The Impact of Alternate Methodological and Structural Assumptions on Results of Cost-effectiveness Analysis: Empirical Evidence using Three Indian Economic Evaluations

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Abstract

Background: Despite advancement in methods and application of economic evaluations (EEs), there are several uncertainties. **Objectives:** To assess the impact of alternate methodological and structural assumptions for four key principles of EE, on the results of cost-effectiveness analysis. **Materials and Methods:** Three previously published model-based EEs were used: (1) Integrated Management of Neonatal and Childhood Illnesses (IMNCIs) intervention; (2) intervention for multiple myeloma, and (3) safety-engineered syringes (SES) intervention. A series of empirical analyses was undertaken to assess the impact of alternate assumptions for discount-rate, time-horizon, study perspective, and health outcome measure, on incremental cost-effectiveness ratio (ICER), and interpretation of cost-effectiveness. **Results:** Increasing discount rate resulted in an increase in ICERs, for all three case-studies; however, there was no change in the conclusions. Using shorter time-horizons resulted in a significant increase in ICERs, the multiple myeloma intervention remained cost-ineffective, SES intervention became cost-ineffective, whereas IMNCI intervention remained cost-effective, despite a three-fold increase in ICER. On using disability adjusted life years instead of quality adjusted life years, ICERs increased to 0.04, 2 and 4 times for SES, IMNCI and multiple myeloma interventions, respectively. On analyzing results from a societal perspective, a decline in ICERs was observed. The decline was significant for IMNCI where the intervention turned dominant/cost-saving. In the other two case-studies decline in ICERs was modest, 32% for multiple myeloma, and 4% for SES. **Conclusion:** We observed a significant impact of using alternate assumptions on ICERs which can potentially impact resource-allocation decisions. Our findings provide strong argument in favor of standardization of processes and development of country-specific guidelines for conduct of EE.

Key words: Cost-effectiveness analysis, economic evaluation, health technology assessment

Introduction

Despite advancements in methods and application of economic evaluations (EEs), there are several uncertainties. There have been several attempts to develop good practice guidelines and country-specific guidelines for conducting EEs; however, majority of these guidelines are flexible allowing analysts to make methodological assumptions.[1,2] Moreover, majority of these guidelines are not mandatory, resulting in wide variation across the methods used.[3]

Systematic reviews of EE have identified key principles, including study perspective, time horizon, discount-rate, and health outcome measure where choice of metrics is not uniform.[4,5] A systematic review of Indian EEs reported the use of different study perspectives – societal (38%), payer (48%); time horizons – short (38%), medium (27%) and lifetime (17%); and outcome measures – quality adjusted life years (QALY) (29%), disability adjusted life years (DALY) (9%), and clinical outcomes (20%).[4] Similar heterogeneity in methods has been reported by other reviews undertaken globally.[5]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/IJPH

DOI: 10.4103/ijph.ijph_315_23

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Submitted: 02-Mar-2023 **Revised:** 22-Sep-2023
Accepted: 23-Sep-2023 **Published:** 04-Apr-2024

How to cite this article: Sharma D, Aggarwal AK, Bahuguna P, Prinja S. The impact of alternate methodological and structural assumptions on results of cost-effectiveness analysis: Empirical evidence using three Indian economic evaluations. Indian J Public Health 2024;68:9-14.

Another review comparing QALY-based and DALY-based outcome measures, found modest differences in incremental cost-effectiveness ratios (ICERs), which were less likely to impact cost-effectiveness interpretation relative to commonly used thresholds.[6] However, these modest differences in ICERs could potentially impact funding decisions for these interventions.

Similarly, ICERs exhibit high sensitivity to the choice of time horizon, which is likely to impact evidence on intervention cost-effectiveness.[7] Another area of concern is discrepancy between perspective of analysis and type of costs included. Inclusion (or exclusion) of specific costs significantly affects ICERs. Inclusion of productivity costs often results in lower ICERs, making the intervention more favorable in majority (76%) of the cases.[8] In addition, the methodology for valuing productivity costs also plays a significant role, with more favorable ICERs being reported with the use of human capital approach (HCA) as compared to the friction cost approach (FCA).[8]

The present study was undertaken as part of the development of the Indian Reference Case for undertaking EE, commissioned by the Health Technology Assessment (HTA) agency in India.[9] As a preliminary step to development of the reference case, we undertook a review of EE guidelines and found substantial variations in recommendations for EE principles.[2] In view of these differences, it was considered important to determine the absolute impact of these variations on ICERs, and the recommendation on cost-effectiveness thereafter. To explore these methodological underpinnings, we assessed the impact of using alternate methodological and structural assumptions for four key principles of EE on results of cost-effectiveness analysis.

