement of helmet use by bicyclists aged below 15 years	Baseline coverage	5%	5%
	Target coverage	80%	80%

Table 4: Traffic law enforcement costing assumptions

Variable\Interventions	Speed cameras	Breath-testing (alcohol)	Seat belts	Motorcycle helmets	Bicycle helmets
% vehicles pulled over per annum	10%	10%	10%	20%	5%
Vehicles processed per officer per hour	4	4	4	4	4
Officers per checkpoint	3	3	2	3	2
Duration of checkpoint (hours)	4	4	4	4	2
Set-up / dismantle / paperwork time (hours)	2	2	2	2	1
Vehicles used per checkpoint	2	2	1	0	0
Traffic cones used per checkpoint (sets of 10)	2	2	2	0	0
Breathalyser kits used per checkpoint	0	1	0	0	0
Speed cameras used per checkpoint	1	0	0	0	0

Table 5 Number of vehicles per 1000 population

Per 1000 population	Southeast Asia	Eastern sub-Saharan Africa
Vehicle rate – cars	28	29
Vehicle rate - motorcycles	309	4
Vehicle rate - bicycles	127	43

General conclusion

This thesis aimed to provide a quantitative assessment of allocative efficiency within three main health categories: communicable diseases, noncommunicable diseases, and road-traffic injuries, using the GCEA approach, focusing on two economically and epidemiologically diverse regions – Eastern sub-Saharan Africa and Southeast Asia. As discussed earlier, GCEA can be a powerful approach to CEA studies as the analysis is not compelled by what is currently being done but could help revisiting and possibly revise past choices made, giving the policy makers a rational basis if they decide to reallocate resources from less to more cost-effective interventions. It can also identify a series of cost-effective interventions that can be implemented through a stepwise approach to achieve maximum health benefits.

As presented in chapter II, as we look across HIV, TB, and malaria programme areas, commonly used interventions were cost-effective, this joined the conclusion drawn, for example, in [1] for HIV, [2] for TB. In the reference year 2010, most of the interventions included in our study had a virtual cost-effectiveness of less than I$100/HLY gained. The most cost-effective interventions were: interventions targeting female sex workers (in southeast Asia) and voluntary male medical circumcision (in eastern sub-Saharan Africa) at 95% coverage for HIV; basic care and control interventions (treatment + detection + drug susceptibility testing) at 50% coverage for tuberculosis in both regions; management of severe cases of *P. vivax* malaria in southeast Asia as well as *P. falciparum* in eastern sub-Saharan Africa. Moreover, analysis of the currently implemented interventions in comparison to the expansion path over this period allows to conclude for a good performance of the global community regarding those communicable diseases over the first decade of the 21st century. As stated in previous chapter, the role of international assistance, financial and technical, arguably was critical to these achievements. If we refer, for example, to the latest global health financing report from WHO [3], ‘across a set of aid receiving countries, 46% of external funds for health and 20% of domestic government health spending went to combat HIV/ AIDS, malaria and tuberculosis’.

As the global community move towards universal health coverage, our study presented in chapter III identified a core package of cancer services that ensure treatment and palliative care for all. Results demonstrated that vaccination against human papillomavirus (two doses) for girls aged 9–13 combined with prevention of cervical cancer by screening of women aged 30–49 through visual

inspection with acetic acid linked with timely treatment of pre-cancerous lesions (in Southeast Asia) and vaccination against human papillomavirus (two doses) for girls aged 9–13 (in eastern sub-Saharan Africa) were the most cost-effective interventions. For breast cancer, in both regions, the treatment of breast cancer stages I and II with surgery ± systemic therapy at 95% coverage was found to be the most cost-effective intervention. For colorectal cancer, the most cost-effective intervention was treatment of colorectal cancer stages I and II with surgery ± chemotherapy and radiotherapy at 95% coverage. Cancer has received low priority, donor support and domestic resource allocation in low resource settings [4]. Cancer interventions presumed high costs and low health impact are contributing factors. Our study highlights that cancer interventions are cost-effective and can be implemented in a step-wise approach.

Interventions to improve road safety are cost-effective compared to other public health measures, [5], [6], [7], [8]. In chapter IV, our study demonstrated that to prevent road traffic injuries, the combination of individual interventions that simultaneously enforces multiple road safety measures proved to be the most cost-effective scenarios; drink driving legislation and its enforcement via random breath testing of drivers at roadside checkpoints (in southeast Asia) and enforcement of speed limits via mobile/handheld cameras (in eastern sub-Saharan Africa) at 80% coverage were the most cost-effective individual interventions. Interventions included in our study are in line with the proposed Save-LIVES technical package published by WHO in [9].

A possible challenge to the GCEA approach is to distinguish technical inefficiencies in the production of a given intervention from the allocative efficiency. However, this is addressed in those studies by assuming a constant capacity of the health systems in the cost evaluation, which ensures that variations in cost-effectiveness result from genuine differences in costs and effects of the interventions being compared rather than poor implementation or failures of health systems. A second challenge is the question of how to deal with additional costs of changing strategies (i.e. transition costs) which can be addressed using the programmatic expansion path demonstrated in chapter II.

As specified earlier in the thesis, these results ought not to be used in a formulaic way but should be analysed to identify the order of magnitude differences in the cost-effectiveness of different interventions. Besides, and as highlighted prior, efficiency is only one criterion out of many that influence public health decision-making. Thus, there is always a need to offset efficiency concerns

with other criteria, including the impact of interventions on equity, poverty, implementation capacity and feasibility.

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