The impact and cost-effectiveness of pulse oximetry and oxygen on acute lower respiratory infection outcomes in children in Malawi: a modelling study

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Summary

Background acute lower respiratory infections (ALRIs) are the leading global cause of post-neonatal death in children younger than 5 years. The impact, cost, and cost-effectiveness of routine pulse oximetry and oxygen on ALRI outcomes at scale remain unquantified.

Methods We evaluate the impact and cost-effectiveness of scaling up pulse oximetry and oxygen on childhood ALRI outcomes in Malawi using a new and detailed individual-based model, together with a comprehensive costing assessment for 2024 that includes both capital and operational expenditures. We model 15 scenarios ranging from no pulse oximetry or oxygen (null scenario) to high coverage (90% pulse oximetry usage and 80% oxygen availability) across the health system. Cost-effectiveness results are presented in incremental cost-effectiveness ratios (ICERs) and incremental net health benefits (INHBs) using a Malawi-specific cost-effectiveness threshold of US$80 per disability-adjusted life-year (DALY) averted.

Findings The cost-effective strategy is the full scale-up of pulse oximetry to 90% usage rate and oxygen to 80% availability. This combination results in 72% (95% CI 72–72) of hypoxaemic ALRI cases accessing oxygen, averting 71 000 (68 100–74 000) DALYs per year of implementation and 28% (27–29) of potential ALRI deaths, at an ICER of US$35 (33–36) per DALY averted and $924 (887–963) per death averted. The INHB is 40 200 (37 300–43 100) net DALYs averted.

Interpretation Pulse oximetry and oxygen are complementary cost-effective interventions in Malawi, where health expenditure is low, and should be scaled up in parallel.

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Introduction

Acute lower respiratory infections (ALRIs) are the leading global cause of death in children after the neonatal period.[1] The UN Inter-agency Group for Child Mortality Estimation estimated that in 2021, globally, 725 557 deaths in children younger than 5 years are from ALRI.[2] An estimated 31% of children with WHO-classified pneumonia in low-income and middle-income countries (LMICs) have hypoxaemia (abnormally low blood oxygen levels defined as an arterial oxygen saturation <90%).[3] Pulse oximeters are non-invasive, portable devices that are more accurate for detecting hypoxaemia and more reliable for supporting oxygen treatment decisions than clinical signs alone;[4] however, availability of pulse oximeters and basic oxygen service capacity are low in most LMICs due to historical lack of investments, weak health systems, and poor governance structures.[5]

Donors and governments of high-burden countries need to be informed about the potential impact and cost-effectiveness of pulse oximetry and oxygen to consider whether these interventions represent a sound investment compared with other strategies for improving health outcomes. Previous studies in LMICs have provided estimates of the cost-effectiveness of oxygen in treating ALRIs, suggesting US$25–225 per disability-adjusted life-year (DALY) averted. However, these estimates are from localised empirical studies, which have focused mostly on concentrator-based systems[6–9] rather than national oxygen systems. National oxygen systems require capital and sustained investments and rely upon a variety of oxygen production, storage, and distribution sources beyond concentrators to reach full scale. A recent study using The Lives Saved Tool estimated that scaling up pulse oximetry and oxygen could avert 19–24% of mortality associated with ALRIs in children younger than 5 years between 2023 and 2030 in Chad, Ethiopia, and Bangladesh; however, this study did not evaluate cost-effectiveness.[10]

We aim to fill this evidence gap by modelling the impact and cost-effectiveness of scaling up routine pulse oximetry and oxygen systems on childhood ALRI outcomes in

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Research in context

Evidence before this study

Acute lower respiratory infections (ALRIs) are the leading cause of death globally in children aged 2–59 months. Oxygen therapy, guided by pulse oximetry, is required to treat severe ALRI cases with low blood oxygen levels (hypoxaemia), but it is not always available. The impact and cost-effectiveness of pulse oximetry and oxygen on ALRI outcomes at scale remain unquantified. We searched PubMed with no language restrictions for studies on the cost-effectiveness using search terms: ((cost-effective*) OR (cost-utility) OR (cost-benefit)) AND (pulse oximetry) AND (oxygen) on Aug 2, 2024 from database inception, yielding 120 results. We found four empirical studies on the cost-effectiveness of pulse oximetry and oxygen on ALRI in children, and six additional empirical studies looking at bronchiolitis, peri-operative pulse oximetry, or adults. However, there were no studies modelling the impact and cost-effectiveness of pulse oximetry and oxygen for whole countries or under different availabilities and intervention coverages.

Added value of this study

This study provides the first quantification of the impact of scaling up routine pulse oximetry and oxygen systems on ALRI mortality and cost per disability-adjusted life-year (DALY) averted in Malawi. We find that scaling up both interventions in combination is the cost-effective strategy under a range of health system conditions, including reduced quality of care and referral services. Routine pulse oximetry even under limited oxygen availability has diagnostic benefit, and oxygen-use efficiency is driven by the use of pulse oximetry. In any oxygen system, when pulse oximetry is implemented at all health system levels compared with none, access to oxygen therapy by children with ALRI and hypoxaemia doubles, and net benefit quintuples with mortality reduced by an additional 15–20 percentage points.

Implications of all the available evidence

Our study indicates that pulse oximetry and oxygen are complementary cost-effective interventions in Malawi (where health expenditure is low), and they should be scaled up concurrently to maximise impact. Additional analysis should be done in other high-burden countries, although given our findings of low cost per DALY averted across a range of scenarios and sensitivity analyses, our results suggest pulse oximetry and oxygen are likely to be cost-effective in these countries too.

Malawi, using a new individual-based model incorporating disease dynamics and health system interactions. We conducted a thorough costing assessment of scaling up oxygen systems at the national level, covering a mix of oxygen sources including pressure swing adsorption (PSA) plants, concentrators, and cylinders.

Methods

ALRI model

For more on the ***Thanzi La Onse* model** see www.tlomodel.org

We developed a model of ALRI for children younger than 5 years in Malawi as a module integrated within the *Thanzi La Onse* model, which is programmed in Python language version 3.8 and used pandas data analysis library 2.[11] The model covers the natural history of ALRI disease, care seeking, and care management within the Malawian health-care system, modelled at four relevant levels: level 0 (village clinics), level 1a (health centres), level 1b (rural, community, or mission hospitals), and level 2 (central or district hospitals). The ALRI model is fully detailed in the appendix (pp 11–68). Table 1 presents the key parameters and costs for the cost-effectiveness evaluation of pulse oximetry and oxygen interventions.

See Online for appendix

To map out the epidemiology, the incidence of ALRI was calculated from community health worker and health facility data from Malawi[12] as 15 cases per 100 person-years for children younger than 5 years. The proportion of ALRI cases with low oxygen saturation levels (ie, those with an SpO_2 <93%) was set at 21·9%, which is associated with disease type and pulmonary complications (appendix pp 29–35). ALRI cases present a range of signs and symptoms (appendix pp 36–39), which determine the initial contact with the health system and the care management cascade (appendix pp 47–59). A natural mortality rate (in the absence of treatment) was applied to all cases, differing by oxygen saturation, disease complications and severity of symptoms, and other comorbidities (eg, HIV and acute malnutrition). The simulation generated an ALRI cohort with a weighted average natural mortality rate of 7·47% (appendix pp 40–45).

For the health-care provision modelling, quality of care was captured through health workers' performance in implementing Integrated Management of Childhood Illness (IMCI) guidelines, set at 75% sensitivity overall across the health system (appendix p 54–57).[13] Based on the classification given and respective care provision, treatment failure rates of oral and parenteral antibiotics were applied (appendix pp 60–67). The effect of oxygen is represented through hypoxaemic cases having higher odds (odds ratio [OR] 1·92) of parenteral antibiotic treatment failure in the absence of oxygen therapy.[6] The appendix (pp 107–108) lists the simulation outputs on fraction of cases and risk of death without treatment by case type (IMCI classification, oxygen saturation, general danger signs, abnormal chest radiography), respective effectiveness of treatment with oral antibiotics, and parental antibiotics with and without oxygen therapy.

In the absence of pulse oximetry, the identification of hypoxaemic cases relies on the IMCI classification of pneumonia (based on clinical signs and symptoms). For the provision of oxygen without routine pulse oximetry, only clinical cases classified as severe are provided with

	Value	Source and justification
ALRI epidemiology		
ALRI incidence per 100 child-years, for ages 1–11 months, 12–23 months, and 24–59 months	34·51; 18·55; 6·07	Appendix pp 20–29: describes the estimation of pathogen-attributed incidence, pneumonia or other ALRI disease type incidence, and ALRI incidence by age group
Proportion of ALRI with low oxygen saturation levels (SpO_2 <93%)	0·219	Appendix pp 29–35: describes the modelling of disease progression, and the estimated parameter value based on Malawi studies; nearly half (48·7%[12]) are SpO_2 <90%
Overall ALRI mortality without treatment; mortality without treatment by SpO_2 (≥93%, 90–92%, <90%)	0·07472; 0·0340; 0·1473; 0·2976	Simulation output values. Appendix (pp 40–45): describes the mortality model, including the increased risk of death by SpO_2
Overall treatment failure of 3-day oral antibiotic for fast-breathing pneumonia; overall treatment failure of 5-day oral antibiotic for chest-indrawing pneumonia; overall treatment failure of first-line parenteral antibiotics; overall treatment failure of second-line parenteral antibiotics	0·101; 0·108; 0·193; 0·196	Appendix pp 60–67: the risk of treatment failure differs by case type: oxygen saturation, severe symptoms, abnormal chest radiography, malnutrition, HIV not on ART
Odds ratio of parenteral treatment failure in hypoxaemic cases without oxygen therapy compared with those with oxygen therapy	1·92 (95% CI 1·43–2·56)	Used the inverse of OR=0·52 (95% CI 0·39–0·70)[6]
Proportion of initial care seeking by facility level (0: village clinics; 1a: health centre; 1b: rural hospital; 2: district hospital)	0·094; 0·596; 0·155; 0·155	Appendix pp 48–50: describes data sources and assumptions; symptom severity increases care seeking at hospitals
Pulse oximetry and oxygen costs		
Equivalent annual cost of pulse oximeter (1 device)	$248·51	Appendix p 80: describes the capital and operational costs for first year of implementation and the estimation of equivalent annual cost
Pulse oximeter, cost per patient at: hospital (levels 2 and 1b); health centre (level 1a); village clinics (level 0)	$0·167; $0·096; $0·063	Appendix pp 80–81: describes the estimation of the unit cost based on the equivalent annual cost and outpatient department visits by facility level
Equivalent annual cost of PSA plants (existing PSA system; +planned PSA system)	$1 343 489; $2 907 718	Appendix pp 81–85: describes the capital and operational costs for first year of implementation and the estimation of equivalent annual cost
Equivalent annual cost of delivery trucks (existing PSA system; +planned PSA system)	$98 463; $236 312	Appendix pp 87–88: describes the capital and operational costs for first year of implementation and the estimation of equivalent annual cost
Equivalent annual cost of cylinders plus fuel for distribution (existing PSA system; +planned PSA system)	$234 326; $316 752	Appendix pp 86, 88–90: describes the capital and operational costs for first year of implementation and the estimation of equivalent annual cost
Equivalent annual cost of concentrators (existing PSA system; +planned PSA system)	$562 244; $838 925	Appendix pp 86, 90–91: describes the capital and operational costs for first year of implementation and the estimation of equivalent annual cost
Equivalent annual cost of pulse oximeters for monitoring oxygen administration (existing PSA system; +planned PSA system)	$216 878; $391 447	Appendix pp 86, 91–92: describes the capital and operational costs for first year of implementation and the estimation of equivalent annual cost
Equivalent annual cost of ventilators (existing PSA system; +planned PSA system)	$262 557; $525 114	Appendix pp 86, 93: describes the capital and operational costs for first year of implementation and the estimation of equivalent annual cost
Equivalent annual cost of patient monitors (existing PSA system; +planned PSA system)	$162 698; $324 971	Appendix pp 86, 94: describes the capital and operational costs for first year of implementation and the estimation of equivalent annual cost
Equivalent annual cost of resuscitation sets (existing PSA system; +planned PSA system)	$15 617; $32 887	Appendix pp 86, 95: describes the capital and operational costs for first year of implementation and the estimation of equivalent annual cost
Equivalent annual cost of suction devices (existing PSA system; +planned PSA system)	$155 522; $310 810	Appendix pp 86, 96: describes the capital and operational costs for first year of implementation and the estimation of equivalent annual cost
Total equivalent annual cost of oxygen system (existing PSA system; +planned PSA system)	$3 051 794; $5 884 936	The sum of the annual equivalent costs of each component of the oxygen system
Outpatient consultation cost: district hospital (level 2); rural hospital (level 1b); health centre (level 1a); village clinic (level 0)	$2·58; $2·47; $2·17; $1·76	Appendix pp 99–100: WHO-CHOICE estimates plus inflation to 2024
Inpatient bed days cost: district hospital (levels 2); rural hospital (level 1b)	$7·94; $6·89	Appendix pp 99–100: WHO-CHOICE estimates plus inflation to 2024
Antibiotics unit cost (amoxicillin 250 mg tablet; ampicillin 500 mg vial; gentamicin 10 mg/mL ampoule; ceftriaxone 1 g vial)	$0·02734; $0·25752; $0·15037; $0·6801	Appendix pp 98–99: MSH 2015 estimates plus inflation to 2024
Oxygen service availability		
Overall oxygen availability of existing PSA plants system; oxygen availability of existing PSA system by facility level: district hospital (level 2); rural hospital (level 1b); health centre (level 1a)	40·0%; 51·6%; 33·3%; 31·3%	Appendix pp 74–79: describes the estimation of oxygen availability by facility level. The distribution of oxygen was assumed to be proportional to the demand of each facility level. At the health centre (level 1a), oxygen serves for patient stabilisation; full provision requires referral to higher-level facilities (level 1b or 2)
Overall oxygen availability of +planned PSA plants system; oxygen availability of +planned PSA system by facility level: district hospital (level 2); rural hospital (level 1b); health centre (level 1a)	80·0%; 88·1%; 75·4%; 73·9%	Appendix pp 74–79: describes the estimation of oxygen availability by facility level. The distribution of oxygen was assumed to be proportional to the demand of each facility level. At the health centre (level 1a), oxygen serves for patient stabilisation; full provision requires referral to higher-level facilities (level 1b or 2)

All costs are in 2024 US dollars. Equivalent annual costs: capital costs were depreciated over the useful lifespan of the equipment, plus operational cost for year 1. ALRI=acute lower respiratory infection. ART=antiretroviral therapy. MSH= Management Sciences for Health. OR=odds ratio. PSA=pressure swing absorption.

Table 1: **Key parameters for ALRI epidemiology and pulse oximetry and oxygen cost components of the model**

oxygen if SpO_2 is lower than 90% (monitoring pulse oximeters are included in the oxygen system). Therefore, hypoxaemic cases not classified as severe are not identified as needing oxygen therapy. In the presence of pulse oximetry, both severe and non-severe classifications with SpO_2 lower than 90% are identified as needing oxygen support.

The *Thanzi La Onse* project received ethical approval from the College of Medicine Malawi Research Ethics Committee (P.10/19/2820) in Malawi. Only anonymised secondary data are used in the *Thanzi La Onse* model, including in the ALRI model used in this paper; therefore, individual informed consent was not required.

Costing of pulse oximetry and oxygen

Two oxygen systems were costed for analysis: the current system of oxygen provision, here referred to as existing PSA system (low oxygen availability), and the scale-up in these provisions, referred to as +planned PSA system (high oxygen availability), as described in the Malawi National Medical Oxygen Ecosystem Roadmap 2021–26.[14] Both systems comprise a mix of oxygen sources, including pressure swing adsorption plants, which provide the bulk of the oxygen supply; oxygen concentrators to address gaps in distribution; and cylinders for oxygen delivery to the patient, storage, and distribution. Other components included in the systems costs were delivery trucks for cylinder distribution (as a proxy to address the cost of logistical structure challenges), pulse oximeters for monitoring safe administration of oxygen to patients, ventilators, patient monitors, and resuscitation and suction devices. The total cost of the oxygen system components (capital plus operating costs) in the first year of implementation was budgeted, and capital costs of equipment were annualised over their useful life[15] (eg, PSA costs spread over 15 years) to get the equivalent annual costs for year 1 (ie, 2024). All costs are reported in 2024 US dollars (appendix pp 80–96).

Assuming a daily oxygen production rate of 6·0 to 8·5 effective h, we estimate the existing PSA system would meet 40% of oxygen demand in Malawi and the +planned PSA system would meet 80% of oxygen demand (appendix pp 74–79).

The cost incurred for the treatment of children with hypoxaemic ALRI was estimated to be around 25·9% of the total oxygen system, based on the total litres required for oxygen therapy of the ALRI cohort in the simulation compared with the national volume demand.[14] Therefore, ALRI can be said to account for $789 050 of the existing PSA system costs and $1 521 566 of the +planned PSA system annually. The cost per child treated with oxygen (for an average of 3 days) was estimated to be $23 for infants younger than 2 months and $46 for children aged 2–59 months, from our estimated unit cost per L of $0·0053 (appendix p 97), which is consistent with the estimates reported in *The Lancet Global Health* Commission on Medical Oxygen Security.[5]

We assumed routine pulse oximetry coverage required one device per health worker at the outpatient department, with each pulse oximeter estimated to cost $250 per year. This equivalent annual cost includes all capital expenses for an expected lifespan of 5 years, plus yearly maintenance. The unit cost is then based on the number of patients seen at the outpatient department in each health facility level.[13] Additional costs to the health system resulting from increased demand for services and consumables with the implementation of the interventions include antibiotics, outpatient consultation and hospitalisation bed days (table 1).

Scenarios and model simulation settings

The scenarios start with no oxygen and no pulse oximetry (the null scenario), and are then grouped into three blocks, the first without any oxygen service availability, the second with oxygen availability at 40% (existing PSA system), and the third with oxygen availability at 80% (+planned PSA system). Each block has scenarios sequentially scaling up pulse oximetry to: central or district hospitals (level 2); rural, community, or mission hospitals (levels 2 and 1b); health centres (levels 2, 1b, and 1a); and village clinics (levels 2, 1b, 1a, and 0; appendix pp 69–73). We created a representative mix of ALRI cases by running the natural history model on a population of 150 000 children younger than 5 years. When we applied the age-specific pathogen-attributed incidences, it yielded 20 752 symptomatic infections. For each incident case we considered 20 replicates, each time re-applying the disease characteristics (symptoms, severity, and death), to represent the total ALRI cases (n=415 040) in the population of 3 000 000 children younger than 5 years in Malawi in 2024. The effect of health-care system interventions were applied to each ALRI case who sought care. We re-ran the model for each of the 15 scenarios, using the same seed (equal random number generation) so the result differences were due to scenario parameters and not random variation.

Across all scenarios, health system settings and conditions are constant: 100% antibiotics availability, health worker diagnostic accuracy at 75%, referral rate of 85% for severe cases seen at levels 0 and 1a to facility levels 1b and 2, 90% pulse oximetry usage rate if available, and 60% seek follow-up care with oral treatment failure.

Analyses

For this economic evaluation, we took the health-care provider perspective, as the health system is mostly government-funded and donor-funded. The cost-effectiveness analysis was conducted for a single year cohort (2024), capturing health outcomes in DALYs due to premature death and health-care costs incurred in this period—eg, outpatient consultation, inpatient bed days, antibiotics, pulse oximetry, and oxygen therapy.

DALYs were computed for each death in the cohort, which equals the health-adjusted life expectancy in

Malawi (2021 WHO estimates[16]) at the age of death, and discounted at 3% per year as recommended by the International Decision Support Initiative reference case.[17] For an average age of 1·45 years in the cohort, one death is equivalent to 26·6 DALYs.

For each intervention scenario, we calculated the number of deaths averted (lives saved) and DALYs averted relative to the null scenario. We also calculated the incremental cost effectiveness ratios (ICERs), noting which strategies were dominated by less costly and more effective scenarios, and which strategies were extendedly dominated (ie, had an ICER greater than that of the next, more effective alternative). We then plotted each scenario on the cost-effectiveness plane as DALYs averted against incremental costs, and determined the cost-effectiveness frontier as the scenarios averting the most DALYs for the least incremental cost. We used a very stringent cost-effectiveness threshold (CET) of $80 per DALY averted, equivalent to the CET of $65 used to select interventions to be prioritised for funding Malawi's national Health Sector Strategic Plan III 2023–30,[18,19] inflated to 2024 US$ value.[20] Notably, a CET of $80 is only 16% of Malawi's per capita GDP. Using this CET, we calculated the incremental net health benefits (INHBs) for each scenario as incremental net DALYs averted. This metric represents the DALYs averted by the intervention strategy, adjusted for the DALY value of the difference in costs, using the CET of $80.

To quantify the uncertainty in the outcome estimates due to stochastic processes in the model, we performed a non-parametric bootstrap analysis with 1000 resamples of the paired individual-level outcomes between the null scenario and intervention scenarios. Within each iteration, the model outputted differences in cost, deaths averted, DALYs averted, and the resulting ICERs and incremental net benefits. We report the mean estimate and 2·5 and 97·5 percentiles of the bootstrap distribution in the Results.

To assess the effect of individual parameters on model outcomes, we conducted deterministic one-way sensitivity analyses by varying input values of key parameters, whereby ALRI accounted for 50% of the total oxygen need in Malawi (rather than the default 25·9%); pulse oximetry costs were doubled, to conservatively account for device wear and tear; outpatient and inpatient costs were twice as much as default; the referral rate of severe cases diagnosed at facility levels 1a and 0 was reduced to 60%; health worker diagnostic performance were 100% or 50%; health system conditions were perfect (defined as 100% health worker diagnostic performance, 100% referral rate of severe cases diagnosed, and 100% pulse oximetry usage rate); the relationship between oxygen production capacity and service availability followed a saturation curve, whereby additional planned PSAs covered 70% of the national demand (rather than default of 80%); the incidence of ALRI was reduced by half; the baseline odds of death was reduced by half; and the effect of oxygen was reduced by decreasing the OR of parenteral treatment failure in hypoxaemic cases without oxygen therapy compared with those with oxygen therapy to 1·43 (the inverse of OR=0·7).[6] Bootstrap methods were also applied to each sensitivity analysis, with results reported as mean and 95% CIs.

Descriptive statistical analyses informing some parameter values were performed in Stata and costing assessments were completed in Excel. The analysis scripts for simulation outputs, bootstrap iterations for uncertainty quantification, and cost-effectiveness analysis were programmed and executed in Python version 3.8.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In total, 415 040 cases of children with ALRI were simulated for 2024; baseline characteristics of the cohort can be found in the appendix (pp 104–106). Implementation of routine pulse oximetry at all hospitals of varying capacity, without oxygen (no oxygen availability and pulse oximetry at levels 2 and 1b) and the scale-up of oxygen systems to 80% service availability along with

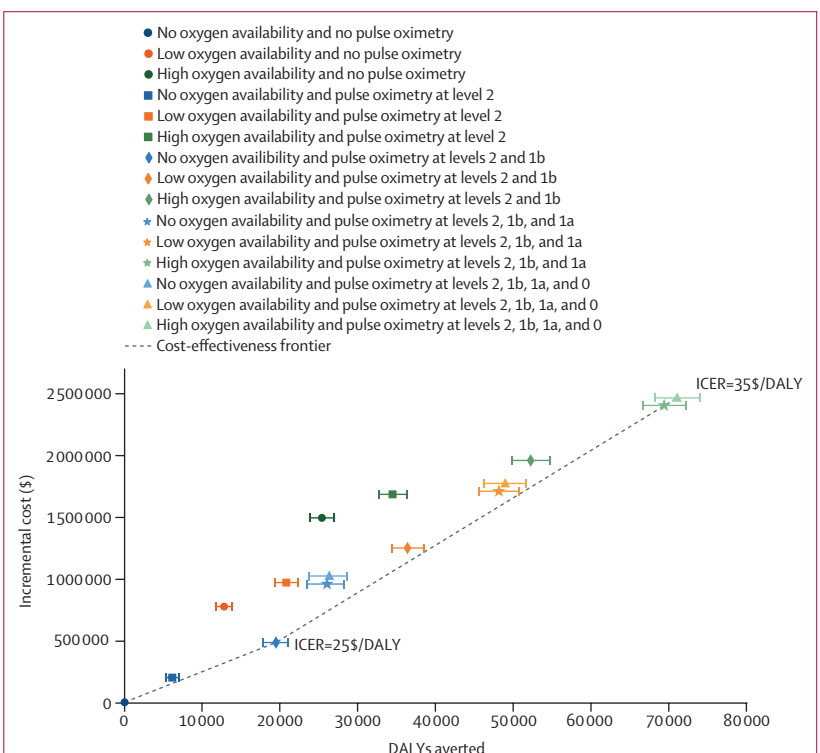

Figure: **Pulse oximetry and oxygen scale-up scenarios on the cost-effectiveness plane: incremental effectiveness in DALYs averted of intervention scenarios against the incremental cost, relative to the null scenario**
DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio.

	Simulation output		Bootstrap results reporting the mean estimate (95% CI)				
	Total deaths	Total cost (US$)*	Access to oxygen†	Mortality reduction	DALYs averted	ICER ($/DALY averted)	Incremental net health benefit (DALYS averted)
No oxygen availability and no pulse oximetry (null scenario)	9485	5 127 777	0	NA	NA	NA	NA
No oxygen availability and pulse oximetry at level 2	9255	5 327 670	0	2·4% (2·1–2·8)	6100 (5200–7000)	Extendedly dominated	3600 (2700–4600)
No oxygen availability and pulse oximetry at levels 2 and 1b	8754	5 611 671	0	7·7% (7·0–8·4)	19 500 (17 600–21 100)	25 (23–27)	13 400 (11 600–15 100)
No oxygen availability and pulse oximetry at levels 2, 1b, and 1a	8509	6 085 817	0	10·3% (9·3–11·2)	26 000 (23 400–28 300)	Extendedly dominated	14 000 (11 400–16 400)
No oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0	8498	6 150 698	0	10·4% (9·4–11·3)	26 300 (23 600–28 700)	Extendedly dominated	13 500 (10 800–15 900)
Low oxygen availability and no pulse oximetry	9005	5 902 980	18·2% (17·8–18·5)	5·1% (4·6–5·5)	12 800 (11 700–13 900)	Dominated	3100 (2000–4200)
Low oxygen availability and pulse oximetry at level 2	8704	6 097 465	22·4% (22·0–22·7)	8·2% (7·7–8·8)	20 800 (19 300–22 400)	Dominated	8700 (7200–10 200)
Low oxygen availability and pulse oximetry at levels 2 and 1b	8119	6 377 019	27·1% (26·7–27·5)	14·4% (13·6–15·2)	36 400 (34 200–38 500)	Extendedly dominated	20 700 (18 700–22 800)
Low oxygen availability and pulse oximetry at levels 2, 1b, and 1a	7678	6 837 542	35·6% (35·1–36·0)	19·1% (18·2–20·0)	48 100 (45 500–50 700)	Extendedly dominated	26 700 (24 200–29 400)
Low oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0	7647	6 900 486	36·7% (36·3–37·2)	19·4% (18·4–20·3)	48 900 (46 200–51 600)	Extendedly dominated	26 800 (24 100–29 400)
High oxygen availability and no pulse oximetry	8533	6 621 392	34·7% (34·3–35·1)	10·0% (9·4–10·7)	25 400 (23 800–27 100)	Dominated	6700 (5100–8300)
High oxygen availability and pulse oximetry at level 2	8191	6 812 152	41·9% (41·5–42·4)	13·6% (13·0–14·4)	34 400 (32 600–36 400)	Dominated	13 400 (11 600–15 300)
High oxygen availability and pulse oximetry at levels 2 and 1b	7524	7 086 551	52·5% (52·0–52·9)	20·7% (19·8–21·6)	52 200 (49 700–54 800)	Extendedly dominated	27 700 (25 200–30 200)
High oxygen availability and pulse oximetry at levels 2, 1b, and 1a	6879	7 532 457	69·5% (69·1–70·0)	27·5% (26·5–28·5)	69 300 (66 500–72 300)	Extendedly dominated	39 300 (36 500–42 200)
High oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0	6816	7 593 675	71·9% (71·5–72·4)	28·1% (27·1–29·2)	71 000 (68 100–74 000)	35 (33–36)	40 200 (37 300–43 100)

Low oxygen availability refers to 40% overall oxygen service availability of the existing PSA system. High oxygen availability refers to 80% overall oxygen service availability of the +planned PSA system. Level 2 refers to central or district hospitals, level 1b refers to rural, community, or mission hospitals, level 1a refers to health centres, and level 0 refers to village clinics. Dominated refers to more costly and less effective, extendedly dominated refers to dominated by a linear combination of two or more other alternatives. ALRI=acute lower respiratory infections. DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio. NA=not applicable. *Cost includes antibiotics, outpatient consultation, inpatient bed days, pulse oximetry, and oxygen incurred for ALRI children (full breakdown of costs in the appendix p 114). †Proportion of hypoxaemic cases who receive oxygen therapy.

Table 2: **Cost-effectiveness results for each scenario of pulse oximetry and oxygen scale-up for ALRI in children younger than 5 years in Malawi**

pulse oximetry across all levels of the health system (high oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0) are on the cost-effectiveness frontier, whereas all other scenarios were dominated or extendedly dominated (figure). The full scale-up scenario was the cost-effective strategy, averting 71 000 (95% CI 68 100–74 000) DALYs at an ICER of $35 (33–36) per DALY averted, with an INHB of 40 200 (37 300–43 100) net DALYs averted on population burden of disease (table 2). This strategy achieved a 28% reduction in ALRI mortality compared with the null scenario, at an incremental cost of $924 (887–963) per death averted. As illustrated in the cost-effectiveness plane, within each oxygen availability block, the progressive implementation of pulse oximetry across the four health system levels moved the strategy towards the cost-effectiveness frontier, showing complementarity between pulse oximetry and delivery of oxygen.

The implementation of routine pulse oximetry results in DALYs being averted even when oxygen therapy is not available. The resulting benefit arises from identifying cases with SpO_2 below 90% that would otherwise be under-classified as non-severe and managed as outpatients. The addition of the diagnostic tool can correct health workers' assessment accuracy and can also pick up cases missed by the IMCI clinical algorithm, particularly in primary care settings, including small-capacity hospitals. In the absence of an oxygen system, introduction of routine pulse oximetry in primary care settings (no oxygen availability and pulse oximetry at levels 2, 1b, and 1a, or no oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0) had a comparable effect to the full scale-up of oxygen systems without pulse oximetry (high oxygen availability and no pulse oximetry), both resulting in almost 1000 deaths averted in 1 year. Moreover, when considering the costs, the INHBs of pulse oximetry only strategies are double that of the full oxygen scale-up only strategy.