Materials and Methods

We undertook a series of analyses to demonstrate the impact of alternate methodological and structural assumptions for study perspective, time horizon, discount-rate, and health outcome, on incremental costs, benefits, ICERs, and recommendations on cost-effectiveness compared to commonly used threshold of one time GDP per-capita. We used models of three previously published EEs as case studies.[10-12] These include cost-effectiveness of intervention for integrated management of neonatal and childhood illnesses (IMNCIs), intervention for managing multiple myeloma, and safety-engineered syringes (SES) intervention. The models were chosen such that they represented different type of interventions (therapeutic, preventive, and programmatic), diseases types, (communicable and noncommunicable), and target population groups (children and adults).

Analysis 1: Varying the discount rate

The IMNCI and the SES models used a discount rate of 3%,[10,12] while the multiple myeloma model used a discount rate of 5%.[11] The discount rates for each of the case studies were varied to 1.5%, 2%, 3%, 3.5%, 4%, and 5% in accordance to the commonly recommended rates by various country-specific EE guidelines [Supplementary Table 1].[2]

Analysis 2: Varying the time horizon

All three case studies used long-term time horizons ranging from 15 years (IMNCI) to a lifetime (SES and multiple myeloma).[10-12] We analyzed how sensitive are the cost-effectiveness ratios to shorter time horizons of 1, 5, and 10 years, and how incremental costs and benefits vary as a function of time.

Analysis 3: Changing the measure of health outcome

The multiple myeloma and SES models used QALYs as the health outcome, while the IMNCI model used DALYs.[10-12] The former two models were modified to report incremental cost per DALY averted, while for the latter incremental cost per QALY gained was computed.

DALYs were calculated using standard equations.[13] The average age of disease onset and death for SES model health states were sourced from published literature [Supplementary Table 2a]. Disability weights for health states related to HCV and HBV were obtained from Global Burden of Disease (GBD) study, while those for HIV-related health states were obtained from a study by Eaton *et al*., [Supplementary Table 2a].[14]

Similar analysis was done for estimating DALYs for multiple myeloma model. The age of onset of multiple myeloma was taken as 50 years (same as original analysis)[11] and life expectancy was calculated using age-stratified life tables. Disability weights for model health states were sourced from the GBD study, [Supplementary Table 2b].

Quality of life weights for IMNCI model's health states were obtained from published literature, [Supplementary Table 2c]. Data on the number of infants in individual health states and their duration were consistent with those used in the original case study.[10]

Analysis 4: Changing the study perspective

The multiple myeloma and IMNCI studies reported results from both health system and societal perspective, while SES study reported results only from a societal perspective. However, all three case studies did not include indirect costs due to productivity.

To assess the impact of indirect costs on the ICERs, we recalculated incremental costs by accounting for productivity losses due to premature mortality and morbidity (equations 1 and 2). HCA was used to estimate productivity losses, as it is the most commonly used and recommended approach.[2]

$$N \times LFPR \times average\ daily\ wage \times d \quad (1)$$

$$N \times reduced\ productivity \times LFPR \times average\ daily\ wage \times d \quad (2)$$

Where N is the number of premature deaths or individuals having disability, reduced productivity is reduction in productivity due to disability, LFPR is the labor force participation rate, and *d* is the duration of lost productivity.

Ethics approval

The study was approved by the Institutional Ethics Committee, Postgraduate Institute of Medical Education and Research, Chandigarh (INT/IEC/2020/SP2-1598). Informed consent was obtained from the principal investigator of the three case studies used for the analysis.

Results

Impact of discount rate on cost-effectiveness

An increase in the discount rate from 0% to 5% resulted in a corresponding increase in the ICERs in all three case studies [Figure 1]. However, the extent of impact was variable. While the ICER in the IMNCI case study increased marginally (INR 8), a substantial increase of INR 153,295 and INR 74,297 was observed in the multiple myeloma and SES case studies, respectively. Despite the increase in ICERs, there was no change in the interpretation of cost-effectiveness of these interventions when compared against a CET of 1-time GDP per-capita.