We found that efficient oxygen systems are driven by the use of pulse oximetry. Access to oxygen therapy for children with ALRI and hypoxaemia doubles when

	Costs		Health workers' IMCI performance		Health system conditions		Scale-up constraints	Epidemiology		
	ALRI oxygen consumption of 50%*	Cost of outpatient/ inpatient ×2	Perfect 100%	Imperfect 50%	Referral rate 60%	All perfect†	Planned PSAs system: 70% availability	Reduce baseline incidence by half‡	Reduce baseline odds of death by half	Reduce effect of oxygen§
No oxygen availability and no pulse oximetry	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
No oxygen availability and pulse oximetry at level 2	3600 (2700 to 4600)¶	1600 (681 to 2544)	−1300 (−1700 to −900)	11 000 (9800 to 12 400)	3600 (2700 to 4600)	−1200 (−1677 to −731)	3600 (2700 to 4600)¶	1200 (464 to 1924)	2600 (1900 to 3400)	5500 (4600 to 6500)
No oxygen availability and pulse oximetry at levels 2 and 1b	13 400 (11 600 to 15 100)¶	8400 (6600 to 10 200)	−1300 (−2400 to −200)	29 100 (26 900 to 31 200)	13 400 (11 600 to 15 100)	−1500 (−2552 to −460)	13 400 (11 600 to 15 100)¶	6400 (5100 to 7900)	7800 (6600 to 9000)	18 700 (16 900 to 20 500)
No oxygen availability and pulse oximetry at levels 2, 1b, and 1a	14 000 (11 400 to 16 400)¶	4000 (1400 to 6400)	−10 100 (−11 700 to −8300)	38 300 (35 300 to 41 000)	14 800 (12 300 to 17 100)	−12 100 (−13 700 to −10 500)	14 000 (11 400 to 16 400)¶	5100 (3100 to 7000)	8700 (7000 to 10 300)	23 300 (20 900 to 25 600)
No oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0	13 500 (10 800 to 15 900)¶	2800 (48 to 5112)	−11 300 (−13 000 to −9500)	38 600 (35 500 to 41 200)	14 200 (11 600 to 16 600)	−13 900 (−15 700 to −12 200)	13 500 (10 800 to 15 900)¶	4500 (2400 to 6400)	8800 (7000 to 10 400)	23 300 (20 900 to 25 800)
Low oxygen availability and no pulse oximetry	−6100 (−7200 to −5000)	3300 (2200 to 4400)	7300 (6000 to 8500)	−1400 (−2300 to −500)	2400 (1400 to 3500)	8700 (7400 to 10 100)	3100 (2000 to 4200)¶	−1100 (−2000 to −212)	1800 (967·0 to 2580·0)	−2800 (−3500 to −1900)
Low oxygen availability and pulse oximetry at level 2	−554 (−2000 to 880)	6900 (5400 to 8300)	6400 (5000 to 7800)	13 400 (11 900 to 15 100)	8000 (6600 to 9400)	7800 (6500 to 9300)	8700 (7200 to 10 200)¶	1700 (458 to 2878)	5400 (4300 to 6500)	3600 (2300 to 4900)
Low oxygen availability and pulse oximetry at levels 2 and 1b	11 500 (9500 to 13 600)	16 100 (14 000 to 18 200)	7600 (5900 to 9300)	34 400 (32 000 to 36 800)	20 000 (17 900 to 22 100)	8800 (7300 to 10 600)	20 700 (18 700 to 22 800)¶	8600 (7000 to 10 300)	11 500 (10 000 to 12 900)	17 900 (15 900 to 19 900)
Low oxygen availability and pulse oximetry at levels 2, 1b, and 1a	17 500 (15 000 to 20 100)	17 200 (14 700 to 19 900)	3100 (1100 to 5200)	50 300 (47 300 to 53 300)	26 000 (23 500 to 28 600)	3700 (1700 to 5700)	26 700 (24 200 to 29 400)¶	10 900 (8900 to 13 000)	15 300 (13 500 to 17 100)	26 300 (23 800 to 28 800)
Low oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0	17 500 (14 900 to 20 200)	16 600 (13 900 to 19 300)	2300 (200 to 4500)	51 300 (48 300 to 54 400)	26 000 (23 400 to 28 700)	2800 (730 to 4905)	26 800 (24 100 to 29 400)¶	10 600 (8600 to 12 700)	15 700 (13 800 to 17 500)	26 700 (24 100 to 29 200)
High oxygen availability and no pulse oximetry	−11 100 (−12 700 to −9400)	7100 (5500 to 8700)	14 800 (13 100 to 16 700)	−1900 (−3100 to −600)	5200 (3600 to 6700)	17 100 (15 400 to 18 800)	3600 (2200 to 5200)	−1700 (−2932 to −356)	4400 (3200 to 5600)	−4100 (−5300 to −2900)
High oxygen availability and pulse oximetry at level 2	−4400 (−6200 to −2500)	11 800 (10 000 to 13 800)	14 200 (12 400 to 16 100)	15 100 (13 300 to 17 200)	11 900 (10 100 to 13 700)	16 600 (14 800 to 18 500)	10 000 (8300 to 11 900)	1800 (339 to 3385)	8800 (7300 to 10 100)	2800 (1200 to 4300)
High oxygen availability and pulse oximetry at levels 2 and 1b	9900 (7500 to 12 500)	23 400 (20 900 to 25 900)	16 700 (14 600 to 18 700)‖	39 700 (37 000 to 42 400)	26 200 (23 800 to 28 700)	19 200 (17 200 to 21 200)‖	23 400 (21 000 to 25 800)	10 500. (8600 to 12 500)	16 200 (14 500 to 18 000)	17 900 (15 800 to 20 200)
High oxygen availability and pulse oximetry at levels 2, 1b, and 1a	21 500 (18 700 to 24 400)	30 200 (27 400 to 33 200)	16 500 (14 200 to 18 600)	62 600 (59 400 to 65 900)	36 800 (33 900 to 39 600)	19 000 (16 800 to 21 300)	33 600. (30 800 to 36 500)	16 400 (14 100 to 18 600)	23 100 (21 200 to 25 200)	30 300 (27 500 to 33 000)
High oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0	22 400 (19 600 to 25 300)‖	30 500 (27 600 to 33 400)‖	16 300 (14 000 to 18 600)	64 600 (61 300 to 67 900)‖	37 600 (34 600 to 40 400)‖	18 800 (16 600 to 21 200)	34 300 (31 400 to 37 200)‖	16 800 (14 400 to 19 100)‖	23 800 (21 700 to 25 900)‖	31 200 (28 500 to 34 100)‖

Full outputs of scenarios under sensitivity analyses (mortality, DALYs, costs breakdown, and ICERs) are detailed in the appendix (pp 118–163). Sensitivity analyses to pulse oximetry costs (doubled) are in the appendix (pp 158–160). ALRI=acute lower respiratory infection. DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio. IMCI=Integrated Management of Childhood Illness. NA=not applicable. OR=odds ratio. *Default ALRI consumption is 25·9% of total oxygen demand. †All perfect—100% health workers' IMCI performance, 100% referral rate of severe cases diagnosed, 100% pulse oximetry usage rate. ‡ALRI Incidence of 7·5 per 100 child-years makes up 13·2% of the national oxygen demand; thus, 13·2% of the total system cost. §OR of treatment failure without oxygen is 1·43. ¶Remains unchanged from the main analysis results. ‖The cost-effective strategy.

Table 3: **Sensitivity analysis results: incremental net health benefits (net DALYs averted) for each intervention strategy versus the null scenario under different conditions**

routine pulse oximetry is implemented at all levels of the health system compared with none (18% to 37% in the low oxygen system, and 35% to 72% in high oxygen system; table 2). Identifying oxygen need with routine pulse oximetry brings effective use of oxygen closer to the maximum availability.

If investments towards effective operation of the existing oxygen system achieved an oxygen service availability of 40%, the introduction of routine oximetry at all facility levels (low oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0) yields greater INHB (26 800 [95% CI 24 100–29 400]) net DALYs averted) than investing in

additional planned PSA plants without concurrent implementation of pulse oximetry further into primary care hospitals (high oxygen availability and pulse oximetry at level 2; 13 400 [11 600–15 300] net DALYs averted; table 2). Thus, investing in additional oxygen capacity without implementing routine pulse oximetry means it will not fulfill its potential impact.

Indeed, in scenarios with oxygen availability, mortality further reduces by 15–20% (increasing percentage with increasing oxygen availability) when pulse oximetry implementation at outpatient settings covers all facility levels compared to none (table 2). In terms of population-level health gains, full implementation of pulse oximetry can nearly triple the net health benefit of oxygen implementation scenarios (low or high oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0 compared with low or high oxygen and pulse oximetry at level 2; table 2).

Sensitivity analyses (table 3) of cost changes consistently indicate that the strategy leading to the greatest incremental net health benefit is the full-scale implementation of both oxygen and pulse oximetry across all levels of the health system (high oxygen and pulse oximetry at four levels). Even if childhood ALRI were to consume 50% of the oxygen system's capacity, equivalent to near doubled oxygen costs, the full-scale implementation remains the cost-effective strategy.

Similarly, full-scale implementation consistently emerged as the cost-effective strategy across the epidemiological variations tested in sensitivity analyses, including a 50% reduction in ALRI incidence, halved baseline mortality odds, and diminished oxygen therapeutic effect.

In terms of health system constraints, sensitivity analyses of reduced quality of care and ineffective referral pathways confirm that full-scale implementation remains the strategy yielding the greatest net DALYs averted. In parallel, we ran simulations under improved quality care and within a theoretical optimal health system; both showed that scaling up oxygen systems is impactful in perfect conditions, while implementation of pulse oximetry can be limited to hospitals. This finding supports the importance of adhering to IMCI guidelines and maintaining an effective health system to optimise efficiency of oxygen systems, while also highlighting how routine pulse oximetry can help address and mitigate underlying system inefficiencies. Additionally, even a reduction in the oxygen service availability achieved with +planned PSA system reached the same conclusion on the cost-effective strategy.

Discussion

Scaling up oxygen to meet 80% of the national demand and pulse oximetry to all levels of the health system in Malawi is cost-effective. At $35 per DALY averted (with sensitivity analyses results ranges between $27–52), it represents outstanding value for money, even in comparison to competing essential interventions in Malawi's current health benefits package.[18] The incremental net health benefit of 40 200 DALYs averted is as good as a hypothetical intervention that eliminated, at zero cost, all DALYs due to African trypanosomiasis, schistosomiasis, onchocerciases, and lymphatic filariasis combined.[21] There is also strong complementarity of pulse oximetry and oxygen: the model shows that access to pulse oximetry drives the efficiency of oxygen systems.

When quality of IMCI implementation (and therefore diagnosis of severe pneumonia requiring inpatient management) is low, the incremental net health benefits of scaling up pulse oximetry alone or in combination with oxygen are even greater. This finding is particularly relevant to settings where implementation of IMCI for pneumonia diagnosis is generally poor (eg, Malawi), with respiratory assessments such as respiratory rates often not being performed.[22–24] The main signs used to classify severity in IMCI are also subjective, further affecting misdiagnosis. Pulse oximetry detects hypoxaemia in cases that would be missed because they do not have clinical signs that could be detected with the current IMCI algorithm,[25] including fatal hypoxaemic cases.[26] Therefore, a focus on quality pulse oximetry adoption provides a clear opportunity for a more objective measure of disease severity, but only if health-care workers are motivated and equipped to conduct these measurements.[27]

Additionally, there is potential for further effect from routine pulse oximetry use and oxygen treatment not covered in this economic evaluation. Such potential impact includes the effect of providing oxygen therapy to children with moderate levels of hypoxaemia (SpO_2 measurements between 90% and 92%),[28] and the potential effects of pulse oximetry in correctly prescribing antibiotic therapy for non-hypoxaemic cases presenting with an abnormal SpO_2 (below 95%).[29] Therefore, the impact and cost-effectiveness of both interventions could potentially be greater than presented in this analysis, depending on the other implementation considerations.

Implementation of routine pulse oximetry across the health system should be a priority in any oxygen system expansion. Currently, there is an unrealised opportunity to maximise the efficient use of existing oxygen systems. Our findings feed into wider calls to expand access to oxygen as an essential medicine globally, which have gained momentum since the COVID-19 pandemic. Efforts by *The Lancet Global Health* Commission on Medical Oxygen Security[5] and the Global Oxygen Alliance, which aims to raise $4 billion in oxygen investments from 2024–30,[30] should lead to scale-up of both routine pulse oximetry and oxygen concurrently, especially in the highest burden countries.

This modelling study provides a comprehensive analysis of the potential benefits of oxygen and pulse oximetry implementation in the Malawi health system context. However, the successful implementation of

these interventions is hindered by a multitude of crucial factors[14] including subpar quality of care and referral systems as analysed and surging demand for health services resulting from the expansion of interventions. This expansion requires a well equipped health workforce, which poses a substantial challenge in Malawi.[31] Although the cost of increased demand for care services is included in outpatient and inpatient costs, translating these projections into the reality of increasing staff numbers poses another bottleneck in improving oxygen accessibility and quality of care.

It is possible that we overestimated or underestimated the effect of pulse oximetry, as we had to assume 100% sensitivity and specificity in measuring SpO_2. This assumption is because the modelling of hypoxaemia and SpO_2 levels is informed by published studies that use pulse oximeter devices with the same level of accuracy (+/–2%).[12] Thus, non-detected or overdiagnosed cases are reflected in the mortality rates. For the model to truly handle accuracy we would need arterial blood gas measurement data from children in LMICs, which are not currently available. We also acknowledge the concerns regarding potential lower accuracy in individuals with darker skin tones.[32] However, the magnitude of these issues and their actual effect on the identification of true hypoxaemia cases is unclear, given that SpO_2 measurement accuracy is multifactorial. We did not model oxygen overuse, as pulse oximetry for monitoring oxygen use is a key component included in the oxygen system to guide oxygen therapy.

Further limitations of the model are that it assumes complete availability of antibiotics as the base intervention for pulse oximetry and oxygen to be effective. The model also assumes a uniform distribution of oxygen supply across the country and does not include transportation costs associated with referrals (appendix pp 101–103). As with all modelling exercises, we relied on data from many published studies to inform our model parameters. It is not always clear from these studies how they addressed issues such as missing data, which could potentially introduce bias in our parameter estimates. Stochastic uncertainty arising in the model due to random variability was quantified through bootstrap iteration, and parameter sensitivity was examined through one-way sensitivity analyses across plausible and extreme parameter ranges. Both approaches confirm the robustness of the findings on the cost-effectiveness of pulse oximetry and oxygen. Nevertheless, structural uncertainty related to conceptual modelling assumptions could not be fully assessed, and implementation challenges or unexpected clinical usage patterns could potentially influence the cost and effect of oxygen beyond our considered ranges.

In the scale-up of pulse oximetry and oxygen, especially in primary care, implementation needs to be carefully considered beyond the costs and logistics. Supply-side barriers relating to health-worker competency need to be addressed (including delivering training, mentoring, and creating the right conditions for staff motivation) for sustained high-coverage use of pulse oximetry and oxygen by all cadres of staff tasked with implementing them at each level of care.[27] Demand-side barriers also require attention, as oxygen therapy can be unacceptable to caregivers or patients in contexts where knowledge of oxygen therapy is low[33,34] or unaffordable[35] (eg, in health systems where care is funded directly via out-of-pocket payments by patients).

In conclusion, our modelling results indicate that pulse oximetry and oxygen are complementary cost-effective interventions in Malawi and should be scaled up in parallel. However, the way in which scale-up is done should depend on government priorities and feasibility, and a phased approach might be sensible.[36] Given the key message that routine pulse oximetry is crucial to realising the benefits of oxygen investments, there needs to be a focus on quality pulse oximetry implementation across the health-care system. Previous work has shown that pulse oximetry uptake among health-care workers in routine care settings can be achieved.[37] Additional modelling should be done in high-burden countries that face different health system constraints. However, given our findings of low cost per DALY averted across a range of sensitivity analyses, and in comparison to other essential health interventions, it seems likely that pulse oximetry and oxygen will be cost-effective in these countries too.

Contributors

ILL, EDM, VC, PR, ANP, TC, and TBH contributed to conceptualisation of the study. ILL, EDM, EB, JHC, MMG, EJ, TDM, JM-B, EM, SM, MM, DN, AR, BS, LS, AUT, PR, VC, ANP, TC, and TBH contributed to the methodology. ILL contributed to data curation, formal analysis, and visualisation. ILL and TC wrote the original draft. ILL, EDM, EB, JHC, EJ, CK, NL, TDM, JM-B, EM, SM, MM, DN, HN, AR, BS, LS, AUT, PR, VC, ANP, TC, and TBH contributed to reviewing and editing. ILL, PR, ANP, TC, and TBH contributed to funding acquisition. ILL, TC, and TBH accessed and verified the data and are responsible for the decision to submit the manuscript. All the authors had access to the data in the study and accept responsibility for the decision to submit for publication.

Declaration of interests

Besides funding from the Wellcome Trust and UK Research and Innovation going towards authors' institutions, some authors took on private projects, outside the submitted work. ILL declares receiving consulting fees from ICDDR-B for her work for The *Lancet* Commission on Medical Oxygen Security related to this study. TC declares consulting fees donated to his institution from the Global Fund for related work, personal consulting fees from the UN Economic Commission for Africa, and non-paid work chairing a Trial Steering Committee for a trial of adolescent mental health interventions in Nepal. ANP declares receiving consulting fees from the Bill & Melinda Gates Foundation. All other authors declare no competing interests.

Data sharing

All data used in this study are available in our supplementary material and via our GitHub repository: https://github.com/UCL/TLOmodel/releases/tag/Li_Lin_et_al_ALRI_CEA_Ox_PO.

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References

1 UNICEF. Levels and trends in child mortality: United Nations Inter-agency Group for child Mortality Estimation (UN IGME), report 2023. United Nations Children's Fund, 2024.

2 UN Inter-agency Group for Child Mortality Estimation. Deaths in under 5 years. https://childmortality.org/causes-of-death/data?type=DEATHS (accessed Aug 24, 2024).

3 Rahman AE, Hossain AT, Nair H, et al. Prevalence of hypoxaemia in children with pneumonia in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Glob Health* 2022; **10:** e348–59.

4 Zar HJ, McCollum ED. Pulse oximetry to detect paediatric hypoxaemia—the fifth vital sign. *Lancet Glob Health* 2023; **11:** e1684–85.

5 Graham HR, King C, Rahman AE, et al. Reducing global inequities in medical oxygen access: the *Lancet Global Health* Commission on medical oxygen security. *Lancet Glob Health* 2025; **13:** e528–84.

6 Lam F, Stegmuller A, Chou VB, Graham HR. Oxygen systems strengthening as an intervention to prevent childhood deaths due to pneumonia in low-resource settings: systematic review, meta-analysis and cost-effectiveness. *BMJ Glob Health* 2021; **6:** e007468.

7 Graham HR, Bakare AA, Ayede AI, et al. Cost-effectiveness and sustainability of improved hospital oxygen systems in Nigeria. *BMJ Glob Health* 2022; **7:** e009278.

8 Conradi N, Opoka RO, Mian Q, et al. Solar-powered O_2 delivery for the treatment of children with hypoxaemia in Uganda: a stepped-wedge, cluster randomised controlled trial. *Lancet* 2024; **403:** 756–65.

9 Mian Q, Huang Y, Conroy A, Opoka R, Namasopo S, Hawkes M. Solar-powered oxygen delivery to treat childhood pneumonia in low-resource settings: a randomised controlled non-inferiority trial and cost-effectiveness study. *Lancet Glob Health* 2019; **7:** S10.

10 Pfurtscheller T, Lam F, Shah R, et al. Predicting the potential impact of scaling up four pneumonia interventions on under-five pneumonia mortality: a prospective Lives Saved Tool (LiST) analysis for Bangladesh, Chad, and Ethiopia. *J Glob Health* 2024; **14:** 04001.

11 Hallett TB, Mangal TD, Tamuri AU, et al. Estimates of resource use in the public-sector health-care system and the effect of strengthening health-care services in Malawi during 2015–19: a modelling study (*Thanzi La Onse*). *Lancet Glob Health* 2025; **13:** e28–37.

12 McCollum ED, Nambiar B, Deula R, et al. Impact of the 13-valent pneumococcal conjugate vaccine on clinical and hypoxemic childhood pneumonia over three years in central Malawi: an observational study. *PLoS One* 2017; **12:** e0168209.

13 Government of Malawi. Harmonised Health Facility Assessment 2018–2019. Government of Malawi, 2019.

14 Government of Malawi, Ministry of Health. Malawi National Medical Oxygen Ecosystem Roadmap 2021–2026. Government of Malawi, 2021.

15 Walker D, Kumaranayake L. Allowing for differential timing in cost analyses: discounting and annualization. *Health Policy Plan* 2002; **17:** 112–18.

16 WHO. Data: Malawi. 2025. https://data.who.int/countries/454 (accessed Aug 24, 2024).

17 Wilkinson T, Sculpher MJ, Claxton K, et al. The International Decision Support Initiative reference case for economic evaluation: an aid to thought. *Value Health* 2016; **19:** 921–28.

18 Government of Malawi. Health Sector Strategic Plan III 2023–2030 reforming for universal health coverage. Government of Malawi, 2024.

19 Connolly E, Mohan S, Twea P, et al. Revision of Malawi's Health Benefits Package: a critical analysis of policy formulation and implementation. *Value Health Reg Issues* 2024; **39:** 84–94.

20 International Monetary Fund. Inflation rate, average consumer prices. April 15, 2025. https://www.imf.org/external/datamapper/PCPIPCH@WEO/USA (accessed Sept 1, 2024).

21 Institute for Health Metrics and Evaluation. GBD 2021. May 16, 2024. https://vizhub.healthdata.org/gbd-compare/ (accessed Dec 18, 2024).

22 Bjornstad E, Preidis GA, Lufesi N, et al. Determining the quality of IMCI pneumonia care in Malawian children. *Paediatr Int Child Health* 2014; **34:** 29–36.

23 Johansson EW, Nsona H, Carvajal-Aguirre L, Amouzou A, Hildenwall H. Determinants of Integrated Management of Childhood Illness (IMCI) non-severe pneumonia classification and care in Malawi health facilities: analysis of a national facility census. *J Glob Health* 2017; **7:** 020408.

24 Kobayashi M, Mwandama D, Nsona H, et al. Quality of case management for pneumonia and diarrhea among children seen at health facilities in southern Malawi. *Am J Trop Med Hyg* 2017; **96:** 1107–16.

25 Mccollum ED, King C, Deula R, et al. Pulse oximetry for children with pneumonia treated as outpatients in rural Malawi. *Bull World Health Organ* 2016; **94:** 893–902.

26 Colbourn T, King C, Beard J, et al. Predictive value of pulse oximetry for mortality in infants and children presenting to primary care with clinical pneumonia in rural Malawi: a data linkage study. *PLoS Med* 2020; **17:** e1003300.

27 Olojede OE, Falade AG, Bakare AA, et al. Understanding pulse oximetry adoption in primary health care facilities in Nigeria: a realist process evaluation of the INSPIRING-Lagos stabilisation room project. *BMJ Public Health* 2024; **2:** e001211.

28 Graham HR, King C, Duke T, et al. Hypoxaemia and risk of death among children: rethinking oxygen saturation, risk-stratification, and the role of pulse oximetry in primary care. *Lancet Glob Health* 2024; **12:** e1359–64.

29 Sylvies F, Nyirenda L, Blair A, Baltzell K. The impact of pulse oximetry and Integrated Management of Childhood Illness (IMCI) training on antibiotic prescribing practices in rural Malawi: a mixed-methods study. *PLoS One* 2020; **15:** e0242440.

30 Global Oxygen Alliance. (GO2AL) Strategy: executive summary 2024–2030. 2023. https://globaloxygenalliance.org/wp-content/uploads/2024/01/GO2AL_StrategyExeSummary_2024-2030-v4.pdf (accessed Aug 24, 2024).

31 Muula AS. The paradox of Malawi's health workforce shortage: pragmatic and unpopular decisions are needed. *Malawi Med J* 2023; **35:** 1–2.

32 Hooli S, Colbourn T, Shah MI, Murray K, Mandalakas A, McCollum ED. Pulse oximetry accuracy in children with dark skin tones: relevance to acute lower respiratory infection care in low- and middle-income countries. *Am J Trop Med Hyg* 2024; **111:** 736–39.

33 Sessions KL, Ruegsegger L, Mvalo T, et al. Focus group discussions on low-flow oxygen and bubble CPAP treatments among mothers of young children in Malawi: a CPAP IMPACT substudy. *BMJ Open* 2020; **10:** e034545.

34 Bakare AA, Salako J, King C, et al, and the INSPIRING Project Consortium. 'Let him die in peace': understanding caregiver's refusal of medical oxygen treatment for children in Nigeria. *BMJ Glob Health* 2024; **9:** e014902.

35 Graham HR, Olojede OE, Bakare AA, et al. Measuring oxygen access: lessons from health facility assessments in Lagos, Nigeria. *BMJ Glob Health* 2021; **6:** e006069.

36 Graham HR, Maher J, Bakare AA, et al. Oxygen systems and quality of care for children with pneumonia, malaria and diarrhoea: analysis of a stepped-wedge trial in Nigeria. *PLoS One* 2021; **16:** e0254229.

37 Rahman AE, Ameen S, Hossain AT, et al. Introducing pulse oximetry for outpatient management of childhood pneumonia: an implementation research adopting a district implementation model in selected rural facilities in Bangladesh. *EClinicalMedicine* 2022; **50:** 101511.

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Supplementary appendix

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APPENDIX
The impact and cost-effectiveness of pulse oximetry and oxygen on acute lower respiratory infection outcomes in children under-5 in Malawi: a modelling study

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Appendix A

Building a Model of Acute Lower Respiratory Infections (ALRI) for the Malawi context

A.1 The TLO simulation model

The ALRI model is integrated within the Thanzi La Onse (TLO) simulation environment, as a disease module. The TLO modelling framework is of a modularised design implemented in Python and numerical libraries (Figure A.1). An efficient individual-based simulation engine is used to track a population and the action of 'events' that are generated 'modules'. There are three main types of module:

- Core modules: these represent basic processes, such as, the 'Demography' module determines the district of residence of each person, the 'Lifestyle' module which determines patterns of risk factors in the population, the 'Contraception' module, which represents the contraceptive use of each women, and the 'HealthSeekingBehaviour' module which determines if and how persons seek healthcare following onset of an illness.

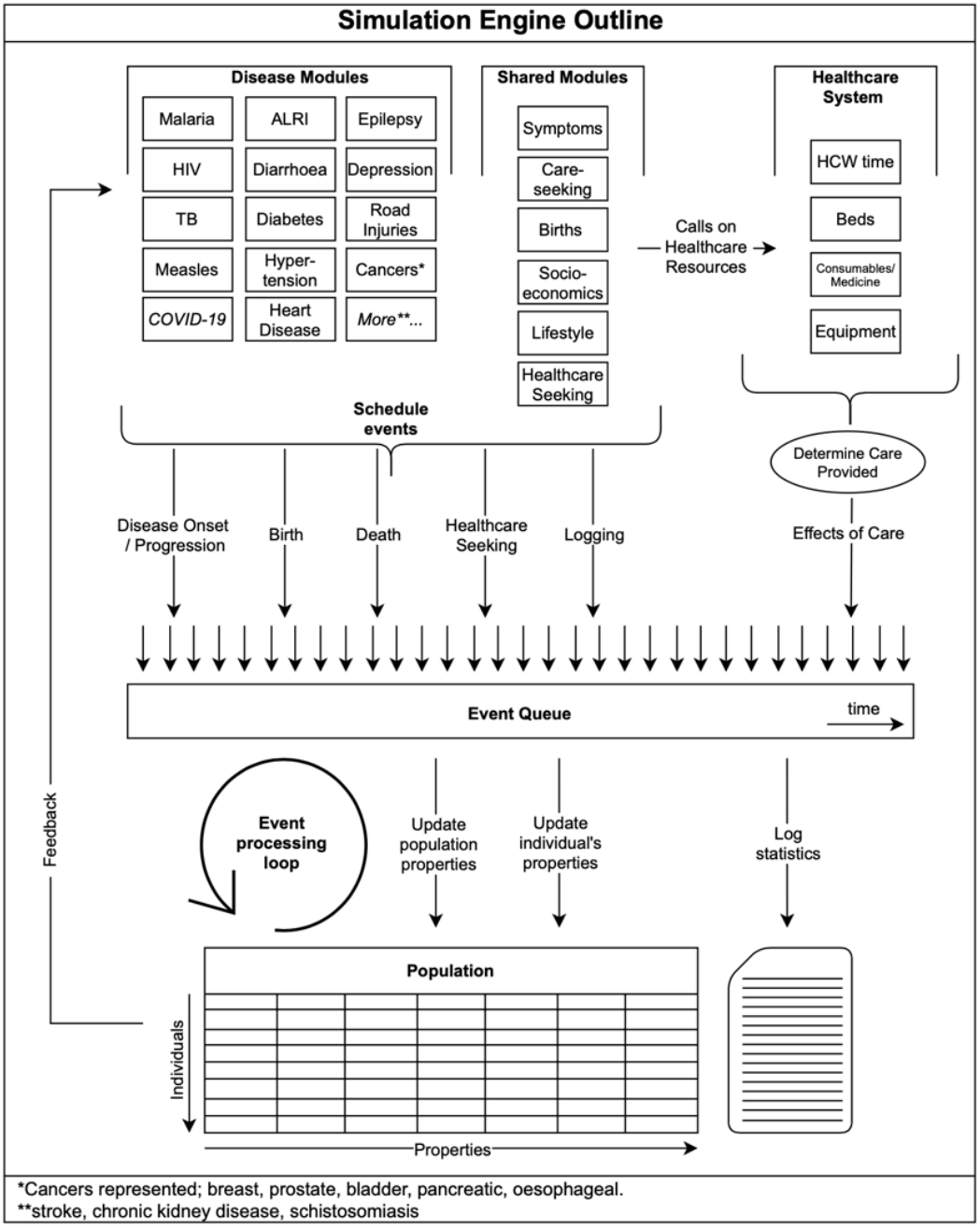
- The 'HealthSystem' module: this represents all functions of the healthcare system – its resources and how these are used to generate effective capabilities, and how these capabilities are distributed among the healthcare needs in the population (generated by the disease modules).

- Disease modules: these represents a specific disease, or set of diseases, including the onset, progression, health outcomes and the effect of any treatment received. If the disease is communicable, transmission is represented within the population. The framework comprises a full grammar of disease module construction and interaction designed such that the access to and effects of treatments are subject to gating/modifying according to resource availability and management decisions in the HealthSystem.

The model outputs the information of the simulation in dataframes, storing all the properties specific to the individual. Each individual in the simulation

takes a row in the dataframe and each column represents a property of the person; properties for a person are contributed by each of the disease modules. We use the dataframe as the simulation output for analysis.

Figure A.1: Outline of the simulation engine



Source: https://www.tlomodel.org/

A.1.1 Purpose of the ALRI model

In a 'whole system and all-disease model', the development of an ALRI disease module is a priority due to its high burden in Malawi. Acute Lower Respiratory Infections still remain one of the top 4 causes of DALYs in this population, with a particular concentration of this burden among children un-

der the age of 5. An ALRI module within the TLO model framework is critical for devising effective resource allocation strategies in child health programmes. Within the TLO simulation model, the ALRI module is responsible for assigning new ALRI cases to the population, simulating the progression of the disease to resolution, and events occurring at the healthcare system.

A.2 Modelling the epidemiology of ALRI

Here we describe the approach to modelling the natural history of ALRI, including the designed model structure, the scope of what is included in the model, the assumptions and simplifications, the choice of parameters and respective values, and how the conceptualised model translates in the TLO simulation model.

A.2.1 Disease definition

In an attempt to model the leading cause of under-5 deaths in sub-Saharan Africa: Pneumonia [1], an immediate challenge became apparent - the lack of clarity and consistency in the definition and classification of pneumonia in the field of pneumonia care and research [2], as well as the lack of a safe and effective 'gold-standard' [3] to identify the causative organisms, further limiting an accurate diagnosis. The WHO's clinical definition of childhood pneumonia is the most commonly used in field studies and in the estimation of the global burden of childhood pneumonia [4]. A suspected case of pneumonia is determined by its clinical symptoms, as having cough and/or difficult breathing with fast breathing for age and/or indrawing of the lower chest wall, and/or any general danger signs [5]. However, this definition of pneumonia has low specificity and includes bacterial and viral pneumonia, viral bronchiolitis, bacterial and viral bronchitis [6] – conditions that can co-exist. This complex pathogenesis of respiratory tract infections, as well as the clinical overlap between them, presents major challenges in conceptualising a natural history model of specific diseases of lower respiratory tract infections. Many research studies now report on the burden of pneumonia in low-income and lower-middle-income countries as 'acute lower respiratory infections' (ALRIs), or 'lower respiratory tract infections' (LRTIs).

The term ALRI encloses the conditions with the codes CA40-45 in the International Classification of Disease (ICD) 11th revision.

For the TLO programme, our aim is to model the underlying disease conditions of a sick individual, who will present for care with signs and symptoms. Then, based on the diagnostic algorithm and diagnostic tests, the healthcare system assigns a disease classification and treatment. Therefore, the ALRI module attempts to differentiate pneumonia from other acute lower respiratory infections and their respective progression in the natural history, while when presented to the health system for care management, the disease is classified and treated based on their clinical presentation.

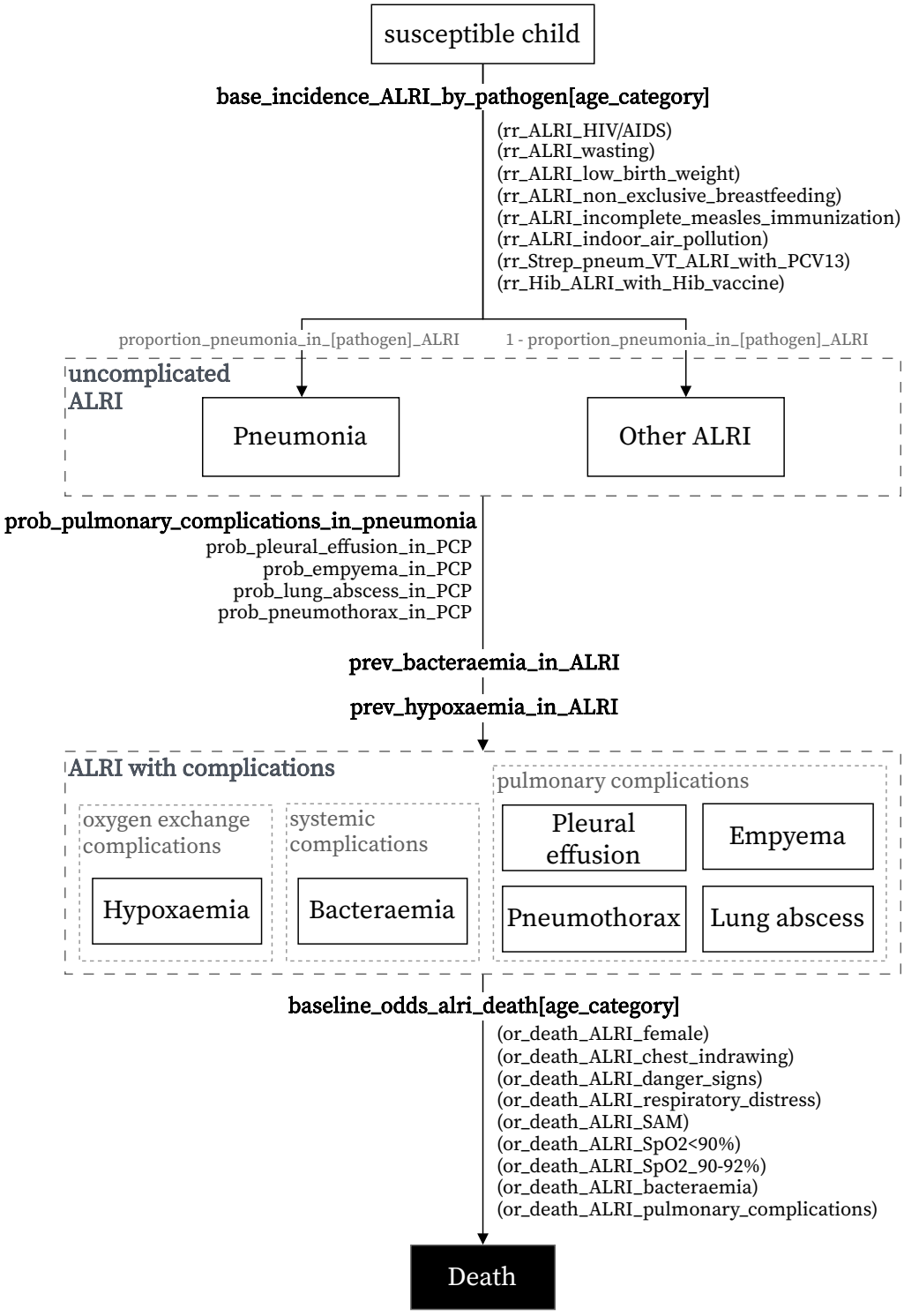
A.2.2 ALRI model structure

The model conceptualisation and parameterisation are interconnected due to the iterative nature of the modelling process and contingent on the data available to inform model behaviour.

In designing the natural history model structure, we reviewed the literature and medical textbooks to understand disease acquisition, progression, mortality, and available interventions. Simultaneously, we identified data-driven publications to inform parameter values, as data availability constrains the model scope. Priority was given to existing relevant systematic reviews. In their absence, recent studies from Malawi, neighbouring countries in southern East Africa, or other Sub-Saharan African countries were sought. Then, with the information collected, a disease model structure was designed in the form of flow diagrams illustrating the transitions between disease states. The model structure and assumptions were reviewed and verified by clinical experts (Dr. Eric McCollumn) at each iteration of the modelling process to ensure accuracy and clinical relevance.

Figure A.2 shows the conceptualised model structure of the natural history of ALRI. The main parameters are included in this illustration.

Figure A.2: Conceptual diagram of the ALRI natural history model



At the individual-level, a susceptible child aged under-5 can acquire a symptomatic acute lower respiratory infection based on the rate of incidence of a causal pathogen (listed in Table A.1). This incidence is associated by various risk factors intrinsic to the individual. Next, ALRI manifests as a respiratory disease, grouped in the ALRI model as Pneumonia or Other ALRI. Pneumonia consists of lung infections that would have abnormal chest radiographs at one

point in the clinical course of the disease. Whereas, Other ALRI includes bronchiolitis in infants and other infectious conditions of the lower respiratory tract, which clinically matches the WHO case definition of pneumonia. The reason for simplifying complex ALRI conditions into just two disease types is that modelling methods require the simplification of complex systems. The choice to filter out pneumonia from the rest of the ALRI conditions can be argued by its severity and its distinctive feature of abnormal radiography. As the disease progresses, in the absence of treatment, complications may arise and death may occur. These include oxygen exchange complications, pulmonary complications, and systemic complications. All the attributes of an ALRI episode are captured in the properties of this disease module described in Table A.1. In the simulation, these properties are updated for each individual with an ALRI episode.

Properties of the natural history

Each individual in the simulation takes the attributes assigned by the modules of the TLO model. The set of properties simulated in the ALRI module are listed in Table A.1, and these are applied to all individuals. For those individuals without an ALRI disease state, will have the properties set to 'False', 'None' or the baseline category, e.g. ri_SpO_2_level is set to '>=93%'.

The prefix 'ri_' stands for respiratory infection, used as a prefix representation of the properties of the ALRI module.

Table A.1 Property states determined by parameters and functions

Property	Description	Type and values	Initial state	Function
ri_current_infection_status	Current acute lower respiratory infection status	**Boolean** True / False	False	Determined by pathogen-attributed incidences
ri_primary_pathogen	Attributable primary pathogen for the acute lower respiratory infection episode	**Categorical**: 'RSV', 'Rhinovirus', 'HMPV', 'Parainfluenza', 'Strep_pneumoniae_PCV13', 'Strep_pneumoniae_non_PCV13', 'Hib', 'H.influenzae_non_type_b', 'Staph_aureus', 'Enterobacteriaceae'[*1], 'other_Strepto_Enterococci'[*2], 'Influenza', 'P. jirovecii', 'other_viral_pathogens'[*3], 'other_bacterial_pathogens'[*4], 'other_pathogens_NoS'[*5]	NaN	Equation (A.1)
ri_secondary_bacterial_pathogen	Secondary bacterial co-infection pathogens in the current ALRI episode	**Categorical**: 'Strep_pneumoniae_PCV13', 'Strep_pneumoniae_non_PCV13', 'Hib', 'H.influenzae_non_type_b', 'Staph_aureus', 'Enterobacteriaceae', 'other_Strepto_Enterococci', 'other_bacterial_pathogens'	NaN	prob_viral_pneumonia_bacterial_coinfection × proportion_bacterial_coinfection_pathogen

Continued on next page

Table A.1 – continued from previous page

Property	Description	Type and values	Initial state	Function
ri_disease_type	ALRI is divided into 2 disease types: Pneumonia, and Other ALRI	**Categorical**: 'pneumonia', 'other_alri'	NaN	base_inc_rate_ALRI_by_{pathogen} × proportion_pneumonia_in_{pathogen}_ALRI
ri_complication_pleural_effusion	Pleural effusion - pulmonary complication associated with ALRI event	**Boolean** True / False	False	prob_pulmonary_complications_in_pneumonia × prob_pleural_effusion_in_PCP
ri_complication_empyema	Empyema - pulmonary complication associated with ALRI event	**Boolean** True / False	False	prob_pulmonary_complications_in_pneumonia × prob_empyema_in_PCP
ri_complication_pneumothorax	Pneumothorax - pulmonary complication associated with ALRI event	**Boolean** True / False	False	prob_pulmonary_complications_in_pneumonia × prob_pneumothorax_in_PCP
ri_complication_lung_abscess	Lung abscess - pulmonary complication associated with ALRI event	**Boolean** True / False	False	prob_pulmonary_complications_in_pneumonia × prob_lung_abscess_in_PCP
ri_complication_Bacteraemia	Bacteraemia - systemic complication associated with ALRI event	**Boolean** True / False	False	Figures A.3 and A.4
ri_complication_hypoxaemia	Hypoxaemia - oxygen exchange complication associated with ALRI event	**Boolean** True / False	False	Figures A.3 and A.4
ri_SpO_2_level	Peripheral oxygen saturation (Sp02) measure by pulse oximetry	**Categorical**: '<90%', '90-92%', '>=93%'	'>=93%'	if ri_complication_hypoxaemia = True, apply proportion_hypoxaemia_with_SpO_2<90%
ri_start_of_current_episode	Date of onset of current ALRI event	**Date**	NaT	random date selection between the date of the current PollingEvent and a day prior to the next PollingEvent

Continued on next page

Table A.1 – continued from previous page

Property	Description	Type and values	Initial state	Function
ri_scheduled_recovery_date	(scheduled) Recovery date from current ALRI event	**Date**	NaT	ri_start_of_current_episode + duration of the episode (set between 1 day to 'max_alri_duration_in_days_without_treatment')
ri_scheduled_death_date	(scheduled) Death date from current ALRI event	**Date**	NaT	Equations (A.4) and (A.5), ri_start_of_current_episode + duration of the episode
ri_end_of_current_episode^{+}	Date on which the last episode of ALRI is resolved	**Date**	NaT	ri_start_of_current_episode + duration of the episode + days_between_treatment_and_cure

^{*1}Enterobacteriaceae includes: E. coli, Enterobacter species, and Klebsiella species.
^{*2}other_Strepto_Enterococci includes Streptococcus pyogenes and Enterococcus faecium.
^{*3}other_viral_pathogens includes Adenovirus, Bocavirus, Coronaviruses NL63, 229E OC43 and HKU1, Cytomegalovirus, Parechovirus/Enterovirus.
^{*4}other_bacterial_pathogens includes Bordetella pertussis, Chlamydophila pneumoniae, Legionella species, Mycoplasma pneumoniae, Moraxella catarrhalis, Non-fermenting gram-negative rods (Acinetobacter species and Pseudomonas species), Neisseria meningitides.
^{*5}other_pathogens_NoS includes all other pathogens not otherwise specified.
$^{+}$ri_end_of_current_episode - variable created for programming purpose, it is used to determine when a new episode can begin, and stops successive episodes interfering with one another.
NaN - Not a Number (numpy.nan is a Python float object, represents a missing value in the data)
NaT - Not a Time (numpy.datetime64 is a Python datetime object, NaT represents a missing date)

The following subsections provide detailed descriptions of each disease progression step within the proposed model structure, including parameterisation methods and data synthesis approaches used to inform the model.

A.2.3 Estimating ALRI incidence

The development and localisation of disease in the lower respiratory tract depend on a complex interaction between the pathogen, the host, and environmental factors. The incidence of ALRI disease is associated with host-related risk factors, including low birth weight, undernutrition, and HIV infection. It is also affected by external / environment-related factors, including lack of exclusive breastfeeding, household crowding (more than 7 people per household), exposure to indoor air pollution, and incomplete immunisation [7]. These risk factors are included in the model, except for household crowding (not captured in the Demography module), and only the severe form of undernutrition - wasting (weight-for-height <-2 standard deviations) - is included.

The aetiology of respiratory infections is age-specific: the overall incidence of acute respiratory infections is highest in early childhood and gradually decreases with age [8], reflecting the pattern of exposure to infection and the development of the child's immunity. In the model, the incidence of ALRI is distributed by age groups: 0-11, 12-23, and 24-59 months. In the estimation of WHO-defined pneumonia incidence in Malawi, the anonymised dataset of McCollum et al., 2017 observational study [9] was used. This study was carried out between January 1st, 2012 and June 30th, 2014 collecting data on clinical pneumonia in children under-5 from active surveillance in 7 hospitals, 18 health centres, and 38 community health workers in two districts in central Malawi. These cases of clinical pneumonia follow the Malawi guidelines, which were adapted from WHO clinical definitions of pneumonia (original guidelines 2005), and were further re-classified by hypoxaemia status (SpO2<90%).

Table A.2 provides the study data values used to estimate the incidence rate by age group. We included cases with admission dates between January and June 2012, because PCV13 vaccine coverage was below 50% during this period, allowing us to to inform incidence rates close to the TLO simulation start year of 2010 and to model the effect of vaccines. The study data provides the total cases seen in the set time period, as well as the pneumonia classification: fast-breathing pneumonia (non-severe), chest-indrawing (severe), and danger-signs pneumonia (very severe). With the total cases and severity classifications at different levels of the health system (hospital, health centres or village clinics), incidence rates can be estimated. This study used the Malawi Census 2008 report to derive the underlying population served by the health facilities in the study. Using this underlying population size, an overall incidence can be estimated.

The lack of specificity of WHO-defined pneumonia means that other non-respiratory conditions such as gastroenteritis, malaria, sepsis may be misclassified as pneumonia. A retrospective study evaluating diseases captured by the WHO definition found that 34% of children who met the WHO criteria for non-severe clinical pneumonia (with fast-breathing for age) had gastroenteritis or other non-respiratory infections, while 5% of severe pneumonia cases (with

lower chest wall indrawing) were not acute lower respiratory infections [10]. To account for this misclassification and, thus, the overestimation of incidence, we applied correction factors in the estimation: multiplying fast-breathing pneumonia cases by 0.66 (to remove 34% non-ALRI) and severe pneumonia cases by 0.95 (to remove 5% non-ALRI). This adjustment filters out non-ALRI cases that match the non-specific WHO pneumonia definition, ensuring the ALRI module models only true lower respiratory infections.

The total number of (corrected) ALRI cases was divided by the underlying population of the respective age group to calculate the monthly incidence per child. This value was then multiplied by 100 children and 12 months to obtain the final incidence per 100 child-years.

Table A.2 Calculation of WHO-pneumonia incidence using McCollum et al., 2017 study data, time period January to June 2012

	<12 months		12-23 months		24-59 months		Total	
	cases	pop	cases	pop	cases	pop	cases	pop
total cases seen in VC, HC, hosp	2396	43119	1222	39930	1147	108617	4765	191665
fb-pneumonia	756		512		656		1924	
severe & very severe pneumonia	1640		710		491		2841	
referred severe cases	269		122		107		498	
Treatment failure return (assumed)	10%							
proportion non-ALRI in fb-pneumonia [10]	34%							
proportion non-ALRI in severe pneumonia [10]	5%							
total - (referred & non-ALRI)	1621		807		718		3146	
Incidence per 100 child-years (2012)	**45.12**		**24.25**		**7.93**		**19.70**	
% change incidence 2012-2024 [11]	23.52% *							
Incidence per 100 child-years (2024)	**34.51**		**18.55**		**6.07**		**15.06**	

Note: cases include all pneumonia cases seen at the hospital (hosp), health centre (HC) and village clinics (VC) within the study during the admission dates between 1st January and 30th June 2012
fb-pneumonia = fast-breathing only pneumonia defined by WHO
pop = underlying population served by the health facilities in the study, estimates derived from Malawi Census 2008 Main Report
The total ALRI cases in the calculation of incidence is the result of a subtraction of 'total cases seen in VC, HC, hosp' by the 'referred severe cases' to avoid duplication, and further subtracting potential non-ALRI cases from that difference.
* % change from 2012 to 2024 estimated using the average change per year from 1990 to 2021 incidence in Sub-Saharan Africa from source [11]. 60.762% change divided by 31 years = 1.96% change per year. Applied for 12 years from 2012 = 23.52% change to 2024.

During that time period (January to June 2012), we estimated ALRI incidence rates in Malawi were 45.12 per 100 child-years among children under 12 months, 24.25 per 100 child-years for ages 12-23 months, and 7.93 per 100 child-years for ages 24-59 months (Table A.2). The overall incidence was 19.7

episodes per 100 child-years, which is consistent with the estimates from the modelling study by McAllister et al. 2019, who reported an incidence of 22.1 episodes per 100 children in 2015 for Malawi[12]. However, this estimate was notably higher than that of the Global Burden of Disease (GBD), which reported 13 episodes per 100 children for 2010. These differences have previously been described by Kovacs et al., 2015 [13], highlighting how methodological approaches in data inclusion, processing, and modelling can lead to substantially different mortality estimates for the same diseases and time period.

Then, projecting to 2024, the 2012 incidence estimates were reduced by 23.52%, based on an average annual decline in incidence of 1.96% in Sub-Saharan Africa [11]. The estimated ALRI incidence in Malawi in 2024 was overall 15.06 cases per 100 child-years in the under-5s, with age-specific rates of 34.51, 18.55, and 6.07 cases per 100 child-years in children under 1 year, 1-2 years, and 2-5 years, respectively.

Incidence by ALRI disease type

As illustrated in the model structure in Figure A.2, the complex ALRI disease system was simplified into two disease types: Pneumonia and Other ALRI. Since each disease type sets a different clinical course, the model requires separate incidence estimates for each type. Therefore, the ALRI incidence estimates (Table A.2) were further disaggregated by disease type. To achieve this, assumptions were made about the relationship between chest radiography findings and ALRI disease syndromes, as described below.

Chest radiography (CXR) is the most widely used test to confirm pneumonia diagnosis; however, this method is not indicated in ambulatory settings and cannot distinguish viral and bacterial pneumonia [14]. Although negative chest radiography (CXR-) excludes pneumonia in most children [15], chest radiographs may not show evidence of pneumonia in early stages of infection, and there is variation in intraobserver and interobserver agreement.

The findings of the Pneumonia Etiology Research for Child Health (PERCH) study informed the parameterisation of ALRI incidence by causal pathogen. This multi-site, hospital-based case-control study (cases were children aged 1–59 months admitted to hospital with severe pneumonia; controls were age-group-matched children randomly selected from communities surrounding study sites) identified the infectious agents causing severe and very severe pneumonia (WHO 2005 definitions) among children aged 1-59 months, stratified by chest radiography results: abnormal (CXR+) versus normal (CXR-) [16]. Among children with clinically severe and very severe pneumonia, 44.44% had confirmed abnormal chest x-ray (CXR+), showing either by consolidation or infiltrates. This proportion is consistent with Begom et al., 2018, who assessed clinical and radiological parameters of severe pneumonia (as per revised guidelines 2013) in Bangladeshi children aged 2-59 months and found that 40% were diagnosed radiologically as pneumonia and 60% as bronchiolitis [17]. For non-severe pneumonia, previous studies showed that 14% had radiological evidence of pneumonia [18].

To account for potential missed cases, the PERCH CXR+ proportions were adjusted using sensitivity and specificity values from a meta-analysis compar-

ing the accuracy of lung ultrasound and chest X-rays for the diagnosis of paediatric community-acquired pneumonia, against the gold standard of clinical diagnosis by expert paediatricians. The sensitivity and specificity values of chest radiography were 86.8% and 98.2%, respectively [19].

The estimated proportion of CXR+ in the ALRI incident cases between January to June 2012 from McCollum et al., 2017 (Table A.2) is 33.38%.

$$\text{CXR+} = \frac{(1924 \times 0.66 \times 0.14) + ((2841 - 498) \times 0.95 \times 0.4444)}{(1924 \times 0.66) + (2343 \times 0.95)} = 0.3338$$

Then, adjusting the CXR+ proportion for the sensitivity (86.8%) and specificity (98.2%) of chest radiography against the gold standard of paediatrician diagnosis yielded an overall proportion of 37.2% for the Pneumonia disease type within ALRI cases. This value was used to differentiate ALRI cases into pneumonia and other non-pneumonia ALRI as the underlying pathology.

Pathogen-attributed incidence

Pathogen-attributable fractions (AFs) of the PERCH study were used to calculate pathogen-attributed ALRI incidence. The pathogen AFs for CXR+ cases are provided in their Supplementary Table 10 [16]. Upon request, the PERCH study team provided pathogen AFs of all cases to the TLO project, the values of Supplementary Figure 7 of the main article of the study [16]. The pathogen AF data were stratified by age: <1 year, and ≥1 year, across all study sites combined. Using the AFs for all cases, AFs for CXR+ cases, and respective case numbers (N), the AFs for CXR- cases were calculated.

$$\text{AF CXR}- = \frac{(\text{AF CXR}_{\text{all}} \times \text{N CXR}_{\text{all}}) - (\text{AF CXR}+ \times \text{N CXR}+)}{\text{N CXR}-}$$

Table A.3 shows all the values used in the estimation of pathogen-attributed incidence of ALRI. The pathogen AFs in the CXR+ cases are used to estimate each pathogen-attributed incidence of Pneumonia, and AFs of CXR- are used to estimate each pathogen-attributed incidence of Other ALRI. The two sets of pathogen AFs, each with separate values by age group (<1 and ≥1) are used in the estimation of respective incidences by age per pathogen, values to input the model parameters of ALRI incidence.

$$\text{Pneumonia incidence} = \text{ALRI incidence} \times 0.372$$
$$\text{Other ALRI incidence} = \text{ALRI incidence} \times (1 - 0.372)$$

Table A.3 Estimated incidence (per 100-child-years) of Pneumonia, Other ALRI and total ALRI by age group per pathogen

					Pneumonia incidence / age group (in months)			Other ALRI incidence / age group (in months)			Total ALRI incidence / age group (in months)		
					0-11	12-23	24-59	0-11	12-23	24-59	0-11	12-23	24-59
	Pathogen-attributed fractions				12.837	6.899	2.257	21.671	11.646	3.810	34.508	18.545	6.067
	Pneumonia (CXR+)		Other ALRI (CXR-)		Pneumonia incidence by age by pathogen			Other ALRI incidence by age by pathogen			ALRI incidence by age by pathogen		
Pathogens	<1 yo	≥ 1 yo	<1 yo	≥ 1 yo									
RSV	0.397	0.165	0.342	0.129	5.096	1.138	0.372	7.405	1.505	0.492	12.501	2.643	0.865
Rhinovirus	0.029	0.154	0.073	0.273	0.372	1.062	0.348	1.572	3.174	1.038	1.945	4.236	1.386
HMPV	0.083	0.061	0.060	0.030	1.065	0.421	0.138	1.295	0.349	0.114	2.360	0.770	0.252
Parainfluenza	0.078	0.067	0.096	0.036	1.001	0.462	0.151	2.089	0.419	0.137	3.091	0.881	0.288
S. pneumoniae PCV13	0.018	0.078	0.019	0.000	0.392	0.912	0.267	0.696	0.000	0.000	1.088	0.912	0.267
S. pneumoniae non-PCV13	0.029	0.024	0.016	0.021	0.372	0.166	0.054	0.340	0.240	0.079	0.713	0.406	0.133
Hib	0.015	0.012	0.006	0.006	0.962	0.414	0.135	0.684	0.368	0.120	1.646	0.781	0.256
H. influenzae non-type-b	0.044	0.048	0.036	0.017	0.565	0.331	0.108	0.774	0.195	0.064	1.339	0.526	0.172
Staphylococcus	0.037	0.01	0.061	0.004	0.475	0.069	0.023	1.332	0.044	0.014	1.807	0.113	0.037
Influenza	0.016	0.028	0.010	0.032	0.205	0.193	0.063	0.223	0.377	0.123	0.428	0.570	0.186
P.jirovecii	0.03	0.004	0.006	0.000	0.385	0.028	0.009	0.128	0.000	0.000	0.513	0.028	0.009
Enterobacteriaceae	0.022	0.025	0.044	0.021	0.282	0.172	0.056	0.959	0.243	0.079	1.242	0.415	0.136
other Strepto/Enterococci	0.021	0.024	0.005	0.010	0.270	0.166	0.054	0.102	0.114	0.037	0.371	0.280	0.092
other viral	0.039	0.093	0.083	0.164	0.501	0.642	0.210	1.792	1.910	0.625	2.293	2.552	0.835
other bacterial	0.056	0.106	0.090	0.109	0.719	0.731	0.239	1.949	1.274	0.417	2.668	2.006	0.656
other pathogens NoS	0.02	0.057	0.032	0.126	0.257	0.393	0.129	0.689	1.465	0.479	0.946	1.858	0.608
Total	0.934	0.956	0.978	0.977	12.919	7.300	2.356	22.030	11.677	3.820	34.949	18.977	6.176

The total pathogen AFs does not sum up to 1, because TB-attributed fraction was excluded from the ALRI incidence. TB has its own module within TLO. Incidences of Hib and S. pneumoniae PCV13-attributed ALRI were adjusted for coverage and effectiveness of their respective vaccines: 93% coverage in 2012 and 86% effectiveness of Hib vaccine, and 50% coverage in 2012, 82% and 68% effectiveness of PCV13 vaccine in ages less than two and between two to five years, respectively (Table A.3). Thus, the total Pneumonia/ Other ALRI/ All ALRI incidence does not sum up to the incidence estimated in Table A.2.

$$
\begin{aligned}
Y_{Inc_{patho[age]}} = {} & \textbf{base\_inc\_rate\_ALRI\_by\_[pathogen][age]} \times \\
& (\textbf{rr\_ALRI\_low\_birth\_weight} \cdot \text{nb\_low\_birth\_weight\_status}) \times \\
& (\textbf{rr\_ALRI\_HIV/AIDS} \cdot \text{hv\_inf}) \times \\
& (\textbf{rr\_ALRI\_wasting} \cdot \text{un\_WHZ\_category}) \times \\
& (\textbf{rr\_ALRI\_non\_exclusive\_breastfeeding\_status} \cdot \text{nb\_breastfeeding}) \times \\
& (\textbf{rr\_ALRI\_indoor\_air\_pollution} \cdot \text{li\_wood\_burn\_stove}) \times \\
& (\textbf{rr\_ALRI\_incomplete\_measles\_vaccination} \cdot \text{va\_measles\_all\_doses}) \times \\
& (\textbf{rr\_Strep\_pneum\_VT\_ALRI\_with\_PCV13\_age<2y} \cdot \text{ri\_primary\_pathogen} = \text{`Strep\_pneumoniae\_PCV13'} \cdot \\
& \quad \text{va\_pneumo\_all\_doses} \cdot \text{age\_years} < 2) \times \\
& (\textbf{rr\_Strep\_pneum\_VT\_ALRI\_with\_PCV13\_age2to5y} \cdot \text{ri\_primary\_pathogen} = \text{`Strep\_pneumoniae\_PCV13'} \cdot \\
& \quad \text{va\_pneumo\_all\_doses} \cdot 2 < \text{age\_years} \leq 5) \times \\
& (\textbf{rr\_Hib\_ALRI\_with\_Hib\_vaccine} \cdot \text{ri\_primary\_pathogen} = \text{`Hib'} \cdot \text{va\_hib\_all\_doses})
\end{aligned}
\tag{A.1}
$$

Property	**Category/Status (Xi = 1)**
nb_low_birth_weight_status	True
hv_inf	True
un_WHZ_category	'WHZ<-3' or '-3<=WHZ<-2'
nb_breastfeeding_status	'none' or 'non-exclusive'
li_wood_burn_stove	True
va_measles_all_doses	False
va_pneumo_all_doses	True
va_hib_all_doses	True

$Y_{Inc_{patho[age]}}$ = Incidence rate of pathogen-attributed [patho] ALRI in age group [age]

The incidence model is calibrated by first fitting an unadjusted linear regression, then adjusting the intercept of the fitted model to match the input incidence values, before applying vaccine effectiveness.

Table A.4 Parameters of ALRI incidence

Parameters [name]	Value	Source
Baseline incidence rate of symptomatic ALRI caused by RSV, by age group [1-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_RSV]**	[0.1250, 0.0264, 0.0086]	ALRI incidences were calculated using data from [9] and [16] + assumptions based on other sources as described above
Baseline incidence rate of symptomatic ALRI caused by Rhinovirus, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_Rhinovirus]**	[0.0194, 0.0424, 0.0139]	
Baseline incidence rate of symptomatic ALRI caused by HMPV, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_HMPV]**	[0.0236, 0.0077, 0.0025]	
Baseline incidence rate of symptomatic ALRI caused by Parainfluenza, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_Parainfluenza]**	[0.0309, 0.0088, 0.0029]	
Baseline incidence rate of symptomatic ALRI caused by Streptococcus pneumoniae PCV13-type, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_Strep_pneumoniae_PCV13]**	[0.0109, 0.0091, 0.0027]	
Baseline incidence rate of symptomatic ALRI caused by Streptococcus pneumoniae non-PCV13-type, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_Strep_pneumoniae_non_PCV13]**	[0.0071, 0.0041, 0.0013]	
Baseline incidence rate of symptomatic ALRI caused by Haemophilus influenzae type-b, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_Hib]**	[0.0165, 0.0078, 0.0026]	
Baseline incidence rate of symptomatic ALRI caused by Haemophilus influenzae non-type-b, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_-H.influenzae_non_type_b]**	[0.0134, 0.0053, 0.0017]	
Baseline incidence rate of symptomatic ALRI caused by Staphylococcus aureus, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_Staph_aureus]**	[0.0181, 0.0011, 0.0004]	
Baseline incidence rate of symptomatic ALRI caused by Enterobacteriaceae, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_Enterobacteriaceae]**	[0.0043, 0.0057, 0.0019]	
Baseline incidence rate of symptomatic ALRI caused by Streptococci and Enterococci, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_Strepto_Enterococci]**	[0.0051, 0.0003, 0.0001]	
Baseline incidence rate of symptomatic ALRI caused by Influenza, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_Influenza]**	[0.0124, 0.0042, 0.0014]	

Continued on next page

Table A.4 – continued from previous page

Parameters [name]	Value	Source
Baseline incidence rate of symptomatic ALRI caused by P.jirovecii, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_P.jirovecii]**	[0.0037, 0.0028, 0.0009]	
Baseline incidence rate of symptomatic ALRI caused by OtherViral, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_other_viral_pathogens]**	[0.0229, 0.0255, 0.0083]	
Baseline incidence rate of symptomatic ALRI caused by other viral pathogens, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_other_bacterial_pathogens]**	[0.0267, 0.0201, 0.0066]	
Baseline incidence rate of symptomatic ALRI caused by other pathogens not otherwise specified, by age group [0-11, 12-23, 24-59 months] **[base_inc_rate_ALRI_by_other_bacterial_pathogens]**	[0.0095, 0.0186, 0.0061]	
Relative risk of ALRI incidence for infants with low birth weight **[rr_ALRI_low_birth_weight]**	3.6	[7]
Relative risk of ALRI incidence for children with untreated HIV/AIDS **[rr_ALRI_HIV/AIDS]**	4.6	[7]
Relative risk of ALRI incidence for wasted children WHZ<-2 **[rr_ALRI_wasting]**	2.8	[7]
Relative risk of ALRI incidence for children under-2 years of age not exclusively breastfed **[rr_ALRI_non_exclusive_breastfeeding]**	2.7	[7]
Relative risk of ALRI incidence for indoor air pollution **[rr_ALRI_indoor_air_pollution]**	1.6	[7]
Relative risk of ALRI incidence for incomplete measles vaccination **[rr_ALRI_incomplete_measles_immunisation]**	1.8	[7]
Relative risk of S. pneumoniae PCV13-type-attributed ALRI incidence for children under-2 years of age with complete PCV13 vaccination **[rr_Strep_pneum_VT_ALRI_with_PCV13_age<2y]**	0.18	[20]
Relative risk of S. pneumoniae PCV13-type-attributed ALRI incidence for children aged 2-5 years with complete PCV13 vaccination **[rr_Strep_pneum_VT_ALRI_with_PCV13_age2to5y]**	0.32	[20]
Relative risk of Hib-attributed ALRI incidence for children with complete Hib vaccination **[rr_Hib_ALRI_with_Hib_vaccine]**	0.14	[21]

Values in list ordered by age group [0-11, 12-23, 24-59 months] - values matching the ALRI incidence by age per pathogen on Table A.3 divided by 100 children to make an incidence rate per child per year

Table A.5 Parameters to breakdown ALRI incidence into disease types

Parameters [name]	Value	Source
Proportion of pneumonia disease type in RSV-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_RSV_ALRI]**	[0.4077, 0.4307]	The fractions were calculated using chest radiography data provided by the PERCH study group and their published data [16]
Proportion of pneumonia disease type in Rhinovirus-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_Rhinovirus_-ALRI]**	[0.1914, 0.2508]	
Proportion of pneumonia disease type in HMPV-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_HMPV_ALRI]**	[0.4514, 0.5464]	
Proportion of pneumonia disease type in Parainfluenza-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_Parainfluenza_-ALRI]**	[0.3240, 0.5244]	
Proportion of pneumonia disease type in Streptococcus pneumoniae PCV13-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_Strep_pneumoniae_PCV13_ALRI]**	[0.3601, 1]	
Proportion of pneumonia disease type in Streptococcus pneumoniae non-PCV13 type-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_Strep_pneumoniae_non_PCV13_ALRI]**	[0.5224, 0.4082]	
Proportion of pneumonia disease type in Haemophilus influenzae type-b-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_Hib_ALRI]**	[0.5843, 0.5293]	
Proportion of pneumonia disease type in Haemophilus influenzae non-type-b-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_H.influenzae_-non_type_b_ALRI]**	[0.4218, 0.6292]	
Proportion of pneumonia disease type in Staphylococcus aureus-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_Staph_aureus_-ALRI]**	[0.2628, 0.6106]	
Proportion of pneumonia disease type in Enterobacteriaceae-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_Enterobacteriaceae_ALRI]**	[0.4800, 0.3390]	
Proportion of pneumonia disease type in Streptococci and Enterococci-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_other_Strepto_-Enterococci_ALRI]**	[0.7509, 1]	
Proportion of pneumonia disease type in Influenza-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_Influenza_ALRI]**	[0.2275, 0.4156]	
Proportion of pneumonia disease type in P. jirovecii-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_P.jirovecii_ALRI]**	[0.7261, 0.5918]	

Continued on next page

Table A.5 – continued from previous page

Parameters [name]	Value	Source
Proportion of pneumonia disease type in other viral pathogens-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_other_viral_-pathogens_ALRI]**	[0.2183, 0.2514]	
Proportion of pneumonia disease type in other bacterial pathogens-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_other_bacterial_-pathogens_ALRI]**	[0.2694, 0.3646]	
Proportion of pneumonia disease type in other pathogens NoS-attributed ALRI per age group [<1, ≥1 year] **[proportion_pneumonia_in_other_-pathogens_NoS_ALRI]**	[0.2714, 0.2116]	
Probability of viral/bacterial co-infection **[prob_viral_pneumonia_bacterial_coinfection]**	0.333	[22]
Proportion of bacterial pathogens in co-infections **[proportion_bacterial_coinfection_pathogen]**		assumed based on PERCH results [16]
Strep_pneumoniae_PCV13 -	0.1073,	
Strep_pneumoniae_non_PCV13 -	0.0715,	
Hib -	0.0377,	
H.influenzae_non_type_b -	0.1410,	
Staph_aureus -	0.1344,	
Enterobacteriaceae -	0.1173,	
other_Strepto_Enterococci -	0.0524,	
other_bacterial_pathogens -	0.3385	

The proportion of Pneumonia cases in ALRI by causal pathogen, were calculated from the fraction of incidence of Pneumonia over ALRI incidence for ages <1 and ≥1 years (Table A.3). The fraction for the older age groups - 12-23, 24-59 months, are grouped under ≥1 years of age, since the pathogen attributable fractions (both CXR+ and CXR-) is the same value for the ≥1.

The input incidence values serve as target values for model calibration. The calibration process involves fitting an unadjusted linear regression to the baseline data, then adjusting the intercept to ensure the model output matches the target incidence values. Only then is vaccine effectiveness applied to the adjusted baseline incidence, and further split by disease type and co-infection rates.

A.2.4 Progression to severe disease

Depending on the site of infection, as well as the type of invasive pathogen, viral or bacterial cause, or co-infection, the host will deploy an array of innate and acquired cellular and humoral defences [23], and a range of disease-associated symptoms and complications can arise.

The model simulates progression of disease through the incorporation of complications arising from a lower respiratory tract infection. These complications include those that occur locally in the pulmonary system, systemically if the infection enters the bloodstream (bacteraemia), and complications related to oxygen exchange, categorised in the model structure as shown in Figure A.2. The complications included in the ALRI disease model are the most common ones arising from pneumonia and bronchiolitis, conditions for which the care

management is included in the WHO guidelines for hospital inpatient care for children [24]. Table A.6 introduces the complications modelled.