Impact of time horizon on cost-effectiveness

The impact of using shorter time horizons on ICERs was considerable in the multiple myeloma and SES case studies. While the SES intervention was cost-effective when a lifetime horizon was used, however, varying the time horizon to shorter periods of 1, 5, and 10 years resulted in an increase in the ICER, and the intervention became cost-ineffective. Similarly, the ICERs for the multiple myeloma model also increased significantly on using shorter time horizons [Table 1].

In the IMNCI model, a three-fold increase in cost-effectiveness ratio was observed on using a time horizon of 1 year; however, it remained below the 1-time GDP per-capita threshold, leaving the overall interpretation for cost-effectiveness unchanged [Table 1].

Measure of health outcome

We observed that in all the three case studies, the ICER per DALY averted were higher than the ICER per QALY gained. However, the extent of this increase was not uniform. In the SES case study the difference in the ICERs was marginal (4%), the ICERs doubled in IMNCI case study with change in outcome, whereas in the multiple myeloma model, the ICER increased to more than four times [Table 2]. Even though using QALYs resulted in more favorable ICERs, however, when compared to an arbitrary threshold of 1-time GDP per-capita, the overall interpretation of cost-effectiveness (or ineffectiveness) of the intervention remained unchanged for all the three case studies.

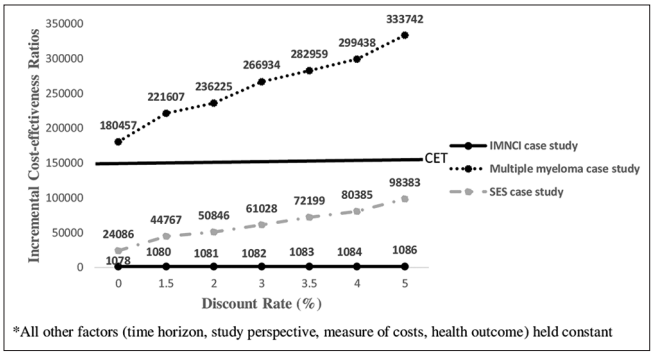

Figure 1: Impact of discount rate on incremental cost-effectiveness ratios. SES: Safety-engineered syringes, IMNCI: Integrated management of neonatal and childhood illnesses.

Impact of varying study perspective

The results from a societal perspective with inclusion of productivity costs showed a decline in the ICERs for all three case studies. The decline was significant in case of the IMNCI. where the intervention turns dominant, i.e. less costly and more effective. In case of the multiple myeloma and SES case studies, we observed a modest decline in the ICERs by 10% and 34%, respectively [Table 3].

The differences in the ICERs depended on the magnitude of productivity costs. The per-person productivity costs were 0.2 million, 1.9 million, and 4 million for the multiple myeloma, IMNCI, and SES case studies, respectively [Supplementary Table 3]. The share of productivity losses averted in the total incremental costs ranged from 97% for the IMNCI case study to 53% and 11% for the multiple myeloma and SES case studies, respectively.

Discussion

EEs are increasingly being used to inform resource allocation decisions in India and elsewhere.[15] However, heterogeneity in methods can limit comparison across interventions,

Table 1: Impact of varying the time horizon on incremental costs and outcomes, and incremental cost-effectiveness ratios

IMNCI (years)	Incremental costs INR	Incremental outcomes DALY	ICER
1	10,411,884	2838	3668
5	26,491,253	22,806	1162
10	47,075,182	44,499	1058
15	68,459,567	63,249	1082
Multiple myeloma (years)	**Incremental costs INR**	**Incremental outcomes QALY**	**ICER**
1	291,020,446	23	12,381,545
5 years	191,381,173	199	961,926
10 years	164,211,461	372	441,292
Lifetime	161,696,132	484	333,742
SES (years)	**Incremental costs INR**	**Incremental outcomes QALY**	**ICER**
1	9,906,754,355	1,829	5,414,505
5	50,658,089,293	32,643	1,551,882
10	81,219,709,087	118,708	684,195
Lifetime	108,062,436,758	1,674,066	61,028

ICER: Incremental cost-effectiveness ratio, DALY: Disability adjusted life year, QALY: Quality adjusted life year, IMNCI: Integrated Management of Neonatal and Childhood Illnesses, SES: Safety-engineered syringes

Table 2: Impact of varying the measure of health outcome on incremental cost-effectiveness ratios

Case study	Incremental DALYs	Incremental QALYs	ICER/DALY averted	ICER/QALY gained
IMNCI	63,249	133,130	1082	514
Multiple myeloma	118	484	1,075,980	263,095
SES	1,604,029	1,674,066	67,369	64,551

ICER: Incremental cost-effectiveness ratio, QALYs: Quality adjusted life year, DALYs: Disability adjusted life years, IMNCI: Integrated Management of Neonatal and Childhood Illnesses, SES: Safety-engineered syringes

Table 3: Impact of varying the study perspective on incremental cost-effectiveness ratios

Case study	Health system	Abridged societal	Societal perspective
IMNCI	1554	1082	−60,750
Multiple myeloma	263,095	333,742	301,896
SES	91,226	64,551	42,095

ICER: Incremental cost-effectiveness ratio, IMNCI: Integrated Management of Neonatal and Childhood Illnesses, SES: Safety-engineered syringes

subsequently impacting policy relevance of the evidence thus generated.[16] Our empirical analysis using three case studies highlights the potential influence of using alternate methodological and structural assumptions on ICER valuation and its interpretation. We observed a significant impact on ICER on varying the discount-rate, time horizon, study perspective, and health outcome measure.

We observed that ICERs tend to increase with an increase in the discount rate. However, the magnitude of the change was dependent on whether all costs were incurred in the beginning or later on in time. In addition, presence of significant cost of managing subsequent adverse-effects or complications which are averted by the intervention, also affects the impact of discount-rate. For interventions like IMNCI, where a large proportion of the costs were incurred early, the impact of varying the discount-rate was minimal compared to the other two interventions. However, in the multiple myeloma and SES case studies, where the intervention costs incurred upfront but benefits accrued later, the impact of discounting was significant. Similar findings have been reported in other studies exploring the influence of discount-rates on ICERs.[17,18] An EE of human papilloma vaccination found substantial changes in the ICERs ranging from €7600/QALY gained (0%-no discounting) to €59,100/QALY gained (discounting @4%).[17] In another analysis of an intervention for diabetes control, ICERs increased from 16.4K USD to 22.2 K USD at discount-rates of 3% and 5% respectively.[18] Similarly, EE of breast screening strategy reported a significant increase in the ICERs from £1200 per life year gained (undiscounted) to £2092 per life year gained[4] on using a 6% discount-rate.[19] Thus, it can be concluded that discounting alters the results of EE, emphasizing the need for thorough exploration when undertaking sensitivity analysis using different discount rates.

The time horizon substantially impacts ICER values, with the extent of change determined by the timing of onset of the health outcomes and the costs incurred. In SES intervention a relatively large proportion of incremental costs were incurred during the 1st year itself (9% of costs against 0.1% of benefits). However, incremental benefits continued accumulating over time, resulting in favorable (cost-effective) ICERs at a lifetime horizon but not at shorter time frames. Similarly, in the multiple myeloma case study, the intervention had high upfront treatment costs in the initial years and gradual attainment of health benefits over time. In case of the IMNCI intervention, a proportional increase in costs and outcomes is seen over time, with a significant proportion of both costs (39%) and outcomes (36%) occurring during the first 5 years, hence we do not observe changes in overall cost-effectiveness of the intervention at shorter time horizons. It can be thus concluded that for interventions where the outcomes were accumulated later during the course of time, using shorter time horizons rendered the intervention as cost-ineffective.

Similar findings have been reported previously. An EE of smoking cessation program reported ICERs of €213,500; €29,300; and €18,500 per QALY gained using a time horizon of 25, 50, and 75 years, respectively.[20] Another study evaluating the cost-effectiveness of sofosbuvir and ledipasvir for hepatitis C treatment reported the ICERs to decrease with an increase in the time horizon (10 years–$148,500, 20 years–$82,100, 30 years–$66,800, and lifetime–$55,400).[21] A systematic review assessing the impact of time horizon on results of CEA concluded that extending time horizons resulted in more favorable ICERs in majority (82%) of the studies.[22] Therefore, it is extremely important for the analyst to cautiously select the time horizon of analysis. In principle long-term horizon should be chosen to account for all relevant costs and effects. Shorter time horizons may be considered for scenario analysis in case of availability of more robust and real-world data at shorter intervals of time and for undertaking budget impact analysis.