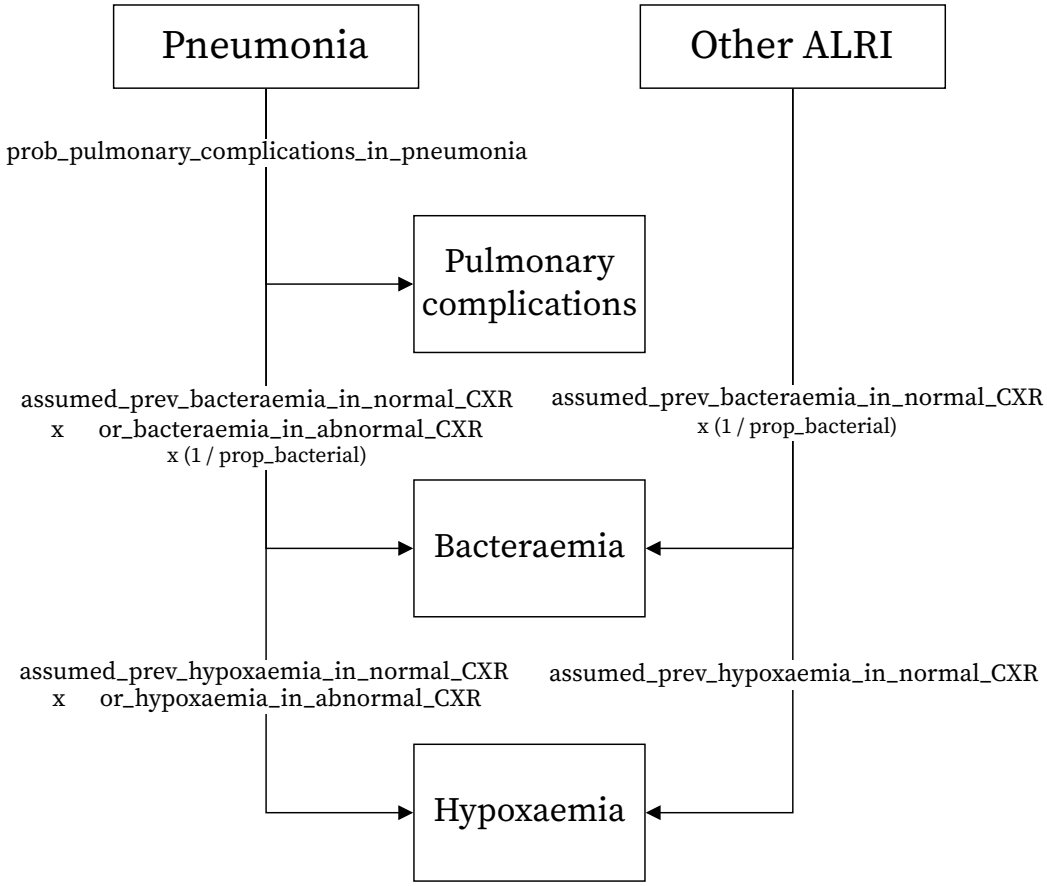
Table A.6 Complications included in the ALRI model and respective description

Complications	Description
Hypoxaemia	Acute respiratory failure, Type I - When acute respiratory failure causes a low level of oxygen in the blood without a high level of carbon dioxide, it's called hypoxemic acute respiratory failure (ICD-11) [25]
Pleural effusion	Presence of fluid in the pleural cavity resulting from excessive transudation or exudation from the pleural surfaces (ICD-11) [25]
Empyema	Suppurative inflammation of the pleural space, typically due to acute bacterial infection (IDC-11) [25]
Lung abscess	A pus-filled cavity in the lung surrounded by inflamed tissue and caused by an infection (MSD) [26]
Pneumothorax	An abnormal collection of air or gas in the pleural space that separates the lung from the chest wall, and that may interfere with normal breathing (ICD-11) [25]
Bacteraemia	The presence of bacteria in the blood. A positive blood culture without signs of infection (ICD-11) [25]

Generally, complications are more common in bacterial pneumonia than in atypical or viral pneumonia. Risk factors for disease progression or development of complications include neonatal age, low birth weight, premature infants, underlying heart or lung conditions, and impaired immune system, such as untreated HIV infection, and malnutrition. However, these risk factors were not incorporated into the severe disease progression modelling, because their effects are already captured in the incidence and mortality rate parameters. Introducing additional risk multipliers for disease severity would bias the ALRI case pool toward high-risk individuals, potentially overestimating the contribution of these risk factors to disease outcomes. Typically, research studies examining the association of risk factors focus on either incidence, severity, or mortality alone, resulting in risk factors not being assessed at each stage while accounting for their effects on other processes in the course of the disease.

In modelling the onset of complications, both ALRI disease type and causal pathogens were incorporated. Disease type determines the probability of complications, as presented in Figure A.3 with parameters reflecting the difference in risk between pneumonia and other ALRI. Certain pulmonary complications, namely empyema and lung abscess, are restricted to bacterial aetiologies. Additionally, pulmonary complications increase the risk of bacteraemia and hypoxaemia, as illustrated in Figure A.4. This complication applies only to Pneumonia disease type, as pulmonary complications are not modelled for Other ALRI, due to their rare occurrence in non-pneumonia ALRI cases and insufficient data to inform these probabilities.

Figure A.3: Overview of complications arising in Pneumonia and Other ALRI



Note:
normal_CXR refers to ri_disease_type = 'Other ALRI'
abnormal_CXR refers to ri_disease_type = 'Pneumonia'
assumed_prev values are adjusted based on overall prevalence of complication and odds ratio of complication by disease type (Equation (A.3)), and odds ratios are converted to relative risks (Equation (A.2))

As presented in Figure A.3, both Pneumonia and Other ALRI disease types can progress to a complicated state with bacteraemia and hypoxaemia, while only Pneumonia has the probability of acquiring pulmonary complications. The prevalence of bacteraemia in ALRI (*prev_bacteraemia_in_alri*), value presented in Table A.8, covers both the prevalence of bacteraemia in Other ALRI (*assumed_prev_bacteraemia_in_normal_CXR*) and the prevalence of bacteraemia in Pneumonia (*assumed_prev_bacteraemia_in_normal_CXR* × *or_bacteraemia_in_abnormal_CXR*). Given the high sensitivity (86.8%) and specificity (98.2%) of chest radiography for pneumonia against the gold standard [19], source estimates for '*abnormal_CXR*', as named in the parameters, is assumed to be equivalent to pneumonia disease, while '*normal_CXR*' is applicable to other non-pneumonia ALRI. The same applies to hypoxaemia: the prevalence of hypoxaemia in ALRI (*prev_hypoxaemia_in_alri*) covers both the prevalence of hypoxaemia in Other ALRI (*assumed_prev_hypoxaemia_in_normal_CXR*) and the prevalence of hypoxaemia in Pneumo-

nia (*assumed_prev_hypoxaemia_in_normal_CXR* × *or_hypoxaemia_in_abnormal_CXR*).

The reference group prevalence values ('assumed_prev_' parameters), initially assumed a value for, are calibrated to ensure that when combined with the risk group (using the odds ratio), the resulting weighted average matches the target overall prevalence. This calibration step is covered by the following equations:

$$\text{RR} = \frac{\text{OR}}{(1 - \text{prob\_ref}) + (\text{prob\_ref} \times \text{OR})} \tag{A.2}$$

$$\text{adjusted\_p} = \frac{\text{Prevalence}}{\text{prop\_case\_group} \times \text{RR} + (1 - \text{prop\_case\_group})} \tag{A.3}$$

OR = odds ratio of the case group for the outcome
prob_ref = prevalence of outcome in reference group
prop_case_group = proportion of case group over total (case + ref group)
Prevalence = overall prevalence (in both groups)
adjusted_p = adjusted prevalence value of reference group

The Equation (A.2) converts the odds ratio (OR) into a relative risk (RR). Then, having the RR, the prevalence value in the reference group can be adjusted to match the overall prevalence through the Equation (A.3).

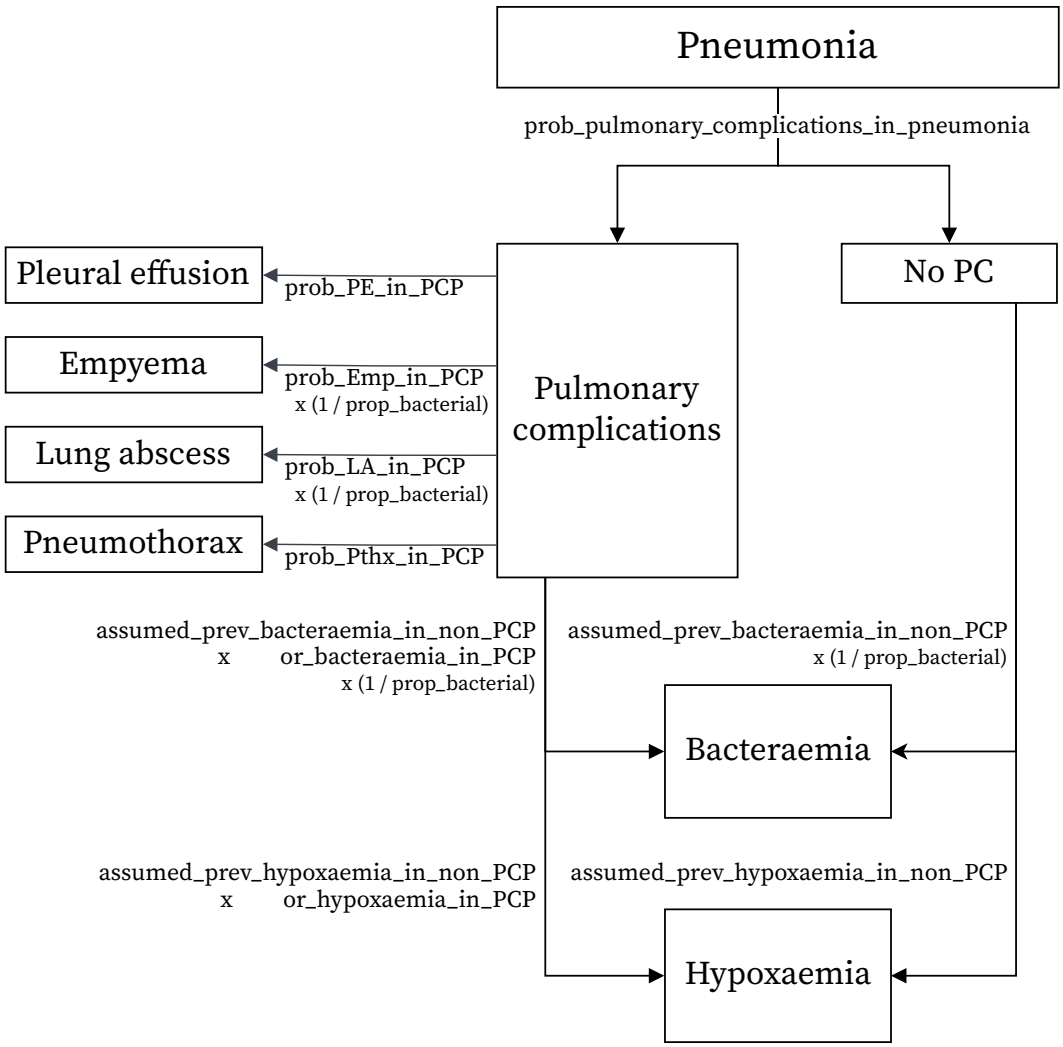
For example, the relationship between the probability of hypoxaemia in Pneumonia versus Other ALRI is described by an odds ratio (parameter *or_hypoxaemia_in_abnormal_CXR*, value presented in Table A.8; abnormal CXR values were applied to the pneumonia disease type). The odds ratio is converted to relative risk using Equation (A.2), then used to calibrate the parameter *assumed_prev_hypoxaemia_in_normal_CXR* through Equation (A.3). Other parameters required for this estimation are *prev_hypoxaemia_in_alri*, and *proportion_pneumonia_in_alri* (proportion of the case group, output from the model simulation). Table A.8 lists their respective values, which are used in the calculations below.

$$\text{RR} = \frac{2.07}{(1 - 0.1875) + (0.1875 \times 2.07)} = 1.7241$$

$$\text{adjusted\_p} = \frac{0.219}{0.372 \times 1.7241 + (1 - 0.372)} = 0.1725$$

The 'adjusted_p' represents the adjusted prevalence value in the reference group, which in this example is the probability of hypoxaemia in Other ALRI (parameter *assumed_prev_hypoxaemia_in_normal_CXR*). This calibrated value is used to set the baseline hypoxaemia risk in Other ALRI and, when multiplied by the relative risk (RR), determines the probability of hypoxaemia in Pneumonia disease type. The same calibration method is applied to bacteraemia parameters.

Figure A.4: Links between complications in pneumonia disease



where:
PCP = pulmonary complicated pneumonia
odds ratios (or_bacteraemia/hypoxaemia_in_PCP) are converted to relative risks in the simulation (Equation (A.2))
'assumed_prev_' parameter values are adjusted in the simulation based on overall prevalence of bacteraemia or hypoxaemia in pneumonia and odds ratio of bacteraemia or hypoxaemia by pulmonary complicated status (Equation (A.3))

If the disease type is pneumonia, a probability of pulmonary complications developing in the course of disease is applied, and a set of pulmonary complications can occur, each with a given probability of onset. Complications such as empyema and lung abscess are restricted to cases with a bacterial aetiology, either as the primary pathogen or as a secondary pathogen in a co-infection. As illustrated in Figure A.4 the term $\times(1/\text{prop\_bacterial})$ increases the *prob_empyema/lung_abscess_in_PCP* according to the proportion of bacterial causes of pneumonia to output an overall probability value matching the source [27]. When pneumonia is complicated by pulmonary complications, the probability of bacteraemia and hypoxaemia is greater compared to non-pulmonary complicated pneumonia. This is reflected in the odds ratio

parameters *or_bacteraemia_in_PCP* and *or_hypoxaemia_in_PCP*, which are converted to relative risks during simulation to adjust the prevalence values of the reference group (non-pulmonary complicated pneumonia) parameters *assumed_prev_bacteraemia_in_non_PCP* and *assumed_prev_hypoxaemia_in_non_PCP*, respectively. This follows the same rational as the example given for hypoxaemia in pneumonia versus other ALRI.

Estimating the prevalence of hypoxaemia

The recent systematic review and meta-analysis study on the prevalence of hypoxaemia in children with pneumonia in low- and middle-income countries [28] has reported a pooled 28% prevalence of hypoxaemia among children with WHO-classified pneumonia in the Africa region. Malawi was one of the countries included in the study. Table A.7 describes the studies included in the estimation of prevalence of hypoxaemia for the ALRI model.

Table A.7 Calculation of hypoxaemia prevalence

Study [Reference]	Cases	Total	Description
McCollum et al. 2013 [29]			Hypoxaemic cases (SpO2<90%)
SpO2<90%	27	159	in pneumonia diagnosis
McCollum et al. 2019 [30]			
SpO2<90%	415	644	Severe hospitalised cases
SpO2 90-92%	38		
McCollum et al. 2017 [9]			Cases from Hospitals,
SpO2<90%	2289	27586	Health centres and community
SpO2 90-92%	2411		
Lanahan et al. 2020 [31]			Non-severe cases
SpO2 90-92%	37	436	
Total	5217	28825	Total hypoxaemic cases in WHO-pneumonia

Malawi-based studies McCollum et al. 2016 [32] and Hooli et al. 2020 [33] included in the pooled estimate for hypoxaemia prevalence in the meta-analysis [28], were excluded in the data synthesis for the model as they use the same dataset as per McCollumn et al. 2017 [9]

The total number of WHO-pneumonia cases pooled from the four studies was adjusted to remove non-ALRI cases, as previously done in the incidence calculation. From the McCollumn et al. 2017 dataset, the proportions of WHO classifications were: 20.25% for very severe, 35.35% for severe, and 44.4% for non-severe pneumonia.

Pooling the denominators of McCollum et al. 2017 and Lanahan et al. 2020 to remove non-ALRI cases: 27586 + 436 = 28022.

$$\text{Removed non-ALRI} = 28022 \times 0.444 \times 0.66 + 28022 \times 0.556 \times 0.95 = 23013$$

$$\text{Total ALRI} = 23013 + 159 + 644 = 23816$$

$$\text{Prevalence} = \frac{5217}{23816} = 21.91\%$$

Table A.8 Parameters of disease progression

Parameters [name]	**Value**	**Source**
Probability of pulmonary complications in pneumonia disease type (CXR+) **[prob_pulmonary_complications_in_pneumonia]**	0.215	[27]
Probability of pleural effusion in pulmonary complicated pneumonia **[prob_pleural_effusion_in_PCP]**	0.938	[27]
Probability of empyema in pulmonary complicated pneumonia **[prob_empyema_in_PCP]**	0.315	[27]
Probability of lung abscess in pulmonary complicated pneumonia **[prob_lung_abscess_in_PCP]**	0.049	[27] *1
Probability of pneumothorax in pulmonary complicated pneumonia **[prob_pneumothorax_in_PCP]**	0.049	[27]
Prevalence of hypoxaemia in ALRI **[prev_hypoxaemia_in_alri]**	0.219	[9, 29–31] + assumptions *2
Odds ratio of hypoxaemia in pneumonia disease type (CXR+) **[or_hypoxaemia_in_abnormal_CXR]**	2.07	[34]
Assumed prevalence of hypoxaemia in other ALRI disease type (CXR-) **[assumed_prev_hypoxaemia_in_normal_CXR]**	0.1875 *3	assumed based on [35]
Prevalence of bacteraemia in ALRI **[prev_bacteraemia_in_alri]**	0.0514	[36]
Assumed prevalence of bacteraemia in other ALRI disease type (CXR-) **[assumed_prev_bacteraemia_in_normal_CXR]**	0.039	model output 'adjusted_p'
Odds ratio of bacteraemia in pneumonia disease type (CXR+) **[or_bacteraemia_in_abnormal_CXR]**	1.76	[37]
Odds ratio of bacteraemia in pulmonary complicated pneumonia **[or_bacteraemia_in_PCP]**	3.1	[38]
Assumed prevalence of bacteraemia in non-pulmonary complicated pneumonia **[assumed_prev_bacteraemia_in_non_PCP]**	0.0678	model output 'adjusted_p' × 'RR'
Assumed prevalence of hypoxaemia in non-pulmonary complicated pneumonia **[assumed_prev_hypoxaemia_in_non_PCP]**	0.24 *4	assumed based on [35]
Odds ratio of hypoxaemia in non-pulmonary complicated pneumonia **[or_hypoxaemia_in_PCP]**	2.236	[39]
Proportion of pneumonia disease type in ALRI **[proportion_pneumonia_in_alri]**	0.372	appendix A.2.3
Proportion of bacterial infection (primary or secondary pathogen) in pneumonia disease type (CXR+) **[proportion_bacterial_infection_in_pneumonia]**	0.475	model output
Proportion of bacterial infection (primary or secondary pathogen) in other ALRI disease type (CXR-) **[proportion_bacterial_infection_in_other_alri]**	0.223	model output

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Table A.8 – continued from previous page

Parameters [name]	Value	Source

PCP - Pulmonary complicated pneumonia

*1 Given the rare probability of necrotising pneumonia, lung abscess, atelectasis and pneumothorax, the probability reported in the source for the two pulmonary complications (necrotising pneumonia and atelectasis) were used for the pulmonary complication modelled (lung abscess and pneumothorax), which were both 4.9%

*2 Estimate calculation described above

*3 Rees et al., 2020 - reported specificity of SpO2<90% in CXR+ = 0.75 → 1 - specificity = 0.25 → 0.25 × 0.75 sought care (assumed) = 0.1875

*4 Rees et al., 2020 - reported sensitivity of SpO2<90% in CXR+ = 0.32 → 0.32 × 0.75 sought care (assumed) = 0.24

A.2.5 Applying symptoms

The module generates a range of signs and symptoms associated with an ALRI episode. The probability of developing a particular symptom is given in Table A.9. These probabilities differ between uncomplicated and complicated state, as well as by disease type. Using STATA version 14, we analysed the McCollum et al. 2017 study dataset [9], here referred to as PCV13 data. Descriptive analysis was performed and the Mantel-Haenszel method was applied to assess associations between symptoms. These analyses were restricted to complete cases only.

The analysis on the prevalence of symptoms was stratified by peripheral oxygen saturation level, using 3 categories: SpO_2<90%, 90-92%, and ≥93%. The probabilities of signs and symptoms for the uncomplicated state of ALRI disease were derived from the SpO_2≥93% stratum, representing ALRI individuals with presumably less severe disease.

The probabilities for chest-indrawing, general danger signs, and respiratory distress, obtained from PCV13 data, were subsequently stratified by disease type (Pneumonia versus Other ALRI) using sensitivity and specificity estimates for individual clinical signs in radiographic pneumonia from Rees et al. 2020 [35]. Sensitivity values representing the probability of each clinical sign being present in confirmed radiographic pneumonia (CXR+) were applied to the pneumonia disease type, whereas false positive rates (1 - specificity) representing the probability of each clinical sign being present in non-radiographic ALRI (CXR-) were applied to the other ALRI disease type.

Based on Rees et al. 2020 [35], chest-indrawing demonstrates 74% sensitivity and 15% specificity for radiographic pneumonia detection. The false positive rate (1 - specificity) indicates that 85% of children without radiographic pneumonia present with chest-indrawing. Then, to derive the probability specific to CXR- ALRI, we adjusted for the 5% of cases that are non-ALRI [10] in the PCV13 data. Thus, among other ALRI (CXR-) the probability of chest indrawing is 80.75% [85% × (1 - 0.05)]. The probability ratio of chest-indrawing between pneumonia (CXR+) and other ALRI (CXR-) is 0.74/0.8075 = 0.9164. Analysis of PCV13 data showed that 56.71% of the participants with oxygen saturation ≥93%, had chest-indrawing. Then, to estimate probabilities by disease type, we used previously estimated proportion of CXR+ cases among ALRIs: 37.2%, and the probability ratio between CXR+ and CXR- of 0.9164.

The equation: $(x \times 37.2\% \times 0.9164) + (x \times (100\% - 37.2\%)) = 56.71\%$

Solving: $x = 58.53\%$ - is the probability of chest-indrawing in other ALRI disease type. While $58.53\% \times 0.9164 = 53.64\%$ is the probability of the clinical sign in pneumonia disease type, as listed in Table A.9.

Based on Rees et al. 2020 [35], the average sensitivity and specificity of clinical signs that make up general danger signs: inability to drink, convulsions, cyanosis, and abnormally sleepy/lethargy, for radiographic pneumonia is 13.5% and 88.25%, respectively. Thus, the false positive rate indicates that 11.75% of children with CXR- (other ALRI) present with general danger signs. The probability ratio of general danger signs between pneumonia (CXR+) and other ALRI (CXR-) is $0.135/0.1175 = 1.149$. Analysis of PCV13 data showed that 13.61% of the participants with oxygen saturation ≥93%, had general danger signs, defined as the presence of any of the following: inability to drink, convulsions, unconsciousness/lethargy, and cyanosis.

The equation: $(x \times 37.2\% \times 1.149) + (x \times (100\% - 37.2\%)) = 13.61\%$

Solving: $x = 12.89\%$ - is the probability of general danger signs in other ALRI. While $12.89\% \times 1.149 = 14.81\%$ is the probability of the clinical sign in pneumonia, as listed in Table A.9.

Based on Rees et al. 2020 [35], the average sensitivity and specificity of clinical signs that make up respiratory distress: head nodding/bobbing, nasal flaring, and grunting, for radiographic pneumonia is 11.67% and 91.7%, respectively. Thus, the false positive rate (1 - specificity) is 8.3%, which represents the proportion of children with CXR- (other ALRI) presenting with respiratory distress. The probability ratio between pneumonia (CXR+) and other ALRI (CXR-) is $0.1167/0.083 = 1.4$. Analysis of PCV13 data showed that 17.22% of the participants with oxygen saturation ≥93%, had respiratory distress, defined as the presence of at least two of the following: grunting, nasal flaring, and/or head nodding.

The equation: $(x \times 37.2\% \times 1.4) + (x \times (100\% - 37.2\%)) = 17.22\%$

Solving: $x = 14.99\%$ - is the probability of respiratory distress in other ALRI. While $14.99\% \times 1.4 = 20.99\%$ is the probability of the clinical sign in pneumonia, as listed in Table A.9.

Table A.9 Parameters of signs and symptoms

Parameters [name]	**Value**	**Source**
Probability of cough in pneumonia disease **[prob_cough_in_pneumonia]**	1	assumed
Probability of difficult breathing in pneumonia disease **[prob_difficult_breathing_in_pneumonia]**	1	assumed
Probability of fever in uncomplicated pneumonia disease **[prob_fever_in_pneumonia]**	0.82	[35]
Probability of tachypnoea (fast-breathing for age) in uncomplicated pneumonia disease **[prob_tachypnoea_in_pneumonia]**	0.9083	PCV13 data
Probability of chest wall indrawing in uncomplicated pneumonia disease **[prob_chest_indrawing_in_pneumonia]**	0.5364	PCV13 data + assumption

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Table A.9 – continued from previous page

Parameters [name]	Value	Source
Probability of general danger signs in uncomplicated pneumonia disease **[prob_danger_signs_in_pneumonia]**	0.1481	PCV13 data + assumption
Probability of respiratory distress in uncomplicated pneumonia disease **[prob_respiratory_distress_in_pneumonia]**	0.2099	PCV13 data + assumption
Probability of cough in other ALRI disease **[prob_cough_in_other_alri]**	1	assumed
Probability of difficult breathing in other ALRI disease **[prob_difficult_breathing_in_other_alri]**	1	assumed
Probability of fever in uncomplicated other ALRI disease **[prob_fever_in_other_alri]**	0.764	estimated using OR=1.41 [34]
Probability of tachypnoea (fast-breathing for age) in uncomplicated other ALRI disease **[prob_tachypnoea_in_other_alri]**	0.876	estimated using OR=1.40 [34]
Probability of chest wall indrawing in uncomplicated other ALRI disease **[prob_chest_indrawing_in_other_alri]**	0.5853	PCV13 data + assumption
Probability of general danger signs in other ALRI disease **[prob_danger_signs_in_other_alri]**	0.1289	PCV13 data + assumption
Probability of respiratory distress in uncomplicated other ALRI disease **[prob_respiratory_distress_in_other_alri]**	0.1499	PCV13 data + assumption
Odds ratio of general danger signs with respiratory distress **[or_danger_signs_in_alri_with_respiratory_distress]**	4.456	PCV13 data
Probability of general danger signs in ALRI episode without respiratory distress, and non-hypoxaemic ($SpO_2 \geq 93\%$) **[prob_danger_signs_in_no_respiratory_distress_SpO2>=93%]**	0.0754	PCV13 data
Odds ratio of respiratory distress with chest indrawing **[or_respiratory_distress_in_alri_with_chest_indrawing]**	10.864	PCV13 data
Probability of respiratory distress in ALRI episode without chest indrawing, and non-hypoxaemic ($SpO_2 \geq 93\%$) **[prob_respiratory_distress_in_no_chest_indrawing_SpO2>=93%]**	0.0529	PCV13 data
Odds ratio of fever in ALRI with complications **[or_fever_in_complicated_alri]**	1.32	PCV13 data *1
Odds ratio of tachypnoea (fast-breathing for age) in ALRI with complications **[or_tachypnoea_in_complicated_alri]**	1.35	PCV13 data *1
Probability of general danger signs in ALRI episode without respiratory distress, and severely hypoxaemic ($SpO_2 < 90\%$) **[prob_danger_signs_in_no_respiratory_distress_SpO2<90%]**	0.2188	PCV13 data
Probability of respiratory distress in ALRI episode without chest indrawing, and severely hypoxaemic ($SpO_2 < 90\%$) **[prob_respiratory_distress_in_no_chest_indrawing_SpO2<90%]**	0.1171	PCV13 data

Continued on next page

Table A.9 – continued from previous page

Parameters [name]	Value	Source
Probability of general danger signs in ALRI episode without respiratory distress, and moderately hypoxaemic (SpO_2=90-92%) **[prob_danger_signs_in_no_respiratory_distress_SpO2_90-92%]**	0.1146	PCV13 data
Probability of respiratory distress in ALRI episode without chest indrawing, and moderately hypoxaemic (SpO_2=90-92%) **[prob_respiratory_distress_in_no_chest_indrawing_SpO2_90-92%]**	0.0845	PCV13 data
Probability of general danger signs in ALRI episode with severe hypoxaemia (SpO_2<90%) **[prob_danger_signs_in_SpO2<90%]**	0.3041	PCV13 data
Probability of general danger signs in ALRI episode with moderate hypoxaemia (SpO_2=90-92%) **[prob_danger_signs_in_SpO2_90-92%]**	0.168	PCV13 data
Probability of chest wall indrawing in ALRI episode with severe hypoxaemia (SpO_2<90%) **[prob_chest_indrawing_in_SpO2<90%]**	0.837	PCV13 data
Probability of chest wall indrawing in ALRI episode with moderate hypoxaemia (SpO_2=90-92%) **[prob_chest_indrawing_in_SpO2_90-92%]**	0.6333	PCV13 data
Probability of respiratory distress in ALRI episode with severe hypoxaemia (SpO_2<90%) **[prob_respiratory_distress_in_SpO2<90%]**	0.4373	PCV13 data
Probability of respiratory distress in ALRI episode with moderate hypoxaemia (SpO_2=90-92%) **[prob_respiratory_distress_in_SpO2_90-92%]**	0.2501	PCV13 data
Proportion of severe (SpO_2<90%) in hypoxaemic ALRI **[proportion_hypoxaemia_with_SpO2<90%]**	0.487	PCV13 data
Probability of respiratory distress in pulmonary complicated ALRI without chest indrawing **[prob_respiratory_distress_in_no_chest_indrawing_pc]**	0.0797	PCV13 data *1
Probability of general danger signs in pulmonary complicated ALRI without respiratory distress **[prob_danger_signs_in_no_respiratory_distress_pc]**	0.1347	PCV13 data *1
Probability of general danger signs in pulmonary complicated ALRI **[prob_danger_signs_in_pulmonary_complications]**	0.2527	PCV13 data *1
Probability of chest wall indrawing in pulmonary complicated ALRI **[prob_chest_indrawing_in_pulmonary_complications]**	0.8015	PCV13 data *1
Probability of respiratory distress in pulmonary complicated ALRI **[prob_respiratory_distress_in_pulmonary_complications]**	0.3539	PCV13 data *1
Odds ratio of severe symptoms (danger signs, respiratory distress) in ALRI with severe pulmonary complications (lung abscess, pneumothorax) **[or_severe_symptoms_in_severe_pulmonary_complications]**	3.376	PCV13 data *2

Continued on next page

Table A.9 – continued from previous page

Parameters [name]	Value	Source
Probability of cough and difficult breathing is 1, as base symptoms to seek care for ALRI		
*1 used cases with abnormal peripheral oxygen saturation of SpO_2 <96% as proxy for complicated ALRI and pulmonary-complicated pneumonia		
*2 used cases with peripheral oxygen saturation of SpO_2 <93% as proxy for severe pulmonary-complicated pneumonia		

A.2.6 Estimating mortality (without treatment)

Under natural disease progression, mortality events should occur through complex disease pathways involving complications and extended timelines. However, the built model simplifies this process by predicting all mortality events at disease onset, rather than simulating the full timeline of complications and disease progression. This approach requires that all cases face some baseline mortality risk, which varies based on the presence of individual risk factors. We modeled the association of radiographic pneumonia (disease type), severe symptoms, SpO_2 level, pulmonary complications, bacteraemia, and bacterial causal pathogen with mortality risk. Other risk factors not explicitly modelled would be captured in the baseline odds of death.

We modelled mortality separately for two age groups: infants under 2 months and children aged 2-59 months, using the respective logistic models shown in Equation (A.5) and Equation (A.4). For the younger age group (<2 months), the odds ratio values of the risk factors for mortality were sourced from a study on young infant mortality in Malawi by Hooli et al., 2020 [33], while the older age group (2-59 month) values are taken from a multi-country study, including data from Malawi, by Rees et al. 2022 [40]. Parameter values of the mortality model are presented in Table A.11.

$$
\begin{aligned}
Y_{\theta_{(2-59mo)}} = {} & \beta_{\theta_{(2-59mo)}0} \times [S_{\theta_{(all\_ages)}1/2/3}] \\
& (\beta_{\theta_{(2-59mo)}1} X_{Sex}) \times \\
& (\beta_{\theta_{(2-59mo)}2} X_{SpO_2<90\%}) \times (\beta_{\theta_{(2-59mo)}3} X_{SpO_2=90-92\%}) \times \\
& (\beta_{\theta_{(2-59mo)}4} X_{Age2-5mo}) \times (\beta_{\theta_{(2-59mo)}5} X_{Age6-11mo}) \times \\
& (\beta_{\theta_{(2-59mo)}6} X_{sympt-CI}) \times (\beta_{\theta_{(2-59mo)}7} X_{sympt-DS}) \times \\
& (\beta_{\theta_{(2-59mo)}8} X_{sympt-RD}) \times (\beta_{\theta_{(2-59mo)}9} X_{SAM}) \times \\
& (\beta_{\theta_{(all\_ages)}1} X_{CXR}) \times (\beta_{\theta_{(all\_ages)}2} X_{bacterial\_patho}) \times \\
& (\beta_{\theta_{(all\_ages)}3} X_{PC}) \times (\beta_{\theta_{(all\_ages)}4} X_{Bacteraemia})
\end{aligned}
\tag{A.4}
$$

$$
\begin{aligned}
Y_{\theta_{(<2mo)}} = {} & \beta_{\theta_{(<2mo)}0} \times [S_{\theta_{(all\_ages)}1/2/3}] \\
& (\beta_{\theta_{(<2mo)}1} X_{sympt-DS}) \\
& (\beta_{\theta_{(<2mo)}2} X_{SpO_2<90\%}) \times (\beta_{\theta_{(<2mo)}3} X_{SpO_2=90-92\%}) \\
& (\beta_{\theta_{(all\_ages)}1} X_{CXR}) \times (\beta_{\theta_{(all\_ages)}2} X_{bacterial\_patho}) \times \\
& (\beta_{\theta_{(all\_ages)}3} X_{PC}) \times (\beta_{\theta_{(all\_ages)}4} X_{Bacteraemia})
\end{aligned}
\tag{A.5}
$$

Dummy	**Property**	**Category/Status ($X_i = 1$)**
X_{Sex}	sex	'Female'
$X_{SpO_2<90\%}$	ri_oxygen_saturation_level	'<90%'
$X_{SpO_2=90-92\%}$	ri_oxygen_saturation_level	'90-92%'
$X_{Age2-5mo}$	age_exact_years	≥1/6 & <1/2
$X_{Age6-11mo}$	age_exact_years	≥1/2 & <1
$X_{sympt-CI}$	symptoms	'chest_indrawing'
$X_{sympt-DS}$	symptoms	'danger_signs'
$X_{sympt-RD}$	symptoms	'respiratory_distress'
X_{SAM}	un_clinical_acute_malnutrition	'SAM'
X_{CXR}	ri_disease_type	'Pneumonia'
$X_{bacterial\_patho}$	ri_primary_pathogen or ri_secondary_bacterial_pathogen	any(['Strep_pneumoniae_PCV13', 'Strep_pneumoniae_non_PCV13', 'Hib', 'H.influenzae_non_type_b', 'Staph_aureus', 'Enterobacteriaceae', 'other_Strepto_Enterococci', 'other_bacterial_pathogens'])
X_{PC}	ri_complications	any(['pleural_effusion', 'empyema', 'lung_abscess', 'pneumothorax'])
$X_{Bacteraemia}$	ri_complications	'bacteraemia'
$[S_{\theta_{(all\_ages)}1/2/3}]$	scaling factor for baseline odds explained below	

The baseline odds of death in each equation were calibrated by adjusting the intercept of the logistic regression model to match the observed mortality rates from hospital studies: 3.2% for children aged 2-59 months (McCollum et al. 2017 [9]) and 3.6% for young infants <2 months (in Hooli et al. 2020 [33]).

We first applied the unscaled logistic models (equations A.5 and A.4) to each ALRI case in the simulation, then calculated the weighted average of predicted probabilities. A scaling factor was computed by dividing the original intercept (unscaled baseline odds) by this weighted average, which was then applied to yield calibrated baseline odds of death (0.00389 for <2 months; 0.00365 for 2-59 months).

Since the hospital-derived mortality rates reflect outcomes with medical care, we needed to estimate mortality without treatment intervention for natural history modelling. To achieve this, we simulated 415,040 ALRI cases and applied the calibrated mortality models using baseline odds of 0.00389 in Equation (A.5) for infants aged <2 months, and 0.00365 in Equation (A.4) for children aged 2-59 months. For each case, the model computed individual mortality probabilities, as well as treatment failure rates specific to each case type combination (uncomplicated vs. complicated ALRI; bacterial vs. viral pathogens). Using this simulation output, we calculated the mortality rate equivalent to 100% treatment failure as a proxy for mortality without treatment. This approach assumes a linear relationship between treatment failure and mortality rates, enabling extrapolation from partial treatment failure data to estimate untreated ALRI mortality. We then calculated mortality ratios comparing complicated versus uncomplicated cases, and bacterial versus viral causes within complicated and uncomplicated categories. These mortality ratios represent the fold-increase in death risk attributable to disease complexity and pathogen type in the complete absence of treatment intervention. The

detailed results of this simulation are presented in Table A.10.

Table A.10 Simulation output of probabilities of death and treatment failures using the baseline odds of 0.00389 (<2 months) and 0.00365 (2-59 months) calibrated to observed hospital mortality data

Case group	IMCI severity	Treatment type	Probability of death	Treatment failure	Fraction of cases
Uncomplicated ALRI	Non-severe	Oral antibiotics	0.03345	0.0866172	0.75516
	Severe	IV antibiotics	0.08049	0.0595926	0.24484
Complicated ALRI	Non-severe	Oral antibiotics	0.09667	0.1151887	0.39473
	Severe	IV antibiotics	0.23971	0.0997603	0.23903
	Non-severe hypoxaemic	IV + Oxygen	0.19774	0.0554447	0.13341
	Severe and hypoxaemic	IV + Oxygen	0.37284	0.1199589	0.23284
Uncomplicated ALRI Viral[*1] pathogen	Non-severe	Oral antibiotics	0.03066	0.0841593	0.75984
	Severe	IV antibiotics	0.07393	0.054121	0.24016
Uncomplicated ALRI Bacterial pathogen	Non-severe	Oral antibiotics	0.04145	0.0936548	0.74207
	Severe	IV antibiotics	0.09760	0.0738379	0.25793
Complicated ALRI Viral pathogen	Non-severe	Oral antibiotics	0.08602	0.1252874	0.32227
	Severe or hypoxaemic	IV +/- Oxygen[*2]	0.24483	0.0881758	0.67773
Complicated ALRI Bacterial pathogen	Non-severe	Oral antibiotics	0.10650	0.1067249	0.48638
	Severe or hypoxaemic	IV +/- Oxygen	0.34317	0.1137638	0.51362

[*1]Viral group includes fungal and NoS causes
[*2]Oxygen provision to SpO_2<90%

Complicated versus Uncomplicated ALRI
For uncomplicated ALRI:
Deaths = (0.03345 × 0.75516) + (0.08049 × 0.24484) = 0.04497
TF = (0.0866172 × 0.75516) + (0.0595926 × 0.24484) = 0.08000
Deaths with 100% TF = 0.04497 × 1 / 0.08000 = 0.56212

For ALRI with complications:
Deaths = (0.09667 × 0.39473) + (0.23971 × 0.23903) + (0.19774 × 0.13341) + (0.37284 × 0.23284) = 0.20865
TF = (0.1151887 × 0.39473) + (0.0997603 × 0.23903) + (0.0554447 × 0.13341) + (0.1199589 × 0.23284) = 0.10464
Deaths with 100% TF = 0.20865 × 1 / 0.10464 = 1.99393
Ratio = 3.55

Bacterial versus Viral Uncomplicated ALRI
For uncomplicated ALRI of viral-causal pathogen:
Deaths = (0.03066 × 0.75984) + (0.07393 × 0.24016) = 0.04105
TF = (0.0841593 × 0.75984) + (0.054121 × 0.24016) = 0.076945
Deaths with 100% TF = 0.04105 × 1 / 0.076945 = 0.5335

For uncomplicated ALRI of bacterial-causal pathogen:
Deaths = (0.04145 × 0.74207) + (0.09760 × 0.25793) = 0.05593
TF = (0.0936548 × 0.74207) + (0.0738379 × 0.25793) = 0.08854
Deaths with 100% TF = 0.05593 × 1 / 0.08854 = 0.63169
Ratio = 1.18

Bacterial versus Viral Complicated ALRI
For complicated ALRI of viral-causal pathogen:

Deaths = (0.08602 × 0.32227) + (0.24483 × 0.67773) = 0.19365
TF = (0.1252874 × 0.32227) + (0.0881758 × 0.67773) = 0.10014
Deaths with 100% TF = 0.19365 × 1 / 0.10014 = 1.93379

For complicated ALRI of bacterial-causal pathogen:
Deaths = (0.10560 × 0.48638) + (0.34317 × 0.51362) = 0.22762
TF = (0.1067249 × 0.48638) + (0.1137638 × 0.51362) = 0.11034
Deaths with 100% TF = 0.22762 × 1 / 0.11034 = 2.0629
Ratio = 1.07

The simulation provided the proportion of bacterial-causal pathogen in complicated ALRI as 44.15%. Given an overall 3.55-fold increased mortality risk for complicated ALRI and a 1.07-fold increased mortality risk for bacterial versus non-bacterial pathogen in complicated ALRI, the base viral mortality risk ratio was calculated as 3.44. This relationship is expressed as:
(base_RR_viral × 1.07 × 0.4415) + (base_RR_viral × (1-0.4415)) = 3.55

The mortality risk ratio between complicated and uncomplicated ALRI represents the increased risk of death between the two groups in the absence of treatment.

The estimated baseline odds of 0.00389 (<2 months) and 0.00365 (2-59 months) were calibrated to match hospital mortality data, which reflect mortality in the presence of treatment. Since most viral cases are self-limiting and do not benefit from antibiotic treatment, we assumed that mortality of uncomplicated viral cases receiving empirical pneumonia treatment approximates mortality rate in the absence of treatment. Under this assumption, we can use the same baseline odds of death, and respective odds ratios or risk ratios determined in mortality studies.

McCollum et al. 2017 reported a case fatality rate (CFR) of 1.55% for cases with $SpO_2 \geq 93\%$. We calibrated the baseline odds of death to match this CFR for the ALRI cohort with SpO>=93%, establishing the base odds of death for all ALRI cases.

Given that 16.9% of children in the simulation cohort are under 2 months of age, we estimated age-specific CFRs for an overall under-5 CFR of 1.55%. Using the relative risk of death of 1.10 for young infants compared to older children [41], we calculated:
$(CFR_{2\text{-}59mo} \times (1\text{-}0.169)) + (CFR_{2\text{-}59mo} \times 1.10 \times 0.169) = 1.55\%$
This yields $CFR_{2\text{-}59mo} = 1.52\%$ and $CFR_{<2mo} = 1.67\%$

For ALRI cases with $SpO_2 \geq 93\%$ in the simulation cohort, the calibration method returned scaled intercept values of 0.0036 for young infants (Equation (A.5)) and 0.00192 for children aged 2-59 months (Equation (A.4)). These values serve as the baseline odds for all cases in the mortality regression model. For ALRI cases with complications but without hypoxaemia ($SpO_2 \geq 93\%$), both the complication-specific odds ratio and the increased mortality risk for complicated ALRI and bacterial pathogens in the absence of treatment are applied.

Table A.11 Parameters of ALRI mortality

Symbol	Parameters	Value	Source
$\beta_{\theta_{(<2mo)}0}$	Baseline odds of death from ALRI in infants aged <2 months, reference group without general danger signs, any complications, and disease type is other ALRI (CXR-) **[base_odds_death_ALRI_age<2mo]**	0.0036 *1	model output
$\beta_{\theta_{(<2mo)}1}$	Odds ratio of death from ALRI in infants aged <2 months presenting with general danger signs **[or_death_ALRI_age<2mo_danger_signs]**	2.4	[33]
$\beta_{\theta_{(<2mo)}2}$	Odds ratio of death from ALRI in infants aged <2 months with SpO_2<90% **[or_death_ALRI_age<2mo_SpO2<90%]**	4.5	[33]
$\beta_{\theta_{(<2mo)}3}$	Odds ratio of death from ALRI in infants aged <2 months with SpO_2 between 90-92% **[or_death_ALRI_age<2mo_SpO2_90_92%]**	3.3	[33]
$\beta_{\theta_{(2-59mo)}0}$	Baseline odds of death from ALRI in children aged 2-59 months, reference group aged 12-59 months, without chest-indrawing, respiratory distress, or general danger signs, any complication, and disease type is other ALRI (CXR-) **[base_odds_death_ALRI_age2_59mo]**	0.00192 *1	model output
$\beta_{\theta_{(2-59mo)}1}$	Odds ratio of death from ALRI in children aged 2-59 months if female sex **[or_death_ALRI_age2_59mo_female]**	1.25	[40]
$\beta_{\theta_{(2-59mo)}2}$	Odds ratio of death from ALRI in children aged 2-59 months with $SpO_2$90% **[or_death_ALRI_age2_59mo_SpO2<90%]**	5.04	[40]
$\beta_{\theta_{(2-59mo)}3}$	Odds ratio of death from ALRI in children aged 2-59 months with SpO_2 between 90-92% **[or_death_ALRI_age2_59mo_SpO2_90_92%]**	1.54	[40]
$\beta_{\theta_{(2-59mo)}4}$	Odds ratio of death from ALRI in children aged 2-59 months aged between 2-5 months **[or_death_ALRI_age2_59mo_in_2_5mo]**	2.35	[40]
$\beta_{\theta_{(2-59mo)}5}$	Odds ratio of death from ALRI in children aged 2-59 months aged between 6-11 months **[or_death_ALRI_age2_59mo_in_6_11mo]**	1.68	[40]
$\beta_{\theta_{(2-59mo)}6}$	Odds ratio of death from ALRI in children aged 2-59 months presenting with chest-indrawing **[or_death_ALRI_age2_59mo_chest_indrawing]**	1.26	[40]
$\beta_{\theta_{(2-59mo)}7}$	Odds ratio of death from ALRI in children aged 2-59 months presenting with general danger signs **[or_death_ALRI_age2_59mo_danger_signs]**	2.45 *2	[40]
$\beta_{\theta_{(2-59mo)}8}$	Odds ratio of death from ALRI in children aged 2-59 months presenting with severe respiratory distress signs **[or_death_ALRI_age2_59mo_respiratory_distress]**	1.58	derived from [9]

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Table A.11 – continued from previous page

Coefficient	Parameters	Value	Source
$\beta_{\theta_{(2-59mo)}9}$	Odds ratio of death from ALRI in children aged 2-59 months with severe acute malnutrition (SAM) **[or_death_ALRI_age2_59mo_SAM]**	2.37	[42]
$\beta_{\theta_{(all\_ages)}1}$	Odds ratio of death from ALRI when disease type is pneumonia (CXR+) **[or_death_ALRI_abnormal_CXR]**	2.79	[43]
$\beta_{\theta_{(all\_ages)}2}$	Odds ratio of death from ALRI when primary or secondary pathogen is bacterial **[or_death_ALRI_bacterial_pathogen]**	4.01	[44]
$\beta_{\theta_{(all\_ages)}3}$	Odds ratio of death from ALRI if any pulmonary complications (pleural effusion, empyema, lung abscess and/or pneumothorax) **[or_death_ALRI_pulmonary_complications]**	2.55	[45]
$\beta_{\theta_{(all\_ages)}4}$	Odds ratio of death from ALRI with bacteraemia **[or_death_ALRI_bacteraemia]**	2.51	[46]
$S_{\theta_{(all\_ages)}1}$	Scaling factor for baseline odds of death in uncomplicated ALRI if causal pathogen is bacterial or with bacterial co-infection, compared to other causal pathogens (mostly viral) **[scaling_factor_base_odds_death_uncomplicated_ALRI_if_bacterial_cause]**	1.18 *3	calculated with model output
$S_{\theta_{(all\_ages)}2}$	Scaling factor for baseline odds of death if complicated ALRI of non-bacterial cause without bacterial co-infection, compared to uncomplicated ALRI **[scaling_factor_base_odds_death_if_complicated_ALRI_viral_cause]**	3.44 *3	calculated with model output
$S_{\theta_{(all\_ages)}3}$	Scaling factor for odds of death in ALRI with complications if causal pathogen is bacterial or with bacterial co-infection, compared to other causal pathogens (mostly viral) **[scaling_factor_death_complicated_ALRI_if_bacterial_cause]**	1.07 *3	calculated with model output

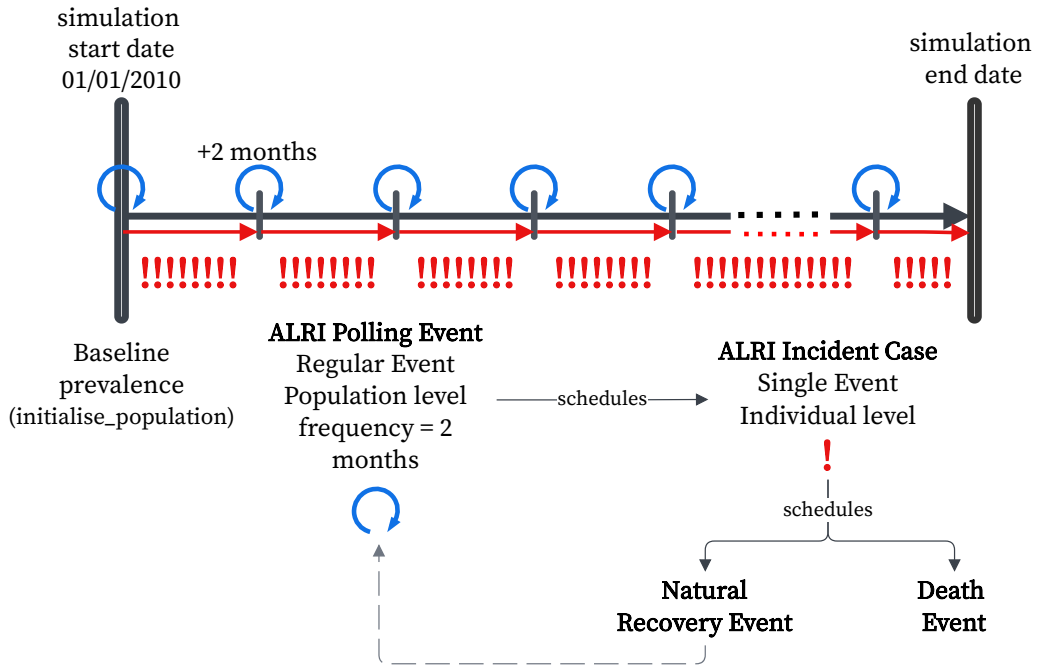
*1 Values derived from a calibration method for scaling the base odds of death against observed mortality of 1.55% in cases with $SpO_2 \geq 93\%$ in McCollum et al. 2017 [9]
*2 estimated weighted average OR from source variables: unconscious (n=945 x OR=1.91) + convulsions (n=1432 x OR=2.87) + cyanosis (n=904 x OR=2.34) / total N=3281
*3 The scaling factors are applied to the baseline odds of death before the odds ratios and risk ratios of risk factors.

A.2.7 Simulation time-steps setting the epidemiology

The TLO simulation environment uses discrete events to set disease incidence and progression (Figure A.1). The natural history of ALRI is initiated by ALRI Polling Event - a regular population-level event scheduled to occur at 2-month intervals throughout the simulation. During each polling event, individuals are probabilistically selected, based on age-specific incidence rates and risk factors Equation (A.1), and scheduled for an Incident Case Event. It is at this individual-level event that all disease characteristics are determined, including the outcome: recovery or death.

Figure A.5 illustrates an overview of how key events of the ALRI module set the time-steps of disease occurrences within a simulation run.

Figure A.5: ALRI module events setting the simulation time-steps



The ALRI module does not simulate baseline prevalence at simulation initiation, as ALRI is an acute disease. Instead, all ALRI properties at set to initial non-disease states in the initialise_population function of the TLO simulation model. The first ALRI Polling Event is scheduled to occur on the simulation start date, effectively distributing the initial disease occurrence over the first 2-month period when incident cases begin to emerge.

ALRI Polling Event (Population-level scheduling)

The ALRI polling event operates on the entire the entire simulation population and determines who acquires an ALRI episode. This regular event is scheduled every 2 months, to accommodate the acute nature of the disease and high incidence rates in the younger age groups. This chosen frequency also considers both the average disease duration and maximum treatment duration required to complete an ALRI episode, ensuring sufficient time between episodes.

During each polling event, probabilities of acquiring symptomatic ALRI from specific pathogens are assigned to each individual in the population under 5 years of age (Equation (A.1)). The actual disease occurrence and pathogen assignment are determined by sampling from these probabilities using the simulation's random number generator. For individuals sampled to acquire an ALRI episode, the corresponding ALRI Incident Case event is scheduled to represent disease onset. The onset date is randomly distributed across the 2-month interval, occurring any time between the current polling event date and the day before the next scheduled polling event.

ALRI Incident Case (Individual-level scheduling)

The ALRI Incident Case event operates at the individual level, with each person selected for an ALRI episode during the ALRI Polling Event to go through this event on their scheduled onset date.

This event initiates the ALRI episode and determines the complete disease trajectory for each case. The following characteristics are established: the disease type (Pneumonia or Other ALRI), presence of bacterial co-infection when the primary pathogen is viral, the duration of the episode, the onset of complications, the onset symptoms, and the scheduled natural outcome (recovery/death) and respective date. The ALRI module properties (Table A.1) are updated according to individual case profile.

The natural history of ALRI concludes with one of two possible outcome events, both scheduled during the ALRI Incident Case event, determined by the mortality model (equations A.5 and A.4):

- **ALRI Natural Recovery Event** - This event is scheduled when recovery is the predetermined natural outcome. It onsets the recovery date and resets all ALRI properties to non-disease states. Following recovery, the individual returns to the susceptible population for future ALRI Polling Events.
- **ALRI Death Event** - This event is scheduled when death is the predetermined natural outcome. It onsets the death date and notifies the Demography module to register the ALRI death, and logs the properties at the time of death. It also informs the HealthBurden module to calculate the years of life lost (YLLs) for burden of disease assessment. This scheduled death event represents a preventable outcome that can be averted through effective treatment interventions. When treatment successfully cures the episode, the scheduled death event is cancelled and replaced with a recovery outcome (ALRI Cure Event).

Simulation modes

The TLO simulation operates as a dynamic model that tracks and continuously updates the entire simulation population over a defined time period, where disease and health system events occur according to their scheduled timing with interactive feedback between modules. This simulation mode enables integration of multiple disease modules and captures the epidemiological flow of health conditions within broader health system contexts and constraints, as well as complex interactions between diseases. However, this simulation approach is computationally intensive and not required for specific analyses such as single condition-based health economic evaluations.

Alternatively, the simulation can operate in cohort mode, whereby it generates a complete 1-year disease experience for the population at the simulation start date. All ALRI incident cases, their disease characteristics, progression pathways, health system interactions, and outcomes are predetermined and scheduled simultaneously. This approach is computationally more efficient and creates a comprehensive dataset of ALRI disease episodes while enabling direct comparison of intervention scenarios with identical baseline populations, making it particularly suitable for evaluating the effect of interventions on specific conditions and conducting cost-effectiveness analyses.

A.3 Integration of healthcare provision

The modelling of healthcare provision for ALRI is integrated within the TLO model framework, therefore the conceptualisation is structured within health seeking behaviour and health system modules (descriptions on `https://www.tlomodel.org/`). Described here is the ALRI care management within the TLO model framework: from health care seeking, to care management at each facility level, and the effect of the interventions on health outcomes.

The overall effectiveness of the health care provision for an ALRI case depends on several factors - those captured in the model include:

- **IMCI classification** - In resource-limited settings such as Malawi, simplified clinical algorithms with 2-3 severity levels guide ALRI care plans and treatment decisions. At lower health system levels (community and primary care), the Integrated Management of Childhood Illness (IMCI) guidelines are less comprehensive than assessments at secondary and tertiary care levels, which include respiratory distress signs, radiography, and auscultatory examination. Though their use remains subject to healthcare worker skills, equipment availability, and resource constraints.
- **Quality of care** - Health workers' ability to correctly classify the disease based on the IMCI guidelines is key in the assignment of the most appropriate treatment.
- **Availability of consumables** - The availability of consumables/drugs, is key in the delivery of care and therefore, determining health outcome. In the cost-effectiveness of analysis, the availability is set at 100%.
- **Treatment effectiveness** - Antibiotic efficacy against the causative bacterial pathogen is a critical determinant of treatment success. However, there are 16 pathogens / group of pathogens modelled in the incidence of ALRI, making it impractical to model pathogen-specific antibiotic efficacy. Instead, we simplified the approach by applying antibiotic effectiveness estimates across IMCI classifications, which aligns with how most studies on childhood pneumonia in LMICs report on effectiveness [47–50]. Treatment effectiveness estimates were calculated as the complement of treatment failure ($P(TE) = 1 - P(TF)$)

A.3.1 Healthcare seeking

Signs and symptoms from an ALRI episode trigger healthcare-seeking, which determines whether an individual will interact with the health system. The TLO model manages symptoms from all disease modules through the Symptom Manager module, which consolidates and organises them for use by the Health Seeking Behaviour module. The latter will then calculate a probability of care-seeking based on the 2016 Malawi Integrated Household Survey data analysis by Ng'ambi et al. 2020 [51]. Those who seek care will then interact with the health system, where care is provided.

Alternatively, setting the function: *force_any_symptom_to_lead_to_healthcareseeking*=True in the registration of the HealthSeekingBehaviour module at the start of the simulation, ensures that any symptom triggers contact

with the health system. Under this configuration, all ALRI cases in the simulation seek care.

The distribution of care seeking across different levels of the health system was based on the 2015-16 Demographic and Health Survey (DHS) report [52] and the 2013-14 Service Provision Assessment (SPA) report [53]. The baseline probability distribution for care-seeking by facility level is: 15.5% at district hospitals, 15.5% at mission, community and rural hospitals, 59.6% at health centres, and 9.4% at community health services (including health posts and village clinics operated by health surveillance assistants (HSAs)). These probabilities shift when individuals present with severe symptoms, resulting in increased odds of seeking care at higher-level facilities (hospitals).

Figure A.6: Overview of care-seeking processes

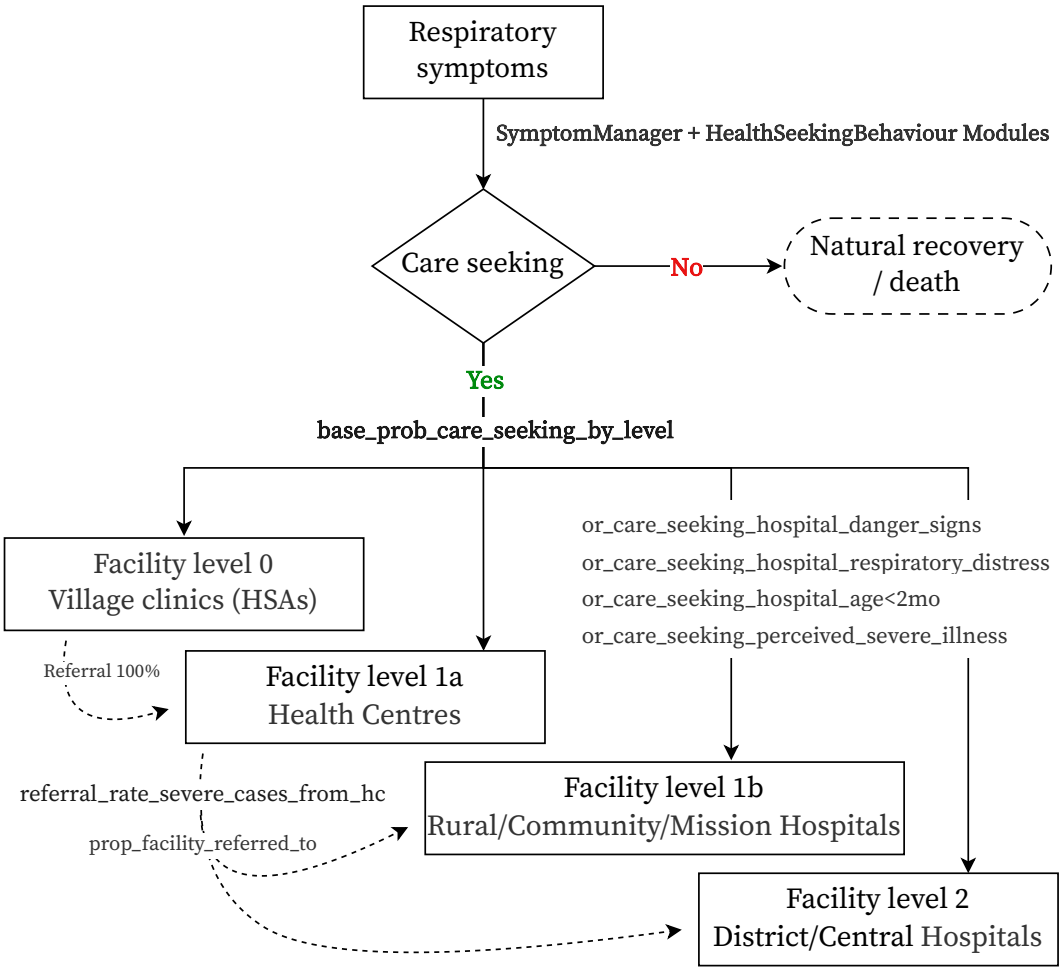


Figure A.6 shows the first point of contact with the health system when care is sought. Individuals may seek care at any health facility level, with the odds of seeking care at hospital level increasing based on symptom severity (Table A.12).

Health system facility levels are linked through a referral system, though Malawi's referral networks across care levels are fragmented and do not function optimally [54, 55]. The model assumes complete referral rates between community health services (facility level 0) and their associated primary care centres (facility level 1a) due to their close operational linkage.

For referrals to higher facility levels, existing evidence suggests 40-65% completion rates from health centres [56], though these data are not specific to severe ALRI cases. Since the model assumes 100% antibiotic availability in the cohort simulation for the cost-effectiveness analysis, referral rates apply only to severe cases requiring further management beyond the initial facility's capacity. In the absence of comprehensive data on completed referral rates within Malawi's healthcare system, clinical expert opinion was sought from Dr. Eric McCollum. Based on this consultation, an ultimate referral rate of 85% was established for severe ALRI cases, accounting for both healthcare provider referral service or patient self-referral/ own transport means.

The distribution of referrals from health centres to hospitals was assumed to be proportional to the availability of facility types, with 35% directed to district hospitals (facility level 2) and 65% to smaller capacity hospitals (facility level 1b) [57].

If treatment fails at outpatient care, individuals may return for follow-up care at the same facility level, according to a modelled probability (Table A.12).

Table A.12 Parameters of care seeking

Parameters [name]	**Value**	**Source**
Probability of care seeking by facility level [2, 1b, 1a, 0] **[base_prob_care_seeking_by_level]**	[0.155, 0.155, 0.596, 0.094]	DHS 2015-16 + SPA 2013
Odds ratio of seeking care at hospital if presenting danger signs **[or_care_seeking_hospital_danger_signs]**	1.27 *3	PCV13 data *1
Odds ratio of seeking care at hospital if presenting respiratory distress **[or_care_seeking_hospital_respiratory_distress]**	1.54 *3	PCV13 data *1
Odds ratio of care seeking if perceived severe illness with display of severe symptoms including chest-indrawing, and general danger signs and/or respiratory distress **[or_care_seeking_perceived_severe_illness]**	2.4 *2	[58]
Odds ratio of seeking care at hospital if age less than 2 months **[or_care_seeking_hospital_age<2mo]**	1.45	PCV13 data *1
Referral rate from health centres for severe pneumonia cases **[referral_rate_severe_cases_from_hc]**	0.85	assumed
Proportion of referrals to facility levels 2 and 1b **[prop_facility_referred_to]**	[0.35, 0.65]	assumed
Probability of seeking follow-up care if oral antibiotic treatment fails **[sought_follow_up_care]**	0.6	assumed

*1 STATA analysis of PCV13 dataset - logistic regression of care seeking at hospital, with independent variables: general danger signs, respiratory distress, chest-indrawing, age (<2 months, 2-11 months, 12-23 months, 24-59 months)

*2 The inverse odds ratio 1/2.4 is applied to follow-up care seeking for cases with oral treatment failure without any of chest-indrawing, danger signs, and respiratory distress.
All assumptions listed were verified by clinical and context expert Dr. Eric McCollum.

*3 Parameter values also applied as odds ratio of follow-up care seeking if presenting with danger signs or respiratory distress

A.3.2 Classifications of clinical pneumonia

Natural history models reflect the underlying disease conditions of a sick child, who presents for care with signs and symptoms, then, based on clinical algorithms and diagnostic tests, the healthcare worker assigns a disease classification and treat accordingly. The modelling of healthcare provision for ALRI follows the Integrated Management of Childhood Illness (IMCI) guidelines, which are widely implemented in Malawi's health system as part of the Essential Health Package.

Children presenting with cough and/or difficulty breathing receive care according to level-specific protocols: integrated Community Case Management (iCCM) at facility level 0, Integrated Management of Childhood Illness (IMCI) at facility levels 1a and 1b, and WHO Pocket book of hospital care for children guidelines at facility level 2.

Tables A.13 and A.14 present the IMCI-pneumonia classifications based on clinical assessment of cough and/or difficult breathing for children aged 2-59 months and young infants aged <2 months, respectively. These are facility-based IMCI guidelines with both original (2005) and revised (2014/15) versions, as Malawi's community-level care continues to follow the original guidelines for ALRI management.

Table A.13 Classification of clinical pneumonia by WHO original (2005) and revised guidelines (2014) for children aged 2-59 months

Original guidelines 2005		**Revised guidelines 2014**	
Severity	Signs / Symptoms	Severity	Signs / Symptoms
Pneumonia (non-severe)	Cough/difficult breathing, and **Fast breathing for age*,** No chest indrawing No danger signs No stridor when calm	**Pneumonia (non-severe)**	Cough/difficult breathing, and **Fast breathing for age, or** **Lower chest indrawing** No danger signs No stridor when calm
Severe Pneumonia	Cough/difficult breathing, and **Lower chest indrawing** No danger signs No stridor when calm		
Very severe Pneumonia	Cough/difficult breathing, and **Any danger sign†, or** Stridor when calm	**Severe Pneumonia**	Cough/difficult breathing, and Any danger sign, or Stridor when calmr

* Fast breathing: 2 months up to 12 months – 50 breaths per minute or more; 12 months up to 5 years – 40 breaths per minute or more.
†Danger signs are any of the following: inability to drink and/or breastfeed, persistent vomiting, lethargy or unconscious, and convulsions - these are the 4 general danger signs assessed at the primary care, while at the secondary care it also includes the assessment of central cyanosis, and severe respiratory distress.
Key clinical symptom defining pneumonia severity in **bold**.