Changing the outcome measure from DALY to QALY reduced ICERs, but not uniformly. The variations can be attributed to relative differences in the values of disability and utility weights, and the age of disease onset. Our findings corroborate with similar analysis comparing incremental cost per DALY averted and QALY gained.[23] Furthermore, our results provide evidence that since incremental costs per QALY gained and per DALY averted are not equal (or similar) thus utility weights cannot be assumed to be inverse (1-disability weight) of disability weights, and therefore, should not be used interchangeably. There lies a fundamental difference in the conceptual framework of the two measures, where DALYs try to

capture years of life lost (YLL) adjusted for disability measured in terms of loss of functioning, whereas QALYs measure years of life lived adjusted for good health.[24] Furthermore, more recently, the disability weights have also been elicited using population preferences, similar to the quality of life weights. However, the techniques used are different where the former have been estimated using discrete choice methods, whereas the latter usually employ time trade-off or standard gamble techniques. In addition, the YLL component of the DALYs is highly dependent on the reference ages (age at death).[24]

We found that the inclusion of indirect costs due to productivity losses resulted in the intervention being more cost-effective in all three case studies. However, the absolute change in ICERs was highly dependent on the effectiveness of the intervention being evaluated and the characteristics of the target population, especially the age profile. We found that the impact on ICERs was the highest in case of IMNCI which was targeted at infants and children. Similar findings have been observed by researchers evaluating cost-effectiveness of vaccination programs for children.[25]

While a majority of the national EE guidelines recommend including indirect costs either in the base case or in secondary analysis,[2] however, these are often ignored by analysts.[26] Furthermore, while a number of valuation techniques are available – HCA, FCA and willingness-to pay-approach; however, there is no consensus toward a gold-standard approach.[27] Moreover, there is inconsistency in the components of indirect costs that are included – absenteeism, presenteeism, and premature mortality; and for whom – patients alone, or patients and caregivers.[25] Apart from methodological limitations, lack of data is also an important reason resulting in omission of indirect costs.[27] Unavailability of data on friction periods, difficulty in assigning a value to lost productivity (especially for homemakers/elderly) and valuation of caregiver's time are some of the most common data and methodological limitations cited.[28]

The findings of our analysis provide empirical evidence for the importance of uniformity in methodological approach. We observed that using alternate methodological and structural assumptions altered the ICERs. While sometimes it did not change the interpretation on cost-effectiveness, however, it is important to note that a variation in the ICERs is quite likely to alter policy decisions for reimbursement or including particular interventions in health benefit packages. Since the health-care budgets are limited and investment or disinvestment decisions are taken collectively based on relative cost-effectiveness ratios of different technologies under consideration, incorrect ICERs can result in incorrect resource allocation decisions. Therefore, it is recommended that standardized methodological principles should be used while undertaking EE. This can be targeted through the development of country-specific reference cases or guidelines for conduct of EEs.

While, we acknowledge that one size fits for all approach is not possible, however, it is recommended to use standard best practices or a reference case approach. In addition, it is extremely important to present methodology and results clearly and transparently using commonly available reporting checklists.[29] Our findings provide implications for national HTA agencies to develop guidelines/reference cases and to set up institutional mechanisms to promote adherence to such guidelines. The ultimate aim is to promote consistency and aid comparability across evaluations to better inform resource allocation decisions.

Strengths and limitations

One of the major strengths of our analysis is that we assessed the impact of alternate methodological and structural assumptions on three diverse health technologies – device, drug and programmatic interventions, targeted at different population groups – infants/children, adults and elderly. Furthermore, we assessed the impact of not just one, but four most important principles of EE. The findings provide important implications on relevance of methodological uncertainties on results of EE and the importance of undertaking sensitivity analysis. Nevertheless, the findings from our analysis cannot be extrapolated to other studies given the difference in nature and context of interventions being evaluated. Furthermore, while the basis for altering the discount-rate, study perspective and outcomes was guided by international HTA guidelines; however, time horizon was varied to shorter periods of 1, 5, and 10 years selected randomly.