Table A.14 Classification of clinical pneumonia by WHO original (2005) and revised guidelines (2015) for young infants aged <2 months

Original guidelines 2005		**Revised guidelines 2015**	
Severity	Signs / Symptoms	Severity	Signs / Symptoms
Severe Pneumonia	Cough/difficult breathing, and **Fast breathing for age*, or** **Lower chest indrawing** No danger signs No stridor when calm	**Pneumonia (non-severe)**	Cough/difficult breathing, and **Fast breathing for age** No chest indrawing No danger signs No stridor when calm
Very severe Pneumonia	Cough/difficult breathing, and **Any danger sign†, or** Stridor when calm	**Severe Pneumonia**	Cough/difficult breathing, and **Lower chest indrawing** **Any danger sign†, or** Stridor when calm

* Fast breathing: <2 months – 60 breaths per minute or more
†Danger signs as described for older age group, with additional assessment of apnoea at the secondary care.
Key clinical symptom defining pneumonia severity in **bold**.
Note: Young infants aged less than 7 days with fast-breathing are considered severe pneumonia

In 2014, WHO updated its guidelines to reclassify lower chest indrawing as a sign of non-severe pneumonia for children aged 2-59 months, whereas it was previously classified as severe pneumonia under the three-level classification. This revision reduced pneumonia classifications to two severity levels, which may present challenges in comparing studies using the earlier classification system. For the infants <2 months, WHO updated the guidelines in 2015 to allow outpatient treatment with oral antibiotics (7-day course) for cases presenting with fast-breathing only.

Malawi implemented the revised guidelines in February 2018. However, at the community level, non-severe pneumonia with chest-indrawing continues to be managed separately from non-severe pneumonia with fast-breathing only, reflecting different treatment protocols (5-day versus 3-day antibiotic courses). For clarity in modeling health system interactions, classifications were named according to their defining clinical signs: fast-breathing pneumonia, chest-indrawing pneumonia, and danger signs pneumonia.

As noted in Tables A.13 and A.14, important differences exist between IMCI classifications at primary care versus secondary and tertiary care level. Higher facility levels assess additional symptoms including apnea in infants under 2 months, cyanosis, and respiratory distress signs such as grunting, nasal flaring, and head nodding, which are incorporated into the classification of severe pneumonia with danger signs, leading to inpatient management.

A.3.3 Care provision by facility level

Following assessment and classification, the respective treatment is provided according to care protocols that differ across the four health system levels (0, 1a, 1b, and 2).

Table A.15 Treatment plan for each classification at different levels of the health system

Key Symptom	**Age**	**Classification**	**Treatment Plan**		
			level 0	level 1a	level 1b/2
Fast breathing	≥7 days	Pneumonia (non-severe)	Treat at home	Treat outpatient	Treat outpatient
	<7 days	Severe Pneumonia	Refer to level 1b	Refer to level 1b/2	Admit to inpatient
Chest indrawing	2-59 months	Pneumonia (non-severe)	Refer to level 1a	Treat outpatient	Treat outpatient
	<2 months	Severe Pneumonia	Refer to level 1b	Refer to level 1b/2	Admit to inpatient
Respiratory distress*	all	Severe Pneumonia	not assessed	not assessed	not assessed at 1b/ Admit to inpatient
Danger signs	all	Severe Pneumonia	Refer to level 1b	Refer to level 1b/2	Admit to inpatient
None of the above	all	Cough or cold	-	-	-

Pneumonia (non-severe) with fast-breathing only → Treat at home / Treat outpatient with 3-day oral amoxicillin (2-59 months old), 7-day oral amoxicillin (<2 months old)
Pneumonia (non-severe) with chest-indrawing → Treat outpatient with 5-day oral amoxicillin
Severe Pneumonia classification → Admit to inpatient care with provision of IV antibiotic therapy (ampicillin + gentamycin) and oxygen if SpO_2<90%
* Respiratory distress signs are not assessed at facility levels 0, 1a, and 1b; only part of the respiratory assessment at facility level 2

Community level

At the community level (facility level 0), Health Surveillance Assistants (HSAs) trained in integrated Community Care Management (iCCM) can treat fast breathing-pneumonia with provision of antibiotics and home care counselling. Other cases (presenting with chest-indrawing or danger signs) are referred to a health facility for further management, as summarised in Table A.15. While the probability of correct identification and classification of the illness depends on training [59], supportive supervision, and guideline adherence [60], these variables were not incorporated in the modelling of quality of care to avoid added complexity and uncertainty. Instead, the model applies a fixed probability for correct classification by the health worker, as described in the next subsection.

Primary care level

At the primary care facilities (levels 1a/1b), clinical diagnosis of pneumonia follows the WHO Integrated Management of Childhood Illness (IMCI) approach, which provides simplified guidance for detecting fast-breathing, chest-indrawing and general danger signs (Tables A.13 and A.14). Under the revised 2014 guidelines, suspected cases are classified as 'non-severe' or 'severe' based on symptom severity and managed accordingly. These classifications indicate severity rather than an exact diagnosis. It does not include chest examination with auscultatory findings such as, wheeze, crackles, bronchial breath sounds, percussion findings [61]. As summarised in Table A.15, treatment varies by

classification: 'cough or cold' cases receive only supportive home care without antibiotics; 'non-severe pneumonia' requires oral antibiotics; and 'severe pneumonia' requires referral for inpatient care, though patients are admitted directly at facility level 1b (rural/community/mission hospitals) if capacity permits.

Secondary care level

At the secondary care level (facility level 2), including central and district hospitals, conduct more comprehensive assessments than primary care facilities, following the WHO Pocket Book of Hospital care for Children (2^{nd} edition). In addition to assessing additional clinical signs (Tables A.13 and A.14), secondary care includes chest examination with auscultatory findings, and chest radiography may be performed for differential diagnosis of respiratory conditions, including ALRI-related pulmonary complications. However, these latter two diagnostic processes were not incorporated in the care provision modelling. At secondary care facilities, non-severe classifications receive outpatient care with oral antibiotic provision, while severe pneumonia classifications receive inpatient care with parenteral antibiotics with oxygen therapy if hypoxaemia is detected, as summarised in Table A.15.

Tertiary care (facility level 3) is not modelled separately from the secondary care because Malawi's four central hospitals also function as district hospitals.

A.3.4 Quality of care - Health workers' performance

Health workers' ability to correctly classify the disease based on IMCI guidelines is key to assigning appropriate treatment. During assessment and classification, healthcare workers assign classifications based on observed signs and symptoms and their diagnostic accuracy, simplified here as their sensitivity in correctly applying IMCI guidelines, whereby the disease classification determines the treatment plan, and thus, the overall outcome of the health system interaction.

Tables A.16 and A.17 present the possible health worker-attributed classifications for each IMCI-based classification at facility level 0 (community health services with iCCM), and levels 1a, 1b and 2 (primary and secondary care with IMCI), respectively. In modelling quality of care through health workers' performance, only under-diagnosis was incorporated, while over-diagnosis was not modelled. This means non-severe pneumonia cannot be incorrectly escalated as severe pneumonia. This assumption can be supported by evidence of high IMCI pneumonia misdiagnosis rates in Malawi [62, 63].

Table A.16 Health worker's clinical classification pathway at facility level 0

Classification based on symptoms (iCCM)	**Parameters determining health worker performance**		**Classification given by health worker**
Fast-breathing pneumonia	sensitivity_of_classification_of_-fast_breathing_pneumonia_-facility_level0	✓	Fast-breathing pneumonia
		×	Cough or cold
Chest-indrawing, or Danger signs pneumonia	sensitivity_of_classification_of_-danger_signs_pneumonia_-facility_level0 prob_iCCM_severe_-pneumonia_treated_as_fast_-breathing_pneumonia	✓	Severe pneumonia
		×	Fast-breathing pneumonia
		×	Cough or cold

Table A.17 Health worker's clinical classification pathway at facility level 1a, 1b and 2

Classification based on symptoms (IMCI)	**Parameters determining health worker performance**		**Classification given by health worker**
Fast-breathing, or Chest-indrawing pneumonia	sensitivity_of_classification_of_-non_severe_pneumonia_-facility_level[1/2]	✓	Pneumonia (non-severe)
		×	Cough or cold
Danger signs pneumonia	sensitivity_of_classification_of_-danger_signs_pneumonia_-facility_level[1/2] prob_IMCI_severe_-pneumonia_treated_as_non_-severe_pneumonia	✓	Severe pneumonia
		×	Pneumonia (non-severe)
		×	Cough or cold

Sensitivity of classification parameters for each facility level - _level1 applies to 1a and 1b (primary care), _level2 applies to 2 (secondary care)

Input sensitivity values for correct classification according to IMCI guidelines and subsequent treatment provision were sourced from the Harmonised Health Facility Assessment (HHFA) 2018-2019 survey. In this report, healthcare providers' correct classification and treatment of pneumonia were estimated based on theoretical examination using patient scenarios, with reported sensitivity calculated from health workers' answers. Whereas, the previous equivalent survey - the Service Provision Assessment (SPA) 2013-2014 - reported variables based on exit interviews that involved reclassification of disease after patient appointments. This approach evaluated health workers' IMCI performance in practice with real case scenarios, providing the most accurate method for estimating performance sensitivity.

Studies using the SPA 2013-2014 survey data reported a 20.6% sensitivity for health workers' ability to correctly classify non-severe pneumonia in children aged 2-59 months [60], with correct 1st line antibiotics prescription in 38.7% of IMCI non-severe pneumonia [62]. These low performance rates were compounded by poor adherence to examination protocols in the assessment of cough and/or difficult breathing for IMCI pneumonia classification, with respiratory rate counted in only 18.6% of cases.

These findings from the SPA 2013-2014 analyses contrast with the more recent HHFA 2018-2019, which reported an average of 75% correct diagnosis and treatment across the health system. The decision to use the most recent sensitivity estimates accounts for the multiple factors influencing treatment provision, particularly antibiotic over-prescription. This prescribing pattern is evident in another SPA 2013-2014 data analysis showing a 59% over-prescription rate in patients without antibiotic indications [63]. Even when only one-third of patients were correctly identified with a pneumonia classification, misdiagnosed cases had a high probability of receiving antibiotics, with only 26.9% receiving no antibiotics [62].

Therefore, in considering these factors, the modelling of health workers' quality of care was simplified into a sensitivity measure for correct classification leading to the respective treatment plan. The sensitivity parameters use the reported 'correct diagnosis and treatment' values from the HHFA 2018-19 survey. For cases not correctly classified, the model allows under-classification of lower severity (danger signs pneumonia to chest-indrawing pneumonia) with oral antibiotic treatment, calibrated to match the overall 'correct diagnosis' rates in the HHFA 2018-19. The calculation for *prob_iCCM_severe_pneumonia_treated_as_fast_breathing_pneumonia* and *prob_IMCI_severe_pneumonia_treated_as_non_severe_pneumonia* are detailed in Table A.18.

Both health facility assessment reports (2013-14, 2018-19) focus on non-severe pneumonia. In the absence of data, the sensitivity values for severe pneumonia classification were assumed to be the same. Table A.18 presents the input values for the health worker sensitivity parameters.

Table A.18 Parameters of health worker sensitivity for correct classification

Parameters	Value	Source	Description
sensitivity_of_classification_of_fast_breathing_pneumonia_facility_level0	0.76	HHFA 2018	These parameters take the values of 'correct diagnosis and treatment' by facility type reported in the HHFA 2018-19. The overall sensitivity across the health system reported was 75% Reported 'correct diagnosis and treatment' by facility type matched with the facility levels in TLO model: Clinic - 0.76 (level 0) Hospital - 0.78 (level 2) Health centre - 0.73 (n=609), Dispensary - 0.79 (n=56), Health post - 0.77 (n=9) => facility level 1 = 0.7355
sensitivity_of_classification_of_danger_signs_pneumonia_facility_level0	0.76	HHFA 2018	
sensitivity_of_classification_of_non_severe_pneumonia_facility_level1	0.7355	HHFA 2018	
sensitivity_of_classification_of_severe_pneumonia_facility_level1	0.7355	HHFA 2018	
sensitivity_of_classification_of_non_severe_pneumonia_facility_level2	0.78	HHFA 2018	
sensitivity_of_classification_of_severe_pneumonia_facility_level2	0.78	HHFA 2018	
prob_iCCM_severe_pneumonia_treated_as_fast_breathing_pneumonia	0.5833	assumed	'correct diagnosis' at village clinic is 90%, not including treatment (HHFA 2018) $0.76 \times (0.24 \times x) = 90\%$ <=> $x = 0.583333$
prob_IMCI_severe_pneumonia_treated_as_non_severe_pneumonia	0.72	assumed	'correct diagnosis' at Hospital is 95%, at health centre is 92% (HHFA 2018) - Overall ∼93% $0.75 \times (0.25 \times x) = 93\%$ <=> $x = 0.72$

* Assuming the difference between 'correct diagnosis' and 'correct diagnosis and treatment' reported in the HHFA 2018-19 equals to the under-treatment given to a pneumonia classification

The sensitivity of correct classification parameters take the 'correct diagnosis and treatment' by facility type values reported in the HHFA 2018-19 - equivalent to the assumption in the model that correct classification leads to respective treatment decision.

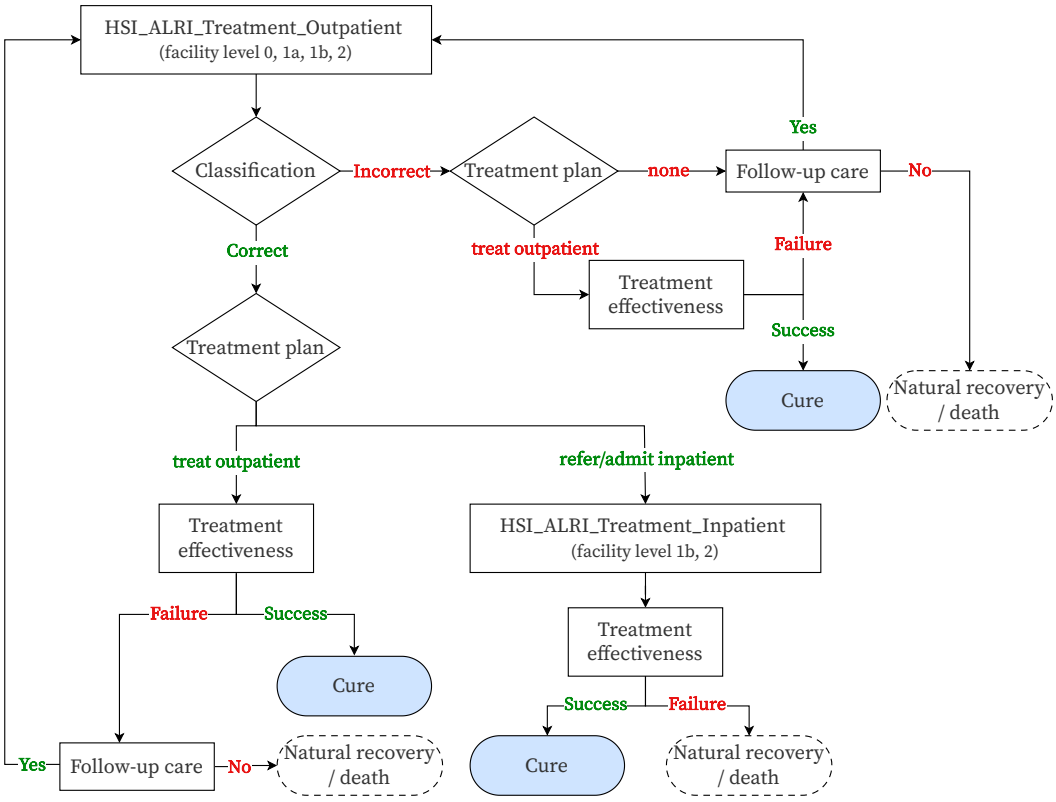
Here we assume no incorrect choice of treatment for the classification given, since this is already incorporated in the sensitivity parameter, meaning the sensitivity value is for both correct classification and correct treatment.

A.3.5 Care cascade

The outcome of health care provision begins with care-seeking. The classification assigned determines the treatment plan, which based on consumables availability, treatment effectiveness for the particular case type is applied. The care cascade leads to two possible outcomes: treatment failure or treatment success. Successful treatment schedules a cure event, while treatment failure results in health outcomes determined by the disease's natural history (recov-

ery or death) or at follow-up care. Figure A.7 illustrates the care cascade from classification and treatment to outcome.

Figure A.7: Flow diagram of care management to outcome



The HSI_ALRI_Treatment_Outpatient event applies the assessment and classification processes to determine the treatment action plan. This is equivalent to HSAs performing iCCM (facility level 0), health workers performing IMCI (facility level 1a, 1b), or health workers performing IMCI/Hospital Pocketbook (facility level 2) for children presenting with respiratory symptoms (cough and/or difficult breathing).

The classification outcome is determined by the health worker's performance, and if SpO_2<90%, the use of pulse oximeter can assist in the classification process by overriding the health worker's assigned classification to severe pneumonia, which requires referral to higher health facility level or admission for inpatient care.

Classification: Cough or cough (no pneumonia)

As summarised in Table A.15, cases presenting with cough and/or difficult breathing without fast-breathing, chest-indrawing, general danger signs, or respiratory distress are classified as cough or cold (no pneumonia). This classification receives no antibiotic treatment under iCCM/IMCI guidelines, only home counselling. Therefore, no treatment effectiveness is applied, and health outcomes are determined at follow-up with provision of 3-day oral antibiotics, or by the the natural history if no follow-up care is sought.

Classification: Fast-breathing pneumonia

As presented in Table A.16 and Table A.17, ALRI cases with fast-breathing only when correctly classified as non-severe pneumonia with fast-breathing, 3-day oral amoxicillin therapy is provided (Table A.15). Treatment effectiveness for the ALRI case type determines the outcome of the health system interaction: treatment success with a cured episode, or treatment failure requiring follow-up care with provision of 5-day oral antibiotics, or revert to the natural history outcome (recovery or death).

If incorrectly classified as cough or cold (misdiagnosis), the individual does not receive antibiotic treatment, and the disease outcome is determined by the natural history or at follow-up with provision of 3-day oral antibiotics.

Classification: Chest-indrawing pneumonia

As summarised in Table A.15, ALRI cases with chest-indrawing at the community level are referred to health facilities with a pre-referral dose of oral antibiotic when correctly classified as chest-indrawing pneumonia. If under-classified as fast-breathing pneumonia, care management at the community level with 3-day oral antibiotics results in either cure or treatment failure, leading to follow-up care with provision of 5-day oral antibiotics, or natural history outcomes.

At health facilities, chest-indrawing cases without general danger signs or respiratory distress receive outpatient care management with 5-day oral amoxicillin. Treatment failure leads to inpatient management at follow-up care or natural history outcomes without follow-up.

Cases misclassified as cough/cold receive no treatment and outcomes are determined by the natural history or at follow-up care with provision of 3-day oral antibiotics.

Classification: Danger signs pneumonia

General danger signs are assessed at both primary and secondary care facilities, whereas respiratory distress signs are assessed only at secondary care facilities. For severe pneumonia classifications, the care plan is inpatient admission with parenteral antibiotics and supportive care, including oxygen provision if SpO_2<90% (Table A.15). Treatment effectiveness from inpatient management results in either cure or treatment failure, with failed cases reverting to natural history outcomes. No follow-up care is modelled for inpatient management.

As described in Table A.17, severe cases can be under-classified as non-severe pneumonia, or misdiagnosed as cough/cold. When under-classified as non-severe pneumonia, treatment effectiveness of outpatient management with 5-day oral antibiotics is applied. If treatment fails, the outcome of the episode is determined at follow-up with inpatient care management, or if not sought follow-up care, the outcome is determined by the natural history. When misdiagnosed as cough/cold, no treatment is provided, and the ALRI episode outcome is determined by natural history or at follow-up care with provision of 3-day oral antibiotics.

A.3.6 Treatment failure

Treatment effectiveness was estimated as the complement of treatment failure ($P(TE) = 1 - P(TF)$). Equation (A.6) and Equation (A.8) estimate the treatment failure rate of outpatient care and inpatient care, respectively.

Outpatient care with oral antibiotics

For the IMCI classification of non-severe pneumonia, fast-breathing and/or chest-indrawing without general danger signs or respiratory distress, the multiplicative model Equation (A.6) estimates the failure rate of oral antibiotic therapy. This model also applies to severe cases given outpatient treatment.

$$\begin{aligned} Y_{TF_{oral}} = \beta_{TF_{oral}0} \times \\ (\beta_{TF_{oral}1} X_{SpO_2=90-92\%}) \times (\beta_{TF_{oral}2} X_{SpO_2<90\%}) \times \\ (\beta_{TF_{oral}3} X_{CXR}) \times (\beta_{TF_{oral}4} X_{MAM}) \times (\beta_{TF_{oral}5} X_{SAM}) \times \\ (\beta_{TF_{oral}6} X_{sympt-DS}) \times (\beta_{TF_{oral}7} X_{sympt-RD}) \end{aligned} \tag{A.6}$$

Dummy Variable	Property	Category/Status ($X_i = 1$)
$X_{SpO_2=90-92\%}$	ri_oxygen_saturation_level	'90-92%'
$X_{SpO_2<90\%}$	ri_oxygen_saturation_level	'<90%'
X_{CXR}	ri_disease_type	'Pneumonia'
X_{MAM}	un_clinical_acute_malnutrition	'MAM'
X_{SAM}	un_clinical_acute_malnutrition	'SAM'
$X_{sympt-DS}$	symptoms	'danger_signs'
$X_{sympt-RD}$	symptoms	'respiratory_distress'

Note: The model is a mix of RR and OR, the baseline risk is converted to odds to applied to OR and converted back into a risk.

For young infants aged less than 2 months with fast-breathing pneumonia, a 7-day course of oral amoxicillin is provided, while children aged 2 months and over are given a 3-day course of oral amoxicillin, at outpatient level. Children (aged 2-59 months) with chest-indrawing classification receive the 5-day course, and respective baseline treatment failures for each antibiotic course ($\beta_{TF_{oral}0}$) are described in Table A.19. Young infants (<2 months old) presenting with chest-indrawing pneumonia, and neonates (<7 days old) with fast-breathing only, are classified as severe pneumonia and treated at inpatient level, with treatment failures as per Equation (A.8).

Hypoxaemic cases (SpO_2<90%) seen at facility level 1a should receive pre-referral oxygen stabilisation therapy, if not, a relative risk of treatment failure is applied as per Equation (A.7). This risk is a proxy for worse outcomes in cases referred from primary care [41].

$$\begin{aligned} Y_{TF_{IV/oral_{no\_stabilisation}}} = \text{to\_prob}\Big(\text{to\_odds}(Y_{TF_{IV/oral}}) \times \\ ((\beta_{TF_{IV/oral\_no-stab}1} X_{SpO_2<90\%} X_{Ox\_not\_provided})\Big) \end{aligned} \tag{A.7}$$

to_odds = probability / (1 - probability)
to_prob = odds / (1 + odds)
$X_{SpO_2<90\%} X_{Ox\_not\_provided}$ - pre-referral oxygen not provided to hypoxaemic cases SpO_2<90%

If no intervention is provided, due to misdiagnosis as cough/cold, treatment failure is 100% for all classifications. The health outcome will then be determined by the natural history model or at follow-up care.

Inpatient care with parenteral antibiotics

For IMCI severe pneumonia classification (cases with general danger signs and/or respiratory distress, as per WHO hospital pocket book guidelines), the following multiplicative model equation (Equation (A.8)) estimates the treatment failure of IV antibiotic therapy, with oxygen provision if needed, at inpatient care. This model also applies to inpatient care of non-severe symptom cases with SpO_2<90%, and cases with oral treatment failure receiving care at follow-up.

$$\begin{aligned} Y_{TF_{IV}} = \beta_{TF_{IV}0} \times \\ (\beta_{TF_{IV}1} X_{HIVnotART}) \times (\beta_{TF_{IV}2} X_{SpO_2<90\%}) \times \\ (\beta_{TF_{IV}3} X_{CXR}) \times (\beta_{TF_{IV}4} X_{MAM}) \times (\beta_{TF_{IV}5} X_{SAM}) \times \\ (\beta_{TF_{IV}6} X_{sympt-DS}) \times (\beta_{TF_{IV}7} X_{sympt-RD}) \end{aligned} \tag{A.8}$$

Dummy Variable	**Property**	**Category/Status ($X_i = 1$)**
$X_{HIVnotART}$	hv_inf	True
	hv_art	'not'
$X_{SpO_2<90\%}$	ri_oxygen_saturation_level	'<90%'
X_{CXR}	ri_disease_type	'Pneumonia'
X_{MAM}	un_clinical_acute_malnutrition	'MAM'
X_{SAM}	un_clinical_acute_malnutrition	'SAM'
$X_{sympt-DS}$	symptoms	'danger_signs'
$X_{sympt-RD}$	symptoms	'respiratory_distress'

At inpatient care, the antibiotic therapy administered for severe pneumonia cases is intravenous injection of ampicillin (or benzyl-penicillin) + gentamicin as the the first line of IV antibiotics, and ceftriaxone as second line, or cloxacillin + gentamicin if 1st line fails. Depending on whether the IV antibiotic provided was 1st line or 2nd line the $\beta_{TF_{IV}0}$ takes either the value of the parameter tf_1st_line_antibiotic_for_severe_pneumonia, or tf_2nd_line_antibiotic_for_severe_pneumonia (Table A.19). The $Y_{TF_{IV}}$ result from Equation (A.8) is the final estimate of the risk of treatment failure for severe pneumonia classification cases that do not require oxygen therapy (no hypoxaemia), or cases that need oxygen (SpO_2<90%) or would benefit from oxygen (SpO_2 90-92%) that were provided with oxygen therapy in their care management. Cases needing oxygen (SpO_2<90%) referred from health centres, require pre-referral stabilisation oxygen therapy in order to have $Y_{TF_{IV}}$ result from Equation (A.8) as the final estimate, else Equation (A.7) is applied.

For cases that need or might benefit from oxygen provision at inpatient care, but were not given such intervention, the computed risk of treatment failure $Y_{TF_{IV}}$ further goes through a modification by the odds ratio of treatment failure if oxygen is not provided represented in the following equation (Equation (A.9)):

$$Y_{TF_{IV\,no-ox}} = \text{to\_prob}\Bigg(\text{to\_odds}(Y_{TF_{IV}}) \times \left(\frac{1}{OR_1} X_{SpO_2<90\%}\right) \times \left(\frac{1}{OR_2} X_{SpO_2=90-92\%}\right)\Bigg) \tag{A.9}$$

to_odds = probability / (1 - probability)
to_prob = odds / (1 + odds)
$\frac{1}{OR_1}$ is the inverse of or_mortality_improved_oxygen_systems
$\frac{1}{OR_2}$ is the inverse of or_mortality_oxygen_provision_to_SpO_2=90-92%

The final estimated risk of treatment failure for severe pneumonia classification cases with SpO_2<93%, managed at inpatient care with IV antibiotic therapy but without oxygen provision, is $Y_{TF_{IV\,no-ox}}$.

Follow-up care after treatment failure

For non-severe pneumonia classifications assigned by health workers and receiving outpatient management, if treatment fails and the disease duration is longer than the course of treatment, these cases are eligible to a probability of 60% to seek follow-up care, with an increased odds of follow-up for conditions with severe symptoms: danger signs and respiratory distress, as well as age below 2 months (Table A.12). Similarly, the non-treatment of cases given the 'cough or cold' classification by the health worker, the 60% probability of follow-up by day 3 is applied.

For severe pneumonia classification provided with inpatient care at the first instance of care provision, follow-up care was not modelled, as they received the ultimate treatment for ALRI, including second line antibiotics when first line treatment fails.

Inpatient follow-up care:

Non-severe classifications with chest-indrawing who failed initial oral antibiotic treatment, and severe classifications incorrectly managed at outpatient care, at follow-up care these cases are provided with inpatient management if last facility level of care provision is at hospital level, or upon referral from health centre level. Thus, following Equation (A.8) plus an increased risk of treatment failure with previous oral antibiotic administration and incorrect initial care provided, emulating delayed prompt correct treatment, and progression of disease Equation (A.10). Otherwise, if referral to hospital level was not possible, another course of oral antibiotics takes effect.

$$Y_{TF_{IV/oral\,fup}} = Y_{TF_{IV/oral}} \times (\beta_{TF_{IV/oral\,fup}1} X_{previous\_oral}) \times (\beta_{TF_{IV/oral\,fup}2} X_{incorrect\_initial\_care}) \tag{A.10}$$

$X_{previous\_oral}$ - initial treatment with oral antibiotics

$X_{incorrect\_initial\_care}$ - initial outpatient care provision to any of the following: SpO_2 level <93%, respiratory distress, or general danger signs

If severely or moderately hypoxaemic and oxygen is not provided at follow-up inpatient management, further Equation (A.9) is applied. In addition, Equation (A.7) is applied if oxygen is needed (SpO_2<90%) without pre-referral stabilisation therapy provided.

Outpatient follow-up care:

Cough or cold classification with no treatment provision, and non-severe classifications given 3-day oral amoxicillin who failed initial oral antibiotic treatment, at follow-up care these cases are provided with outpatient management, with 3-day and 5-day oral antibiotic, respectively. Thus, following Equation (A.6) plus an increased risk of treatment failure with previous oral antibiotic administration, and incorrect initial care provided if moderate to severe hypoxaemic, or with severe symptoms (Equation (A.10)), and without pre-referral stabilisation therapy if severely hypoxaemic (Equation (A.7)).

Table A.19 Parameters of treatment failure

Symbol	Parameters	Value	Source	Description
$\beta_{TF_{oral}0}$	Treatment failure of 3-day course of oral amoxicillin to treat fast-breathing pneumonia with $SpO_2 \geq 90\%$ **[tf_3day_amoxicillin_for_fast_breathing_with_-$SpO_2 \geq 90\%$]**	0.0715	[65] + model output	TF at day 6 or relapse by day 14 - 10.1% (overall TF), the baseline TF was estimated through the model simulation *1
$\beta_{TF_{oral}0}$	Treatment failure of 5-day course of oral amoxicillin to treat chest-indrawing pneumonia with $SpO_2 \geq 90\%$ **[tf_5day_amoxicillin_for_chest_indrawing_with_-$SpO_2 \geq 90\%$]**	0.0802	[66] + model output	TF at day 6 or relapse by day 14 - 10.8% (overall TF), the baseline TF was estimated through the model simulation *1
$\beta_{TF_{oral}0}$	Treatment failure of 3-day course of oral amoxicillin to treat chest-indrawing pneumonia with $SpO_2 \geq 90\%$ **[tf_3day_amoxicillin_for_chest_indrawing_with_-$SpO_2 \geq 90\%$]**	0.0930	[66] + model output	TF at day 6 or relapse by day 14 - 12.5% (overall TF), the baseline TF was estimated through the model simulation *1
$\beta_{TF_{oral}0}$	Treatment failure of 7-day course of oral amoxicillin to treat fast-breathing pneumonia with $SpO_2 \geq 90\%$ in young infants aged 7 days to 2 months old **[tf_7day_amoxicillin_for_fast_breathing_pneumonia_-in_young_infants]**	0.0389	[67] + model output	TF at day 6 or relapse by day 14 - 5.4% (overall TF), the baseline TF was estimated through the model simulation *1
$\beta_{TF_{oral}1}$	Odds ratio of treatment failure of oral antibiotics (amoxicillin) if SpO_2 is between 90-92% **[or_tf_oral_antibiotics_if_SpO_2_90_92%]**	1.42	assumed	OR=2.11 of treatment failure if $SpO_2 < 90\%$ multiply by the fraction of 0.52/0.7731 (OR_1/OR_2)=1.42
$\beta_{TF_{oral}2}$	Odds ratio of treatment failure of oral antibiotics (amoxicillin) if $SpO_2 < 90\%$ **[or_tf_oral_antibiotics_if_$SpO_2 < 90\%$]**	2.11	[68]	
$\beta_{TF_{oral}3}$	Relative risk of treatment failure of oral antibiotics if abnormal chest radiography (pneumonia disease type) **[rr_tf_oral_antibiotics_if_abnormal_CXR]**	1.48	[69]	
$\beta_{TF_{oral}4}$	Odds ratio of treatment failure of oral antibiotics (amoxicillin) if moderate acute malnutrition (MAM) **[or_tf_oral_antibiotics_if_MAM]**	1.88	[70]	

Continued on next page

Table A.19 – continued from previous page

Symbol	Parameters	Value	Source	Description
$\beta_{TF_{oral}5}$	Odds ratio of treatment failure of oral antibiotics (amoxicillin) if moderate acute malnutrition (SAM) **[or_tf_oral_antibiotics_if_SAM]**	2.2	[71]	
$\beta_{TF_{oral}6}$	Relative risk of treatment failure of oral antibiotics (amoxicillin) if general danger signs **[rr_tf_oral_antibiotics_if_danger_signs]**	1.90	Assumption based on [64]	The ratio of the relative risks of IV treatment failure if general danger signs ($\beta_{TF_{IV}6}$) and if respiratory distress ($\beta_{TF_{IV}7}$) is 1.55/1.1=1.409. Thus, for oral antibiotics the relative risk of TF is estimated to be 1.409 × $\beta_{TF_{oral}7}$=1.90
$\beta_{TF_{oral}7}$	Relative risk of treatment failure of oral antibiotics (amoxicillin) if respiratory distress **[rr_tf_oral_antibiotics_if_respiratory_distress]**	1.35	Assumption based on [68]	Relative risk of death of SpO_2<90 in the community vs hospital is 0.40645 [68]. Remove the effect of oxygen on hospital mortality: to_prob(to_odds(6.3%) * (1/0.52)) = 11.45%; then relative risk of death of SpO_2<90 of oral vs parenteral antibiotics without oxygen is 11.45%/15.5%=0.7387; the inverse 1/0.73868=1.3537
$\beta_{TF_{IV\_no-stab}1}$ $\beta_{TF_{oral\_no-stab}1}$	Odds ratio of treatment failure in hypoxaemic cases seen at the health centre without pre-referral stabilisation oxygen therapy **[or_tf_non_stabilised_with_oxygen_prior_to_referral]**	1.72	[41]	Assumed from the increase risk of death of severe cases seen at the health centre before reaching to the hospital
$\beta_{TF_{IV\,fup}1}$ $\beta_{TF_{oral\,fup}1}$	Odds ratio of treatment failure at follow-up care if previous oral antibiotics treatment **[or_tf_at_follow_up_care_with_previous_oral_antibiotic]**	1.47	[71]	
$\beta_{TF_{IV\,fup}2}$ $\beta_{TF_{oral\,fup}2}$	Relative risk of treatment failure at follow-up care if initial care was not appropriate **[rr_tf_follow_up_care_with_initial_incorrect_care]**	1.78	Assumed based on [65]	in the source this value is the RR of treatment failure of non-treatment compared to oral antibiotic for fast-breathing pneumonia classification

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Table A.19 – continued from previous page

Symbol	Parameters	Value	Source	Description
$\beta_{TF_{IV}0}$	Treatment failure of first line parenteral antibiotics for severe pneumonia **[tf_1st_line_antibiotic_for_severe_pneumonia]**	0.1308	[48] + model output	Source value 19.3% - overall 1st line (ampicillin + gentamycin) TF for IMCI severe pneumonia, the baseline TF was estimated through the model simulation *2
$\beta_{TF_{IV}0}$	Treatment failure of second line parenteral antibiotics for severe pneumonia **[tf_2nd_line_antibiotic_for_severe_pneumonia]**	0.1329	[47] + model output	Source value 19.61% - overall 2nd line (ceftriaxone) TF for IMCI severe pneumonia, the baseline TF was estimated through the model simulation *2
$\beta_{TF_{IV}1}$	Relative risk of treatment failure of parenteral antibiotics if HIV positive not on ART **[rr_tf_1st_line_antibiotics_if_HIV/AIDS]**	1.8	[64] *3	Parameter values from source [64] (study in Mwanza, Tanzania) are specific to the treatment failure of 1st line ampicillin and gentamicin in the treatment of severe pneumonia cases at inpatient care, here in the model were also applied to the treatment failure of 2nd line antibiotics
$\beta_{TF_{IV}2}$	Relative risk of treatment failure of parenteral antibiotics if SpO_2<90% **[rr_tf_1st_line_antibiotics_if_SpO_2<90%]**	1.28	[64]	
$\beta_{TF_{IV}3}$	Relative risk of treatment failure of parenteral antibiotics if abnormal chest radiography (pneumonia disease type) **[rr_tf_1st_line_antibiotics_if_abnormal_CXR]**	1.71	[64]	
$\beta_{TF_{IV}4}$	Relative risk of treatment failure of parenteral antibiotics if moderate acute malnutrition (MAM) **[rr_tf_1st_line_antibiotics_if_MAM]**	1.48	[64]	
$\beta_{TF_{IV}5}$	Relative risk of treatment failure of parenteral antibiotics if severe acute malnutrition (SAM) **[rr_tf_1st_line_antibiotics_if_SAM]**	2.02	[64]	
$\beta_{TF_{IV}6}$	Relative risk of treatment failure of parenteral antibiotics if general danger signs present **[rr_tf_1st_line_antibiotics_if_general_danger_signs]**	1.55	[64]	
$\beta_{TF_{IV}7}$	Relative risk of treatment failure of parenteral antibiotics if respiratory distress **[rr_tf_1st_line_antibiotics_if_respiratory_distress]**	1.11	[64]	non-significant in the multivariate model, included

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Table A.19 – continued from previous page

Symbol	Parameters	Value	Source	Description
OR_1	Odds ratio of mortality with improved oxygen systems **[or_mortality_improved_oxygen_systems]**	0.52	[72]	use the inverse $\frac{1}{0.52}$ as OR for TF without provision of oxygen for SpO_2<90%
OR_2	Odds ratio of treatment failure of parenteral antibiotics if oxygen is provided to SpO_2=90-92% by age group: <2 and 2-59 months **[or_tf_1st_line_antibiotics_if_oxygen_provision_to_-SpO_2=90-92%]**	0.8025, 0.648	assumed	1 - (1 - $\beta_{TF_{IV}8}$ / ($\beta_{\theta 10}$ / $\beta_{\theta 11}$)) , where 1 - $\beta_{TF_{IV}8}$: convert OR into likelihood ($\beta_{\theta 10}$ / $\beta_{\theta 11}$): relative OR of mortality in low oxygen saturation (1 - $\beta_{TF_{IV}8}$ / ($\beta_{\theta 10}$ / $\beta_{\theta 11}$)): likelihood of treatment success for oxygen provision in SpO_2=90-92% 1 - this fraction returns in likelihood, convert back to OR weighted OR=0.7731

*1 Using the simulation model cohort, the baseline risk of treatment failure of oral antibiotics was determined by applying a scaling factor such that overall treatment failure in non-severe classifications matches 10.1% for fast-breathing pneumonia, 10.8% for chest-indrawing pneumonia, 12.5% for chest-indrawing pneumonia with 3-day course, or 5.4% for fast-breathing pneumonia in young infants.

*2 Using the simulation model cohort, the baseline risk of treatment failure was determined by applying a scaling factor such that overall treatment failure in severe pneumonia matches 19.3% for 1st line or 19.6% for 2nd line parenteral antibiotics.

*3 Parameter values from source [64] (study in Mwanza, Tanzania) are specific to the TF of 1stline ampicillin and gentamicin in the treatment of severe pneumonia cases at inpatient care

A.3.7 Simulation time-steps of health system interactions

From the natural history events, when an ALRI episode is onset, the onset of symptoms at the start of the disease are registered in the Symptom Manager module. This module pulls together the symptoms from other disease modules and informs the Health Seeking Behaviour module the presenting symptoms of an individual compiled from all the diseases. The health seeking behaviour module is scheduled to check on the presence of symptoms and computes a health seeking probability. HealthSeekingBehaviourPoll Regular event at population level, occuring everyday, an appointment is scheduled within the next 4 days. If the outcome of the polling event is to seek care, the individual is scheduled a generic 1st appointment.

In the cohort simulation, we set the function: *force_any_symptom_to_lead_to_healthcareseeking*=True in the registration of the HealthSeekingBehaviour module, whereby any symptom will cause contact with the health system. Thus, for the cost-effectiveness analysis, all ALRI cases in the cohort seek care, and health system interaction (HSI) event for ALRI is scheduled.

HSI ALRI Treatment Event

As illustrated in Figure A.7, the HSI_Alri_Treatment_Outpatient event is where the health worker's sensitivity of correct classifications is applied, and subsequent consumables and treatment effectiveness take place. If available, routine pulse oximetry is used at the assessment stage, assisting classifications based on SpO_2 measurement. If the classification assigned is non-severe pneumonia, all related functions occur in this event. If the classification assigned is severe pneumonia, then HSI_Alri_Treatment_Inpatient event is scheduled, where inpatient management with parenteral antibiotics and bed days are logged.

Following treatment failure, follow-up care is scheduled. Depending on the initial disease classification of the ALRI episode, either HSI_Alri_Treatment_Outpatient_Followup or HSI_Alri_Treatment_Inpatient_Followup is scheduled. Outpatient care with oral antibiotics is provided to cases classified as 'cough or cold' or 'fast-breathing pneumonia' in their initial appointment. Whereas, 'chest-indrawing pneumonia' classification are provided with inpatient management at follow-up.

ALRI Cure Event

This event is scheduled in the HSI_Alri_Treatment event, where based on the treatment effectiveness for the particular case, a cure is scheduled (ALRI Cure Event). Similarly to the Natural Recovery Event, it onsets the recovery date and resets the ALRI properties back to the non-disease states. Once this occurs, the individual is back on the susceptible population for the ALRI Polling Event.

Appendix B

Costing of oxygen systems in Malawi

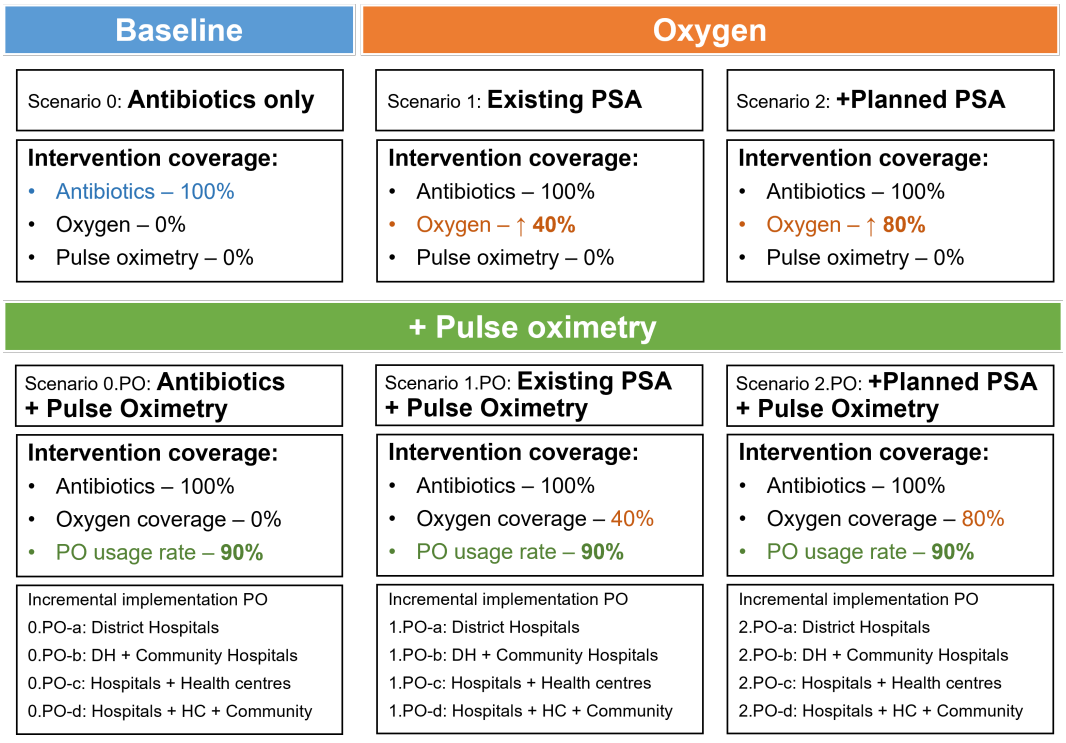
B.1 Intervention scenarios

In this economic evaluation, the impact of interventions were assessed and compared to the baseline intervention of antibiotics only:

1) Oxygen (with monitoring pulse oximeters)
2) Pulse oximetry at outpatient settings
3) 1) + 2)

The intervention combinations at varying levels of implementation across the health system make up a total of 15 scenarios. Figure B.1 shows an overview of the scenarios' intervention coverage.

Figure B.1: Intervention scenarios summary



The health system conditions are constant across all scenarios:

- 100% availability of antibiotics, outpatient and inpatient care services.
- 75% sensitivity of health workers' IMCI performance
- 85% complete referral rate of severe cases seen at the health centre
- 60% seek follow-up care following oral antibiotics failure, with greater odds of seeking follow-up care with a severe symptom

The increased demand for inpatient care with increase diagnosis or treatment requirements by the implementation of the interventions (↑inpatient beds, ↑staff time, parenteral form of antibiotic) is assumed to be available, not modelling the effects of the health systems constraints, and competing resources by other disease modules. The analysis is focused on evaluating the effect on mortality with the implementation of new interventions to the IMCI strategy. By setting the coverage of antibiotics and other healthcare resources to 100%, it enables the evaluation of the effects of new interventions and the additional cost associated with their implementation.

B.1.1 Baseline scenario – Antibiotics only

The baseline scenario is defined as antibiotics only, despite the existing oxygen availability in Malawi. This choice reflects the reported poor use of oxygen in Malawi [29], making this scenario the closest representation to the current status quo. Additionally, opting for this baseline allows for the evaluation of oxygen's impact compared to its absence.

In the baseline scenario, the availability of antibiotics is maintained at 100%, along with other healthcare resources including outpatient appointments and inpatient care services. Subsequently, the interventions to be assessed are introduced on top of these constant baseline conditions, which enables the evaluation of the interventions' effects without the interference of other factors.

In addition to the arguments outlined for modelling full antibiotics availability, an examination of TLO's consumables availability input data (based on OpenLMIS data) revealed that non-availability of oral antibiotic alternatives for pneumonia (amoxicillin, co-trimoxazole, erythromycin, azithromycin) at the health centre level is only 3%. At the community level, non-availability is 26%, but these cases would be directed to the health centre for the required antibiotics. The model currently assumes a full link between community and health centre, but even if a clause is added that only 70% of cases make it to the health centre, the overall coverage still exceeds 90%.

In terms of parenteral antibiotics, non-availability of first-line options (ampicillin or benzylpenicillin + gentamycin) at rural hospitals is only 1.66%, and at district hospitals is <0.12%. However, the TLO consumables module has not included availability data of a few alternatives for 2nd line antibiotics. Furthermore, according to Dr Eric McCollum (clinical adviser), a severely ill child would not be left untreated; instead, they would have been referred elsewhere to receive the appropriate parenteral antibiotic therapy. Hence, the mortality pool would experience minimal change if non-severe cases had no oral antibiotic treatment at the non-availability rate in the TLO model.

B.1.2 Oxygen scenario – Existing, and +Planned PSAs

The Malawi National Medical Oxygen Ecosystem Roadmap 2021-2026 [57] referred to as the 'Roadmap' throughout this report, served as a guiding document in the estimation of coverage of oxygen, and to a certain degree, the estimation of total costs. According to the Roadmap, there are currently eight Pressure Swing Adsorption (PSA) oxygen plants installed in Malawi, which forms the basis of the 'Existing PSA' system scenario in the analysis – referred to as scenario 1. The Roadmap outlines a primary plan to scale up seven additional PSA plants, which forms scenario 2 in the analysis, termed '+Planned PSA' system. This scenario 2 encompasses both the eight existing and the seven planned PSA plants, covering the associated costs and oxygen coverage of the total 15 PSA plants of varying capacity.

It should be noted that the oxygen intervention scenarios include pulse oximeters for monitoring oxygen administration. For cases diagnosed with severe pneumonia, peripheral oxygen saturation (SpO_2) is measured upon inpatient admission, and oxygen therapy is provided if SpO_2<90%.

B.1.3 Pulse oximetry scenario

Routine pulse oximetry at outpatient settings was modelled with a coverage of one device per health worker. This intervention is essential in the detection of hypoxaemia, and assists in diagnosing hypoxaemic cases not suspected by clinical signs or missed severe classifications by health workers due to clinical error. The potential benefit of pulse oximetry in guiding antibiotic treatment decisions for moderate hypoxaemia (SpO_2 between 90-92%) or an abnormal level (SpO_2 between 93-94%) is not incorporated in this analysis, as the focus is specifically on oxygen provision for SpO_2<90%. Therefore, the modelled effects of routine pulse oximetry use in outpatient settings represent solely the detection and treatment of cases with SpO_2<90%.

For the pulse oximetry intervention, coverage was assumed to be 100% with costing of one device per health worker. Unlike oxygen systems implementation, no national strategic plan exists for pulse oximetry implementation in outpatient departments in Malawi. Therefore, coverage was set at maximum levels to measure potential benefit and associated costs. Additionally, a parameter for health workers' consistent use was applied to reflect real-world conditions of imperfect quality of care, set to 90%.

In the baseline scenario, the introduction of routine pulse oximetry intervention without oxygen service availability, is referred to as scenario 0.PO, where 'PO' referencing to pulse oximetry implementation. Scenarios 1.PO, and 2.PO implement a combination of oxygen and pulse oximetry, with oxygen coverage determined by the corresponding PSA implementation scenario. The numerical prefix of these scenarios corresponds to the oxygen scenario number. The implementation of pulse oximetry at outpatient settings was analysed in an incremental rollout across health system facility levels. Starting with the introduction of the diagnostic intervention at facility level 2 (Central/District hospitals), then progressively extends to level 1b (Mission/ Community/ Rural hospitals), level 1a (Health centres), and finally level 0 (Village clinics with health surveillance assistants).

Scenario 0.PO: Baseline (IMCI antibiotics only) & Pulse oximetry

In this scenario, routine pulse oximetry at outpatient settings is added to the baseline of antibiotics only, scenario 0.

- Scenario 0.PO-a: Antibiotics + PO at facility level 2
- Scenario 0.PO-b: Antibiotics + PO at facility level 2, 1b
- Scenario 0.PO-c: Antibiotics + PO at facility level 2, 1b, 1a
- Scenario 0.PO-d: Antibiotics + PO at facility level 2, 1b, 1a, 0

Scenario 1.PO: Existing PSA system & Pulse oximetry

In this scenario, routine pulse oximetry at outpatient settings is added to the 'Existing PSA' scenario (scenario 1), involving an oxygen system based on 8 already installed PSA plants.

- Scenario 1.PO-a: Existing PSA + PO at facility level 2
- Scenario 1.PO-b: Existing PSA + PO at facility level 2, 1b
- Scenario 1.PO-c: Existing PSA + PO at facility level 2, 1b, 1a
- Scenario 1.PO-d: Existing PSA + PO at facility level 2, 1b, 1a, 0

Scenario 2.PO: +Planned PSA system & Pulse oximetry

In this scenario, routine pulse oximetry at outpatient settings is added to the '+Planned PSA' scenario (scenario 2), involving an oxygen system based on 8 already installed, and planned implementation of 7 new PSA plants.

- Scenario 2.PO-a: +Planned PSA + PO at facility level 2
- Scenario 2.PO-b: +Planned PSA + PO at facility level 2, 1b
- Scenario 2.PO-c: +Planned PSA + PO at facility level 2, 1b, 1a
- Scenario 2.PO-d: +Planned PSA + PO at facility level 2, 1b, 1a, 0

Table B.1 Summary description of the 15 scenarios - availability of oxygen service and pulse oximetry

Scenarios	Oxygen availability	Pulse oximetry availability
No oxygen availability and no pulse oximetry [Scenario 0]	None	None
No oxygen availability and pulse oximetry at level 2 [Scenario 0.PO-a]	None	Central/District hospitals (level 2)
No oxygen availability and pulse oximetry at levels 2 and 1b [Scenario 0.PO-b]	None	Central/District hospitals (level 2), and Rural/Community/Mission hospitals (level 1b)
No oxygen availability and pulse oximetry at levels 2, 1b, and 1a [Scenario 0.PO-c]	None	Central/District hospitals (level 2), Rural/Community/Mission hospitals (level 1b), and Health centres (level 1a)
No oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0 [Scenario 0.PO-d]	None	Central/District hospitals (level 2), Rural/Community/Mission hospitals (level 1b), Health centres (level 1a), and Village clinics (level 0)
Low oxygen availability and no pulse oximetry [Scenario 1]	40% service availability (low availability) By facility level: Level 2: 51.6%; Level 1b: 33.3%; Level 1a: 31.3%	None
Low oxygen availability and pulse oximetry at level 2 [Scenario 1.PO-a]		Central/District hospitals (level 2)
Low oxygen availability and pulse oximetry at levels 2 and 1b [Scenario 1.PO-b]		Central/District hospitals (level 2), and Rural/Community/Mission hospitals (level 1b)
Low oxygen availability and pulse oximetry at levels 2, 1b, and 1a [Scenario 1.PO-c]		Central/District hospitals (level 2), Rural/Community/Mission hospitals (level 1b), and Health centres (level 1a)
Low oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0 [Scenario 1.PO-d]		Central/District hospitals (level 2), Rural/Community/Mission hospitals (level 1b), Health centres (level 1a), and Village clinics (level 0)
High oxygen availability and no pulse oximetry [Scenario 2]	80% service availability (high availability) By facility level: Level 2: 88.1%; Level 1b: 75.4%; Level 1a: 73.9%	None
High oxygen availability and pulse oximetry at level 2 [Scenario 2.PO-a]		Central/District hospitals (level 2)
High oxygen availability and pulse oximetry at levels 2 and 1b [Scenario 2.PO-b]		Central/District hospitals (level 2), and Rural/Community/Mission hospitals (level 1b)
High oxygen availability and pulse oximetry at levels 2, 1b, and 1a [Scenario 2.PO-c]		Central/District hospitals (level 2), Rural/Community/Mission hospitals (level 1b), and Health centres (level 1a)
High oxygen availability and pulse oximetry at levels 2, 1b, 1a, and 0 [Scenario 2.PO-d]		Central/District hospitals (level 2), Rural/Community/Mission hospitals (level 1b), Health centres (level 1a), and Village clinics (level 0)

No oxygen availability and no pulse oximetry [Scenario 0] is the null scenario comparator

B.2 Oxygen coverage estimation

The Roadmap reported a total daily oxygen demand of 3,838,535 litres (L), and the total annual oxygen demand is 1,401,065,280 L [57]. It also reported the estimated average daily and annual oxygen demand per facility type. This information was used in the estimation of oxygen availability at the three levels of the health system grouped in TLO (Table B.2).

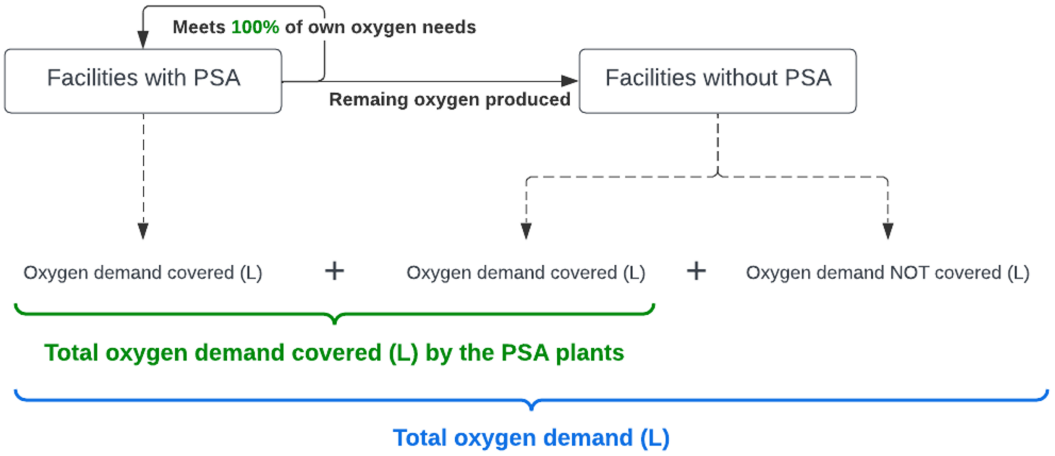
Table B.2 Oxygen demand per facility type reported in the Roadmap

Health facility type	**Number of facilities**	**Daily oxygen demand (L) per facility**	**TLO facility level**	**Annual oxygen demand (L)**
Central Hospital	5	112,948	2	565,798,380
District Hospital	25	39,416		
Mission Hospital	27	25,533	1b	355,020,000
Rural Hospital	25	11,088		
Community Hospital	2	3,023		
Health Centre	457	2,879	1a	480,246,900

*Central Hospitals in TLO health facility levels is level 3. Here grouped with level 2 (District Hospitals), as they serve as District Hospitals to their respective district and Central Hospital to their health zone

Figure B.2 illustrates the process of estimating coverage. In each oxygen scenario, facilities with PSA plants are self-sufficient to meet their own oxygen needs, while the remaining produced oxygen is distributed to non-PSA facilities through cylinders. This distribution was assumed to be proportional to the need at each facility level, estimates shown in Table B.4 for scenario 1 (Existing PSA system), and Table B.5 for scenario 2 (+Planned PSA system). Coverage is equal to the ratio of oxygen demand in liters covered by the PSA plants production and supply rate, over the total oxygen demand nationally.

Figure B.2: Estimation of oxygen coverage process



$$Coverage = \frac{\text{Oxygen Demand Covered (L)}}{\text{Total Oxygen Demand (L)}}$$

Maximum oxygen production (L) per day was estimated to be around 8.704 effective operating hours for existing plants. This was based on the reported maximum of 64 'J' cylinders (6,800L) filling capacity per day for Kamuzu Central Hospital and Queen Elizabeth Central Hospital [73], both of which have PSA plant capacities of 50,000 L/hour (Table B.3). This estimate was further confirmed when the filling capacity of all existing plants was summed (excluding the two plants with piped systems), totalling 205 J-cylinders, totalling 205 J-cylinders, which closely matches the reported 209 daily cylinders filled in the Roadmap (Indicator: 'total cylinders filled at on-site PSA plants').

For the eight existing plants, we adjusted the production rate to 8.446 effective operating hours, resulting in an overall oxygen coverage of 40.0%, compared to the original 41.1%. While for the seven planned additional plants, we assumed 6.074 effective operating hours, to avoid an assumption of a linear relationship between increased production capacity and coverage.

Following oxygen production rate, it was assumed that the distribution and delivery of oxygen-filled cylinders would reach all target facilities. Setting the daily production rate at 8.704 and 6.074 hours addresses the potential bottlenecks and practical constraints associated with production and supply chain challenges in Malawi, given the absence of data on current distribution capacity and specific facilities being targeted.

To complement the estimated availability, oxygen concentrators were incorporated into the oxygen systems implementation model and total associated costs to address potential bottlenecks not accounted for in the effective hour assumption and to further supplement service availability rates.

Table B.3 shows the calculation process of estimating the total oxygen production (L) for each oxygen scenario and the amount to be distributed to neighbouring facilities. The total '*Oxygen (L) available for distribution*' under each oxygen scenario was used to estimate the coverage of oxygen by facility level (2, 1b, and 1a). Overall, the coverage ranges from 40% in 'Existing PSA' scenario, and 80% in '+Planned PSA' scenario.

Table B.3 Calculation of the oxygen demand for facilities with PSA plants and amount available for distribution

	Zone	Zone daily oxygen demand (L)	Facility name	Production capacity (L/h)	Maximum production L/day	Filling capacity	Daily oxygen demand (L) for facility	Oxygen (L) available for distribution	% Zone daily demand (L) met
Existing PSAs	North	599126	Nkhata Bay District Hospital	4830	40794		39416	1378	6.81%
	Central		Daeyang Luke Hospital	10000	84460	No	25533	0	
	Central	1520717	Kamuzu Central Hospital	50000	422300		112948	309352	33.32%
	South		Mercy James	12000	101352	No	112948	0	
	South		Neno District Hospital	1375	11613		39416	0	
	South		Phalombe District Hospital	49000	413854		39416	374438	
	South		Queen Elizabeth Central H.	50000	423300		112948	309352	
	South	1718692	Lisungwi Community Hospital	6900	58277		3023	55254	58.61%
	Total	3838535					485648	1049775	**40%**
Planned PSAs	North		Karonga District Hospital	23800	144561		39416	105145	
	North		Mzuzu Central Hospital	50000	303700		112948	190752	81.63%
	Central		Nkhoma Mission Hospital	21000	127554		25533	102021	
	Central		Kasungu District Hospital	60000	364440		39416	325024	
	Central		Bwaila District Hospital	32000	194368		39416	154952	78.46%
	South		Zomba Central Hospital	50000	303700		112948	190752	
	South		Mangochi District Hospital	16000	97184		39416	57768	81.94%
	Total						894741	2176189	**80%**

Oxygen available for distribution = Maximum production L/day – Daily oxygen demand (L) for facility type
Total coverage = (Maximum production (L/day) + Daily oxygen demand (L) for facility type of piped systems) / total zone daily demand

B.2.1 Scenario 1 — Existing PSA system

There are 8 existing PSA plants in Malawi. Three of which are Central Hospitals, (Mercy James considered Central Hospital in the Roadmap), 4 District Hospitals, 2 Mission and 1 Community Hospital (not yet commissioned). The existing plants have different production capacity which will affect the coverage. As shown in Table B.3, applying the maximum production rate of 8.446 hours per day to all existing PSA plants of different capacities, results in an estimated 6.8% coverage in the North health zone (only 1 existing PSA plant of small capacity, 4.83m^3/h (1m^3=1,000L)), 33.3% coverage in the Central health zone, and 58.6% in the South health zone (if Lisungwi Community Hospital is operational, which is not yet commissioned). Overall, 40% of the total oxygen demand can be met with the estimated current oxygen production plants. In terms of coverage by facility level, the existing PSA plants can cover 51.6% of Central and District hospitals oxygen demand, 33.3% of Mission, Community and Rural hospitals' oxygen demand, and 31.3% of health centres' oxygen demand (Table B.4). This, assuming the amount (L) to be distributed to each level is proportional to the demand of non-PSA facility levels.

B.2.2 Scenario 2 — +Planned PSA system

The Roadmap plans a scale-up of PSA implementation in additional 7 health facilities, 2 of which are Central Hospitals, now covering all Central hospitals. For three of the District hospitals the capacity of the planned PSA plants was not reported as unknown, though in the Roadmap, it was budgeted for a 10,280L/h capacity plant. In consultation with oxygen program experts, Alex Rothkopf (PATH) and Lisa Smith (PATH), updated planned capacities of Bwaila District Hospital – 32m^3/h, Mangochi District hospital – 16 m^3/h, and Kazungu District hospital – 60 m^3/h. The total coverage from the scale-up of these planned PSA plants in addition to the existing plants was estimated assuming a daily production rate of 8.446 hours for the existing plants, and a daily production rate of 6.074 effective hours for the planned plants. This avoids the assumption of a linear relationship between increased production capacity and coverage, which given the logistical challenges would be a questionable assumption. A saturation curve relationship may also dampen the coverage, given that two of the planned PSA plants are Central Hospitals, reaching more patients, one of which located in the North health zone. The North Health zone now increased its coverage to 81.6%, the Central health zone will have a coverage of 78.5%, and the South will have a coverage of 81.9%. An overall 80% coverage nationally (Table B.3). The coverage by facility level for the existing + planned PSA plants can cover 88.1% of Central and District hospitals oxygen demand, 75.4% of Mission, Community and Rural hospitals' oxygen demand, and 73.9% of health centres' oxygen demand (Table B.5). This, assuming the amount (L) to be distributed to each level is proportional to the demand of non-PSA facility levels.

Table B.4 Potential oxygen coverage by facility level in scenario 1 (Existing PSA system)

Scenario 1 - Existing PSA system										
Facility type	**Number of facilities with PSA**	**Number of facilities without PSA**	**Daily Oxygen (L) demand by facility type without PSA**	**TLO facility level**	**Daily Oxygen (L) demand by TLO facility level – all facilities**	**Daily Oxygen (L) demand by TLO facility level without PSA**	**Proportion Oxygen demand by TLO facility level without PSA**	**Amount (L) to be distributed to each level**	**Potential coverage of oxygen by TLO facility level ***	**% Potential coverage by facility level**
Central Hospital	3	2	225896	**2**	1550133	1093048	0.3260	342234	799326	**51.57%**
District Hospital	3	22	867152							
Mission Hospital	1	26	663858	**1b**	972657	944081	0.2816	295593	324149	**33.33%**
Community Hospital	1	1	3023							
Rural Hospital	0	25	277200							
Health centre	0	457	1315703	**1a**	1315745	1315703	0.3924	411948	411948	**31.31%**
Total	8	533	3352832	**Total**	3838535	3352832	1	1049775	1535423	**40%**

*Potential coverage of oxygen by TLO facility level = Amount (L) to be distributed to each level + Daily oxygen demand (L) for facility type with a PSA plant (Table B.3)

Table B.5 Potential oxygen coverage by facility level in scenario 2 (+Planned PSA system)

Scenario 2 - +Planned PSA system										
Facility type	**Number of facilities with PSA**	**Number of facilities without PSA**	**Daily Oxygen (L) demand by facility type without PSA**	**TLO facility level**	**Daily Oxygen (L) demand by TLO facility level – all facilities**	**Daily Oxygen (L) demand by TLO facility level without PSA**	**Proportion Oxygen demand by TLO facility level without PSA**	**Amount (L) to be distributed to each level**	**Potential coverage of oxygen by TLO facility level ***	**% Potential coverage by facility level**
Central Hospital	5	0	0	**2**	1550133	709488	0.2410	524496	1365148	**88.07%**
District Hospital	7	18	709488							
Mission Hospital	2	25	638325							
Community Hospital	1	1	3023	**1b**	972657	918548	0.3120	679046	733135	**75.37%**
Rural Hospital	0	25	277200							
Health centre	0	457	1315703	**1a**	1315745	1315703	0.4469	972647	972647	**73.92%**
Total	15	526	2943739	**Total**	3838535	2943739	1	2176189	3070930	**80%**

B.3 Costs estimation

In this health economic evaluation, we used the simulation to output the effects of several implementation strategies on ALRI outcomes to reflect the cost and impact of 1-year implementation. The analysis year is 2024; therefore, prices and costs of intervention-related capital and operational components represent 2024 US$ values.

Intervention cost calculations were based on information provided in the Roadmap. The estimated total equipment requirements for Malawi's health system, as reported in the Roadmap, were used to budget the cost of a full implementation of oxygen.

Since oxygen capacity scale-up serves all disease areas requiring oxygen, the cost attributed to ALRI in children under-5 was calculated as the proportion of total litres needed for ALRI relative to total national oxygen demand.