Conclusion

The findings of this study provide important implications for researchers and national HTA agencies for standardizing the conduct of EE as well as having transparency in reporting. It is recommended that a consistent approach should be followed while undertaking EE which can be achieved through the development of country-specific guidelines or reference cases. Furthermore, the confidence around the results of EE should be assessed through undertaking robust sensitivity analysis. In addition, there is a need to set up institutional mechanisms for promoting adherence to standardized guidelines. The overall aim is to improve the quality of EEs being conducted ultimately increasing comparability, generalizability, and policy usefulness of the evidence generated.

Acknowledgment

We would like to thank Indian Council of Medical Research, New Delhi, India, for providing scholarship grant to Sharma D.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Discount rates recommended globally

Discount rate (%)	Recommended by
1.5%	Canada
2%	Japan
3%	Czech Republic, Germany, Indonesia, Israel, Italy, Malaysia, Singapore, Spain, Thailand, United States
3.5%	Egypt, England and Wales, Finland, New Zealand, Scotland
4%	France, Ireland, Norway
5%	Australia, Austria, Baltic, China, Croatia, Portugal, South Africa, Taiwan

Supplementary Table 2a: Key parameters used in safety-engineered syringes case study

Parameter	Value	Reference
Average age at onset		
HIV	32.6 years	Cecelia AJ, Christybai P, Anand S, Jayakumar K, Gurunathan T, Vidya P, *et al*. Usefulness of an observational database to assess antiretroviral treatment trends in India. Natl Med J India 2006;19:14-7
HCV	41 years	Chugh Y, Dhiman RK, Premkumar M, Prinja S, Singh Grover G, *et al*. Real-world cost-effectiveness of pan-genotypic Sofosbuvir-Velpatasvir combination versus genotype dependent directly acting anti-viral drugs for treatment of hepatitis C patients in the universal coverage scheme of Punjab state in India. PLoS One 2019;14:e0221769
HBV	38 years	Nayagam S, Conteh L, Sicuri E, Shimakawa Y, Suso P, Tamba S, *et al*. Cost-effectiveness of community-based screening and treatment for chronic hepatitis B: An economic modelling analysis. Lancet Glob Health 2016;4:e568-78
Average age at death		
HIV	59 years	Zheng A, Kumarasamy N, Huang M, Paltiel AD, Mayer KH, Rewari BB, *et al*. The cost-effectiveness and budgetary impact of a dolutegravir-based regimen as first-line treatment of HIV infection in India. J Int AIDS Soc 2018;21:e25085
HCV	64 years	Aggarwal R, Chen Q, Goel A, Seguy N, Pendse R, Ayer T, *et al*. Cost-effectiveness of hepatitis C treatment using generic direct-acting antivirals available in India. PLoS One 2017;12:e0176503
HIV	62 years	Nayagam S, Conteh L, Sicuri E, Shimakawa Y, Suso P, Tamba S, *et al*. Cost-effectiveness of community-based screening and treatment for chronic hepatitis B in The Gambia: an economic modelling analysis. Lancet Glob Health 2016;4:e568-78
Standard life expectancy	69 years	Census of India. Office of the registrar general & census commissioner, India. SRS Based Abridged Life Tables 2013-17. Census of India; 2019
Disability weights: stages of HBV		
Disability weight-Unapparent infection	0	Assumed
Disability weight-Apparent infection	0.006	Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, *et al*. The global burden of viral hepatitis from 1990 to 2013: Findings from the global burden of disease study 2013. Lancet 2016;388:1081-8
Disability weight-Nonfulminating hepatitis	0.006	Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, *et al*. The global burden of viral hepatitis from 1990 to 2013: Findings from the global burden of disease study 2013. Lancet 2016;388:1081-8
Disability weight-Fulminant hepatitis	0.133	Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, *et al*. The global burden of viral hepatitis from 1990 to 2013: Findings from the global burden of disease study 2013. Lancet 2016;388:1081-8
Disability weight-Acquired immunity	0.006	Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, *et al*. The global burden of viral hepatitis from 1990 to 2013: Findings from the global burden of disease study 2013. Lancet 2016;388:1081-8
Disability weight-Asymptomatic carrier	0.006	Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, *et al*. The global burden of viral hepatitis from 1990 to 2013: Findings from the global burden of disease study 2013. Lancet 2016;388:1081-8
Disability weight-Chronic hepatitis	0.133	Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, *et al*. The global burden of viral hepatitis from 1990 to 2013: Findings from the global burden of disease study 2013. Lancet 2016;388:1081-8

Contd...

Supplementary Table 2a: Contd...

Compensated cirrhosis	0.123	James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858
Decompensated cirrhosis	0.178	James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858
Hepatocellular carcinoma	0.540	James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858
Disability weights: stages of HCV		
Normal	0	Assumed
Asymptomatic carrier	0.006	Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, *et al*. The global burden of viral hepatitis from 1990 to 2013: Findings from the global burden of disease study 2013. Lancet 2016;388:1081-8
Chronic hepatitis	0.133	Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, *et al*. The global burden of viral hepatitis from 1990 to 2013: Findings from the global burden of disease study 2013. Lancet 2016;388:1081-8
Compensated cirrhosis	0.123	James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858
Decompensated cirrhosis	0.178	James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858
Hepatocellular carcinoma	0.540	James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858
Disability weights: HIV		
CD4 cell count >500 per mm^3	0.013	Eaton JW, Menzies NA, Stover J, Cambiano V, Chindelevitch L, Cori A, *et al*. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: A combined analysis of 12 mathematical models. Lancet 2014;2:23-34
CD4 cell count 500–350 per mm^3	0.053	
CD4 cell count 350–200 per mm^3	0.221	
CD4 cell count 200–50 per mm^3	0.547	
CD4 cell count <50 per mm^3	0.873	Calculated based on disability weight for CD4 cell count 350-300 and 200-50 per mm^3

GBD: Global burden of disease, HCV: Hepatitis C virus, HBV: Hepatitis B virus

Supplementary Table 2b: Key parameters used in multiple myeloma case study

Parameter	Value	Reference
Average age at onset	50 years	Original model (11)
Age at death	54 years	Original model (11)
Life expectancy at 54 years	25.8 years	Census of India. Office of the registrar general & census commissioner, India. SRS Based Abridged Life Tables 2013-17. Census of India; 2019
DW		
Stage 1	0.294	DW for Cancer, Diagnosis and Primary Therapy. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858
Stage 2	0.484	DW for Cancer, Metastatic. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858
Stage 3	0.508	DW for Terminal Phase with Medication. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858

DW: Disability weight, GBD: Global burden of disease

Supplementary Table 2c: Key parameters used in Integrated Management of Neonatal and Childhood Illnesses case study

Parameter	Value	Reference
		Duration of neonatal illness
Pneumonia	8 days	Original model (10)
Diarrhoea	8 days	Original model (10)
Neonatal illnesses	8 days	Original model (10)
Standard life expectancy at birth	69 years	Census of India. Office of the registrar general & census commissioner, India. SRS Based Abridged Life Tables 2013-17. Census of India; 2019
		Utility weight
Diarrhoea	0.604	Rochanathimoke O, Riewpaiboon A, Postma MJ, Thinyounyong W, Thavorncharoensap M. Health related quality of life impact from rotavirus diarrhea on children and their family caregivers in Thailand. Expert Rev Pharmacoecon Outcomes Res 2017;18:215-22
Pneumonia	0.67	Kulpeng W, Leelahavarong P, Rattanavipapong W, Sornsrivichai V, Baggett HC, Meeyai A, *et al*. Cost-utility analysis of 10- and 13-valent pneumococcal conjugate vaccines: Protection at what price in the Thai context? Vaccine 2013;31:2839-47
Neonatal illnesses	0.70	Tomulic KL, Mestrovic J, Zuvic M, Rubelj K, Peter B, Cace IB, *et al*. Neonatal risk mortality scores as predictors for health-related quality of life of infants treated in NICU: A prospective cross-sectional study. Qual Life Res 2017;26:1361-9
Healthy infants	1	Assumed

Supplementary Table 3: Magnitude of per person productivity costs averted and share of productivity costs using a societal perspective

Case study	Productivity loss averted (per person)	Share of productivity costs in total costs (%)
IMNCI	1,987,917	97
Multiple myeloma	246,669	11
SES	4,723,879	53

IMNCI: Integrated Management of Neonatal and Childhood Illnesses, SES: Safety-engineered syringes