B.3.1 Pulse oximetry unit cost

Table B.6 lists all cost associated with 1 pulse oximeter device. In the estimation of the equivalent annual cost, a useful life of 5 years was used. The costing percentages of shipping (10%), distribution (5%), installation (1%), training (4.6%), and maintenance with spare parts (0.3%/year) were used in the Roadmap's costing estimation of 1052 pulse oximeters (note: Roadmap's pulse oximeters were quantified for a bed ratio; thus, quantified for oxygen monitoring purposes and SpO_2 measurement of clinically diagnosed severe pneumonia). The annualised cost with depreciation over the useful life of 5 years for one handheld device was estimated to be $233.96, which with the recurrent cost of maintenance (+$14.55) resulted in an equivalent annual cost of $248.51.

Table B.6 Costing of 1 Pulse Oximeter device for 1 year of implementation

Cost category	**Cost (USD)**	**Source**	**Notes**
Pulse oximeter	370	UNICEF Catalogue Product: S0845017	
Accessories (sensor)	600	UNICEF Catalogue Product: S0845210	$120 x 5 = 5-year supply for 1 PO
Shipping (10%)	97	Roadmap	10% of device + accessories cost
Distribution (5%)	48.50	Roadmap	5% of device + accessories cost
Installation (1%)	9.70	Roadmap	1% of device + accessories cost
Training (4.6%)	44.62	Roadmap	4.6% of device + accessories cost
Maintenance (0.3%/year)	14.55	Roadmap	1.5% of device + accessories cost
Total cost in Year 1	1184.37	**Equivalent annual cost is $248.51***	

*Annualised capital cost (depreciation) = 1169.82/5 = $233.96 per year + $14.55 maintenance = $248.51

Assuming full coverage of one device per health worker at the outpatient department (OPD), the unit cost of pulse oximeter use was calculated by dividing the equivalent annual cost by the total use of pulse oximetry in the OPD per year. Using data reported from the Malawi Harmonised Health Facility

Assessment 2018-19 on mean outpatient department visits, the calculation of total pulse oximetry use per year by facility level was as follows:
OPD visits per provider per day × % respiratory conditions × (working days per year - absenteeism)

Hospital – 18.9 OPD visits per provider per day × 30% respiratory conditions × (365 days - 365 × 28% days not working) = 1490.076 annual OPD visits per provider at the hospital level. Unit cost of PO use at the hospital level is $0.167 per patient.

Health centre – 43.8 OPD visits per provider per day × 30% respiratory conditions × (260 days - 260 × 24% days not working) = 2596.464 annual OPD visits per provider at the health centre level. Unit cost of PO use at the health centre level is $0.096 per patient.

HSA – 1 worker facility size has 52.5 OPD visits per provider per day × 30% respiratory conditions × 260 working days × 4% days not working = 3931.2 annual OPD visits per provider at the community level. Unit cost of PO use at the HSA level is $0.063 per patient.

B.3.2 Oxygen implementation cost

The oxygen systems costed in this analysis comprises a combination of oxygen sources, including Pressure Swing Adsorption (PSA) plants, which provide the bulk of the oxygen supply, and oxygen concentrators to address gaps in distribution challenges to meet the estimated coverages. Additionally, costing of cylinders for oxygen delivery to the patient, storage, and distribution, delivery trucks as a proxy to address the cost of logistical structure challenges, pulse oximeters for monitoring safe delivery of oxygen, ventilators, patient monitors, resuscitation, and suction devices.

The total cost of PSA plants (capital + operating costs) in the first year of implementation was budgeted, together with the cost of essential equipment in the delivery of oxygen to the patient following its production. These costs were summed to determine the overall implementation cost of Year 1 (2024). Table B.7 lists the costs of each component of the oxygen system for the first year of implementation of each oxygen scenario, and the total implementation cost for 2024. While Table B.8 lists the equivalent annual costs, whereby capital costs were depreciated over the useful lifespan of the equipment plus the operational costs for year 1.

Table B.7 Total implementation costs of oxygen systems in Year 1 (2024)

Oxygen system component	**Total implementation cost of Year 1**	
	Existing PSA	**+Planned PSA**
PSA	5,953,699	13,295,632
Trucks	395,463	949,112
Cylinders	606,182	1,060,466
Concentrators	2,052,443	3,062,417
Pulse oximeters	976,225	1,602,707
Ventilators	1,272,390	2,544,781
Monitors	627,549	1,253,458
Resuscitation	43,960	92,573
Suction	467,921	935,233
Total	**12,395,835**	**24,796,379**

Table B.8 Equivalent annual cost of oxygen systems in Year 1 (2024)

Oxygen system component	**Total equivalent annual cost of Year 1**	
	Existing PSA	**+Planned PSA**
PSA	1,343,489	2,907,718
Trucks	98,463	236,312
Cylinders	234,326	316,752
Concentrators	562,244	838,925
Pulse oximeters	216,878	391,447
Ventilators	262,557	525,114
Monitors	162,698	324,971
Resuscitation	15,617	32,887
Suction	155,522	310,810
Total	**3,051,794**	**5,884,936**

Subsections below describe the costing process to reach the total implementation cost of Year 1 per oxygen scenario, and respective equivalent annual cost.

PSA implementation cost

In estimating the PSA cost based on production capacity, several assumptions were made due to the lack of data to inform these varying costs, described below. These assumptions were discussed and verified with Alex Rothkopf (PATH) and Eric Buckley (Build Health International). Table B.9 shows the existing and planned PSA plants capacity in each health facility, the respective cost of such plant capacity, training cost, and power consumption.

Capital expenditure (CAPEX):

- PSA cost: Assist international (`https://assistinternational.org/`) estimates a 12m^3/hour oxygen plant with cylinder filling capacity to cost $200,000 USD. With an averaging cost of $16,666.67 USD per m^3/h, the cost per plant capacity was estimated for each PSA. Table B.9 shows the

initial cost of PSA oxygen plants for each scenario. Two health facilities with central pipeline systems were costed at \$10,000 per m^3/h for the PSA plant and \$1,000 USD per outlet.

- Base electrical infrastructure: assumed 3% of the PSA cost, with a minimum cap of \$10,000 per PSA plant.
- Back-up generator with transfer switch: assumed \$50,000 per PSA plant, with replacement every 10 years.
- Plant housing/infrastructure: Cost variation was distributed by plant size. PSA capacity <10 m^3/h = \$20,000, ≥ 10 to <15 m^3/h = \$30,000, ≥ 15 to <20 m^3/h = \$40,000, ≥ 20 to $<25 m^3$/h = \$50,000, ≥ 25 to <30 m^3/h = \$60,000, ≥ 30 to <35 m^3/h = \$70,000, ≥ 35 to <40 m^3/h = \$80,000, ≥ 45 to <50 m^3/h = \$90,000, ≥ 50 to <55 m^3/h = \$100,000, ≥ 55 to <60 m^3/h = \$110,000, ≥ 60 m^3/h = \$120,000.
- Shipping and delivery: assumed 3% of the PSA cost. The Roadmap budgeted \$10,000 for any PSA size. This value served as a minimum cost for shipping/delivery if the estimated 3% of PSA cost is less than that minimum.
- Installation, testing, and initial training: The roadmap budgeted a range from \$25,000 to \$45,000 per site. Cost distribution based on plant size was assumed and applied to each PSA plant. PSA capacity <10 m^3/h = \$25,000, ≥ 10 to <20 m^3/h = \$30,000, ≥ 20 to <30 m^3/h = \$35,000, ≥ 30 to <40 m^3/h = \$40,000, ≥ 40 to <50 m^3/h = \$45,000, ≥ 50 m^3/h = \$50,000.
- Miscellaneous: An additional 10% of the capital expenditure subtotal was allocated to cover miscellaneous related costs not explicitly included above.

Operating expenditure (OPEX):

- Energy consumption: Assist International recommends calculation of power consumption to be 1.5 kilowatt hour (kWh) for $1m^3$ (= 1,000 L) of oxygen production. Using the electricity cost in Malawi of \$0.17 per kWh as reported in the roadmap, and assuming 75% energy consumption from utility power and 25% from back-up generator costing \$0.50 per kWh, the average cost of energy consumption is \$0.26. Assuming PSA plants operate for 16 hours per day, and 24 hours for piped systems. Energy consumption cost = 1.5 kWh × PSA capacity (m^3/h) × \$0.26 × run hours × 365 days
- Human resources: Full-time equivalent (FTE) of an 8-hour shift and annual salary for Biomedical engineer is respectively 0.5 FTE and \$3,520; Plant supervisor is 1 FTE and \$3,306; Plant operator and cylinder operator are 1 FTE and \$3,089. Staff salaries in Malawi were sourced from worldsalaries.com and converted using purchasing power parities (PPP) conversion rate of 2024 (analysis year), given the unstable devaluation of the national currency [74]. For PSA plants with capacity ≥ 25 m^3/h, the number of cylinder operators is 2. For piped systems only, there is no costing of cylinder operators. The FTE is multiplied by 2 to account for the costs of two shifts per day, for a 16-hour daily operational time.
- Maintenance: The yearly cost of maintenance with spare parts and service contract is distributed by plant capacity. The cost of spare parts assumed by plant size: <10 m^3/h =\$15,000, ≥ 10 to <20 m^3/h = \$17,500, ≥ 20 to <30 m^3/h = \$20,000, ≥ 30 to <40 m^3/h = \$22,500, and ≥ 40 m^3/h cost \$25,000.

Cost of service contract assumed by plant size: <10 m^3/h = $5,000, ≥10 to <20 m^3/h = $6,000, ≥20 to <30 m^3/h = $7,000, ≥30 to <40 m^3/h = $8,000, ≥40 to <50 m^3/h = $9,000, ≥50 m^3/h = $10,000. The assumptions align with the literature [75].

- Corrective maintenance: Major corrective maintenance was predicted to occur every 10 years. The cost at base year was assumed by plant size: <10 m^3/h = $40,000, ≥10 to <20 m^3/h = $45,000, ≥20 to <30 m^3/h = $50,000, ≥30 to <40 m^3/h = $55,000, ≥40 to <50 m^3/h = $60,000, ≥50 m^3/h = $65,000. For costs in Year 1 – 2024, a straight-line depreciation over 10 years was applied to reflect recurrent inputs consistently in the estimated equivalent annual cost.
- Maintenance of electricals was assumed 5% of the capital expenditure of base electrical infrastructure and back-up generator with transfer switch.
- Miscellaneous: An additional 10% of the operational expenditure subtotal was allocated to cover miscellaneous related costs not explicitly included above.

Table B.9 Production capacity and cost of each existing and planned PSA plants

Oxygen scenario	**Facility name**	**Plant Capacity (m^3/h)**	**Cost of PSA (USD)**
Existing PSA (scenario 1)	Nkhata Bay District Hospital	4.83	80,500
	Daeyang Luke Hospital	10	266,000
	Kamuzu Central Hospital	50	833,333.3
	Mercy James	12	198,000
	Neno District Hospital	1.375	22,916.67
	Phalombe District Hospital	49	816,666.7
	Queen Elizabeth Central Hospital	50	833,333.3
	Lisungwi Community Hospital	6.9	115,000
+Planned PSA (scenario 2)	Karonga District Hospital	23.8	396,666.7
	Mzuzu Central Hospital	50	833,333.3
	Nkhoma Mission Hospital	21	350,000
	Kasungu District Hospital	60	1,000,000
	Bwaila District Hospital	32	533,333.3
	Zomba Central Hospital	50	833,333.3
	Mangochi District Hospital	16	266,666.7

The cost of PSA plant with a central pipeline system is a sum of oxygen generator plus piping system. Assuming one outlet per general bed, and three outlet per ICU bed, the costing of the pipeline system equals to $1,000 × number of beds × number of outlets per bed type. Daeyang Luke Hospital is a mission hospital which based on the roadmap has 166 general beds. Mercy James has 6 paediatric ICU beds and 60 beds in the paediatric surgical ward [76].

Therefore, the initial cost of equipment, spare parts, and accessories of a PSA plant with central pipeline system estimated for Daeyang Luke Hospital was $10,000 × 10 m^3/h + $1,000 × 166 beds = $266,000. For Mercy James, the cost of oxygen generator system $10,000 × 12 m^3/h = $12,000 plus the costs of piping system $1,000 × 60 beds + $1,000 × 6 ICU beds × 3 outlets per ICU bed, totalled $198,000.

The Roadmap assumed a 10,28 m^3/h capacity for The Global Fund planned PSA plants for Kasungu, Bwaila, and Mangochi District Hospitals. Updated sources from PATH provided the capacity sizes used in the analysis. Table B.10 lists the components of capital and operational costs of PSA plants implementation for each oxygen scenario in Year 1 (2024). The capital costs were depreciated over the lifespan of 15 years assumed for PSA plants, and 10 years assumed for the back-up generators.

Table B.10 PSA plants implementation costs at Year 1 (2024) for each oxygen scenarios, and respective equivalent annual costs

	Costs (USD) Year 2024	
Cost category	**Scenario 1**	**Scenario 2**
Initial costs of PSA	3,165,750	7,379,083
Base electrical infrastructure	124,500	252,900
Back-up generator + transfer switch	400,000	750,000
Plant housing/infrastructure	410,000	940,000
Shipping and delivery	124,500	252,900
Installation, testing, initial training	280,000	570,000
Miscellaneous (10%)	450,475	1,014,488
Capital expenditure subtotal	4,955,225	11,159,372
Energy consumption	444,371	1,020,148
HR - Biomedical technician	28,159	52,798
HR - Plant supervisor	52,907	99,200
HR - Plant operator	49,431	92,684
HR - Cylinder operator	55,610	123,579
Maintenance (spare parts)	155,000	310,000
Maintenance (service contract)	56,000	114,000
Maintenance (electrical/ generator)	26,225	50,145
Corrective Maintenance	40,000	79,500
Miscellaneous (10%)	90,770	194,205
Operational expenditure subtotal	998,474	2,136,260
Implementation total (Year 1)	5,953,699	13,295,632

Calculation of annual cost of capital + operational cost (Year 1)		
Annualised CAPEX (15 years)	301,015	688,958
Annualised CAPEX (10 years)	44,000	82,500
OPEX (Year 1)	998,474	2,136,260
Equivalent annual cost	**1,343,489**	**2,907,718**

Equipment cost

The list of equipment covered in the Roadmap are presented in Table B.11 with the respective unit cost and total units required to capacitate oxygen delivery system.

Table B.11 Equipment for oxygen delivery unit cost and total units needed in the Malawi health system

Equipment	Unit cost (USD)	Source	Units by facility level			
			2	1b	1a	Total
Oxygen cylinder	91.39	PATH [77] *1	723	528	2037	3288
Oxygen concentrator	642	UNICEF Catalogue Product: S0845044	500	380	796	1676
- Voltage stabiliser	205.41	UNICEF Catalogue Product: S0002632	1 per concentrator			
- Flow splitter	129.26	UNICEF Catalogue Product: S0845039				
- Surge suppressor	151.35	UNICEF Catalogue Product: S0002631				
- Oxygen analyser	459.57	UNICEF Catalogue Product: S0845029	1 per 10 concentrators			
- Filter set	12.9	UNICEF Catalogue Product: S0004177	1 per concentrator, biennial			
- Humidifier bottle	3.65	UNICEF Catalogue Product: S0845048	1 per concentrator, bimonthly			
Pulse oximeter - portable handheld, with cables and sensor	359.64	Emergency Global Supply Chain System (Covid-19) catalogue 09.12.2022 *2	1038	612	878	2673
Pulse oximeter - table top, with cables and sensor	1866.17	Emergency Global Supply Chain System (Covid-19) catalogue 09.12.2022 *2	145	0	0	
Ventilator	22,548.12	UNICEF Catalogue Product: S0002019	76	0	0	76
Patient monitor with ECG	2,352.39	Emergency Global Supply Chain System (Covid-19) catalogue 09.12.2022 *2	211	79	0	290
Patient monitor without ECG	1,104.07	Emergency Global Supply Chain System (Covid-19) catalogue 09.12.2022 *2	145	0	0	145
Resuscitation (adult)	22	UNICEF Catalogue Product: S0845152	406	343	1012	1761
Resuscitation (child)	20.13	UNICEF Catalogue Product: S0845151	261	253	796	1310
Suction-manual	113.52	UNICEF Catalogue Product: S0760641	482	433	1349	2264
Suction-electric	411	UNICEF Catalogue Product: S0002641	188	189	530	907

*1 median cost reported in 2020: $71 - added (World) inflation rate of 2021: 4.7%, 2022: 8.7%, 2023: 6.8%, 2024: 5.9%. Source: International Monetary Fund

*2 cost reported in 2022, added (World) inflation rate of 2023: 6.8%, 2024: 5.9%. Source: International Monetary Fund

UNICEF Catalogue prices as of July 2024.

Note: Other consumables required in oxygen delivery, such as masks and tubes were not included in the costing of oxygen delivery systems, and indirectly included in the cost of inpatient bed days.

Distribution Trucks

The remaining oxygen produced are distributed to other health facilities in cylinders. However, the Roadmap did not cover distribution costs, as distribution of oxygen supply to facilities in need remain a key logistical challenge. Nonetheless, this issue has been highlighted in the Roadmap, and plans to address it are in the works, including the evaluation of options for strategic oxygen-production source placement and development of an oxygen distribution network [57]. Here, in an attempt to attribute a cost to oxygen supply distribution systems, the costing of vehicles for cylinder distribution was estimated, as a simplified proxy for a more complex solution.

The quantification of transport vehicles for oxygen distribution was assumed to be 1 per PSA plant that has production capacity for distribution. Of the 8 existing PSA plants, two have piped systems without cylinder-filling capacity, and Neno District Hospital's PSA plant has a small production capacity, insufficient for distribution. Thus, 5 existing PSA plants qualified for costing of a delivery vehicle. Whereas, all 7 planned plants have distribution capacity, hence a total of 12 trucks was costed for the expansion scenario.

Costing assumptions for one delivery truck included a capital cost of $50,000 and $10,000 for shipping and registration, plus 10% of the capital expenditure for annual maintenance costs (covering inspections, repairs, insurance). Human resources costs associated with the distribution networks included transport supervisors and drivers. The full-time equivalent (FTE) of an 8-hour shift and annual salary for transport supervisor is respectively 0.3 FTE and $1,783, while for a truck driver is 1 FTE and $1,458. Staff salaries were sourced from worldsalaries.com and converted using purchasing power parities conversion rate of 2024. Assuming two drivers per truck and one transport supervisor per distributing facility, the FTE was multiplied by 2 to account for the costs of two shifts per day, a total of 16 hours per day. In addition, miscellaneous costs equivalent to 10% of capital and operating expenditures were applied.

Table B.12 lists the components of capital and operational costs of delivery trucks for each oxygen scenario in Year 1 (2024). The total implementation cost of transport for cylinder distribution in Year 1 was estimated at $395,463 for the 'Existing PSA' system (scenario 1) and $949,112 for the '+Planned PSA' system (scenario 2). To obtain the equivalent annual cost, the capital costs were depreciated over an assumed useful lifespan of 10 years, and annual operational costs were added. The equivalent annual cost of delivery trucks in 2024 totalled $98,463 for 'Existing PSA' system, and $236,312 for '+Planned PSA' system.

Table B.12 Costing of delivery trucks in Year 1 (2024) for each oxygen scenarios, and respective equivalent annual cost

	Costs (USD) Year 2024	
Cost category	**Scenario 1**	**Scenario 2**
Trucks	250,000	600,000
Shipping and delivery	50,000	120,000
Miscellaneous 10%	30,000	72,000
CAPEX subtotal	330,000	792,000
Maintenance	25,000	60,000
Driver + Supervisor	34,512	82,829
Miscellaneous (10%)	5,951	14,283
OPEX subtotal	65,463	157,112
Implementation total (Year 1)	395,463	949,112
Annual cost of capital + operational cost (Year 1)		
Annualised CAPEX (10 years)	33,000	79,200
OPEX (Year 1)	65,463	157,112
Equivalent annual cost	**98,463**	**236,312**

Oxygen cylinders

The Roadmap estimated that 3,288 oxygen cylinders of 'J' size (6,800L) are required to supply oxygen across the country. Table B.11 displays the number of cylinders per facility level. For the 'Existing PSA' system, with an oxygen availability of 40% of the total demand, the quantity of cylinders estimated in the Roadmap would require refilling every two weeks (26 times a year, Table B.13) to meet the coverage. However, using the same number of cylinders to supply the oxygen coverage for the '+Planned PSA' system would require more than one refill per week for hospitals (facility level 2 and 1b). Therefore, the quantity of cylinders per facility level was doubled in the estimation of total capital and operating expenditure, resulting in 1446, 1056, and 4074 cylinders for facility levels 2, 1b and 1a, respectively; a total of 6576 cylinders.

The capital expenditure subtotal included shipping costs at 10%, distribution at 5%, and training at 10% of the capital cost of cylinders. The operating expenditure included maintenance costs for biennial testing and spare parts at 10% of the capital cost of cylinders, plus fuel costs for transport and distribution of cylinders to health facilities.

Total annual fuel cost was based on the refill rate per facility level, the number of days to complete refills, and fuel cost per day. We assumed that each truck travels an average of 100km per day with a consumption rate of 40 litres per 100km, plus a return trip (x2). With the current cost of diesel in Malawi in 2024 at MWK2,734.00 per litre, and using an unofficial market exchange rate of 1697.82 MWK per 1 USD (January 2024, data.IMF.org), the cost of fuel per litre was estimated at approximately \$1.61. Therefore, the average daily fuel cost per truck was calculated as \$1.61 $\times$ 40L $\times$ 2 = \$128.8. Table B.13 shows the annual refill rate of the cylinders in each oxygen scenario.

Table B.13 Annual refill rate and number of days to transport cylinders for oxygen distribution

Scenario	Facility level	Oxygen availability (%)	Oxygen availibility (L)	Annual refill rate	Days to transport cylinders
Existing PSA	2	51.57%	291,782,225	60	6
	1b	33.33%	118,328,166	33	11
	1a	31.31%	150,365,304	11	33
	Overall	40%	560,426,112	26	14
+Planned PSA	2	88.07%	498,298,633	51	7
	1b	75.37%	267,578,574	38	10
	1a	73.92%	354,998,508	13	28
	Overall	80%	1,120,852,224	26	14

Oxygen availability in litres is the total annual oxygen demand (L) met by the oxygen production in scenarios 1 and 2. The annual refill rate is calculated based on this coverage and 'J' size cylinders available (capacity 6,800L).

$$\text{Refill rate per year} = \frac{\text{Availability (\%)} \times \text{Total annual oxygen demand } (L)}{\text{number of cylinders} \times 6,800}$$

The number of days to distribute the cylinder for complete refill cycle is 365 days ÷ refill rate, a cost of $128.8 per day for fuel was applied. For example, the yearly cost of fuel for transport in 'Existing PSA' scenario was $139,949, calculated as follows:

(60 refills × 6 days × $128.8) + (33 refills × 11 days × $128.8) + (11 refills × 33 days × $129) = $46,368 +$46,754 + $46,827 = $139,949

Table B.14 lists the capital and operating expenditures of cylinders for each oxygen scenario in Year 1 (2024). The total implementation cost of cylinders for the first year was estimated at $606,182 for the 'Existing PSA' system (scenario 1), and $1,060,466 for the '+Planned PSA' system (scenario 2). To estimate the equivalent annual cost for 2024, the capital cost of cylinders was annualised over a useful life of 10 years [78]. Recurring re-training cost (every 5 years) was depreciated to capture these costs in year 1, with the annual equivalent added to the estimation of total implementation and equivalent annual costs.

Table B.14 Costing of cylinders in Year 1 (2024) for each oxygen scenarios, and respective equivalent annual cost

	Costs (USD) Year 2024	
Cost category	**Scenario 1**	**Scenario 2**
Cylinder	300,490	600,981
Shipping	30,049	60,098
Distribution	15,025	30,049
Training	30,049	60,098
Miscellaneous	37,561	75,123
CAPEX subtotal	413,174	826,348
Transport	139,949	141,809
Re-training	6,010	12,020
Maintenance	30,049	60,098
Miscellaneous	17,000	20,191
OPEX subtotal	193,008	234,117
Implementation total (Year 1)	606,182	1,060,466

Annual cost of capital + operational cost (Year 1)		
Annualised CAPEX (10 years)	41,317	82,635
OPEX (Year 1)	193,008	234,117
Equivalent annual cost	**234,326**	**316,752**

Oxygen concentrators

Table B.11 provides a breakdown of the number of concentrators and spare parts/accessories required per facility level. In scenario 2 ('+Planned PSA' system), the costing assessment covered the total quantity recommended in the Roadmap. The Biomedical Equipment Survey 2020 report [79] estimated that the current availability of concentrators is 66.77% of the total recommended. Thus, for scenario 1, the oxygen system involving existing PSA plants, costing assessment covered 1123 oxygen concentrators. Other capital costs included shipping at 10%, distribution at 5%, and installation, commissioning, and training of personnel at 10% of the capital expenditure of concentrators, accessories, and spare parts.

Operational expenditure included annual energy consumption costs of $521 for 1,676 concentrators in scenario 2, as reported in the Roadmap, and $365 (adjusted cost) for scenario 1. Maintenance costs (service and spare parts) were estimated at 10% of the capital cost of concentrators and key accessories, including oxygen analyser. In addition, yearly miscellaneous costs equivalent to 10% of capital and operational subtotals were applied.

Table B.15 presents the total capital and operational expenditures for oxygen concentrators in the first year of implementation for each oxygen scenario.

Table B.15 Costing of oxygen concentrators in Year 1 (2024) for each oxygen scenarios, and respective economic equivalent annual cost

	Costs (USD) Year 2024	
Cost category	**Scenario 1**	**Scenario 2**
Oxygen concentrator	1,293,741	1,930,819
- Oxygen analyser	51,931	77,024
- Filter set	14,487	21,620
- Humidifier bottle	24,594	36,704
Shipping	138,475	206,617
Distribution	69,238	103,308
Installation & Training	138,475	206,617
Miscellaneous	173,094	258,271
CAPEX subtotal	1,904,035	2,840,981
Energy	349	521
Maintenance	134,567	200,784
Miscellaneous	13,492	20,131
OPEX subtotal	148,408	221,436
Implementation total (Year 1)	2,052,443	3,062,417
Annual cost of capital + operational cost (Year 1)		
CAPEX depreciation (5 years)	370,060	552,157
CAPEX depreciation (2 years)	9,960	14,864
CAPEX (1 year)	33,816	50,469
OPEX (Year 1)	148,408	221,436
Equivalent annual cost	**562,244**	**838,925**

For the '+Planned PSA' scenario, the total implementation cost of oxygen concentrators in Year 1 was estimated at $3,062,417, while for the 'Existing PSA' scenario it was $2,052,443 (Table B.15). When the capital costs of concentrators and analysers were depreciated over a useful life of 5 years, and 2 years for the filter sets, the equivalent annual cost of oxygen concentrators was $562,244 for the 'Existing PSA' system and $838,925 for the '+Planned PSA' system.

Pulse oximeters

Pulse oximeters are essential in any oxygen system for the detection of hypoxaemia in patients with severe respiratory conditions, and for safe administration and monitoring of oxygen provision. The costing of pulse oximeters for monitoring oxygen was based on the total number of inpatient beds and respective types. There are 145 intensive care units (ICU) and occupational therapy (OT) beds in Malawi's health system [57]. The recommended ratio to supply the health system is one tabletop device per ICU/OT bed, while general bed types were costed for handheld devices at a ratio of one per ten beds, totalling 2528, as listed in Table B.11. These quantities were costed for the '+Planned PSA' scenario. For the 'Existing PSA' scenario, equipment quantities such as pulse oximeters, ventilators, patient monitors, resuscitation

and suction devices were set to 50% of the recommended levels for the expansion of oxygen systems ('+Planned PSA' system). This proportional reduction reflects the difference in oxygen capacity: the existing system can achieve 40% of national oxygen demand compared to 80% for the planned expansion. This adjustment ensures equipment allocation is proportional to oxygen system capacity.

Additional costs included shipping (10%), distribution (5%), installation (1%), and training (4.5%). Annual maintenance costs were calculated at 0.3% of the capital cost of monitoring pulse oximeter devices. Plus, miscellaneous costs set at 10% of both capital and operational expenditures were applied.

Table B.16 shows the total implementation cost and breakdown by capital and operational expenditures of monitoring pulse oximeters in Year 1.

Table B.16 Costing of pulse oximeter devices for monitoring oxygen administration in Year 1 (2024) for each oxygen scenarios, and respective equivalent annual cost

	Costs (USD) Year 2024	
Cost category	**Scenario 1**	**Scenario 2**
Pulse oximeter (Handheld)	454,584	909,168
Pulse oximeter (Tabletop)	270,595	270,595
Shipping	72,518	117,976
Distribution	36,259	58,988
Installation	7,252	11,798
Training	32,633	53,089
Miscellaneous	87,384	142,161
CAPEX subtotal	961,224	1,563,775
Maintenance	13,638	35,393
Miscellaneous	1,364	3,539
OPEX subtotal	15,001	38,932
Implementation total (Year 1)	976,225	1,602,707
Annual cost of capital + operational cost (Year 1)		
Annualised CAPEX (4 years)	150,638	301,276
Annualised CAPEX (7 years)	51,239	51,239
OPEX (Year 1)	15,001	38,932
Equivalent annual cost	**216,878**	**391,447**

For the '+Planned PSA' system (scenario 1), the total cost was estimated at $1,602,707 while for the 'Existing PSA' system (scenario 2), with an assumed current availability to be 50% of the total requirement for an expansion, the total cost was estimated at $976,225. Then based on the useful life of 4 years for the handheld device and 7 years for the tabletop, as per the Roadmap, a straight-line depreciation was applied to the capital cost to estimate the equivalent annual cost. These were $216,878 for 'Existing PSA' system, and $391,447 for '+Planned PSA' system.

Ventilators

The cost estimation covered 76 ventilators at intensive care units/ occupational therapy (ICU/OT) (Table B.11) for '+Planned PSA' scenario. While for the 'Existing PSA' scenario, the total quantity of equipment was proportionally reduced to 50%, as described earlier, totalling 38 ventilators.

Table B.17 outlines the total implementation costs in Year 1, and the estimated equivalent annual cost for each oxygen scenario. Capital costs included costs of shipping at 10%, distribution at 5%, and installation with personnel training at 10% of the capital expenditure of ventilators. Operational costs included maintenance of accessories and spare parts at 10% of the capital cost. Additionally, a miscellaneous cost at 10% of both capital and operational expenditure subtotals was factored in.

Table B.17 Costing of ventilators in Year 1 (2024) for each oxygen scenarios, and respective equivalent annual cost

	Costs (USD) Year 2024	
Cost category	**Scenario 1**	**Scenario 2**
Ventilator	856,829	1,713,657
Shipping	85,683	171,366
Distribution	42,841	85,683
Installation + Training	85,683	171,366
Miscellaneous	107,104	214,207
CAPEX subtotal	1,178,139	2,356,279
Maintenance	85,683	171,366
Miscellaneous	8,568	17,137
OPEX subtotal	94,251	188,502
Implementation total (Year 1)	1,272,390	2,544,781
Annual cost of capital + operational cost (Year 1)		
Annualised CAPEX (7 years)	168,306	336,611
OPEX (Year 1)	94,251	188,502
Equivalent annual cost	**262,557**	**525,114**

In total, the implementation cost of ventilators was estimated to be $1,272,390 for 'Existing PSA' scenario and $2,544,781 for '+Planned PSA' scenario. With a lifespan of 7-years, capital costs were depreciated over the period of their useful life, generating an equivalent annual cost of $262,557 and $525,114 for 'Existing PSA' and '+Planned PSA' systems, respectively.

Patient monitors

The cost estimation covered 290 patient monitors with ECG and 145 monitors with ECG (Table B.11) for '+Planned PSA' scenario. While for 'Existing PSA' scenario, the total quantity of equipment was reduced to 50%, as described earlier, totalling 145 monitors with ECG and 73 without ECG. Table B.18 outlines the total implementation costs in Year 1, and the estimated equivalent annual cost for each oxygen scenario. Capital costs included costs of shipping at 10%, distribution at 5%, and installation with personnel training at 10% of the capital cost for the patient monitors. Operational costs included maintenance of accessories and spare parts at 10% of the capital cost. Additionally, a miscellaneous cost at 10% of both capital and operational expenditure subtotals was factored in.

In total, the implementation cost of patient monitors was estimated to be $627,549 for 'Existing PSA' system and $1,253,458 for '+Planned PSA' system. The equivalent annual cost for 2024 by summing the depreciated capital costs over 5 years of useful life and the operational costs of year 1, resulted in estimates of $162,698 and $324,971, for 'Existing PSA' and '+Planned PSA' systems, respectively.

Table B.18 Costing of patient monitors devices in Year 1 (2024) for each oxygen scenarios, and respective equivalent annual cost

	Costs (USD) Year 2024	
Cost category	**Scenario 1**	**Scenario 2**
Patient monitor with ECG	341,966	683,932
Patient monitor without ECG	80,626	160,148
Shipping	42,259	84,408
Distribution	21,130	42,204
Installation + Training	42,259	84,408
Miscellaneous	52,824	105,510
CAPEX subtotal	581,064	1,160,610
Maintenance	42,259	84,408
Miscellaneous	4,226	8,441
OPEX subtotal	46,485	92,849
Implementation total (Year 1)	627,549	1,253,458

Annual cost of capital + operational cost (Year 1)		
Annualised CAPEX (5 years)	116,213	232,122
OPEX (Year 1)	46,485	92,849
Equivalent annual cost	**162,698**	**324,971**

Resuscitation set

The cost estimation covered 1,761 adult and 1,310 paediatric resuscitation equipment (sets) (Table B.11) for the '+Planned PSA' scenario. For the 'Existing PSA' scenario, the total quantity of equipment was reduced to 50%, totalling 881 adult and 655 paediatric resuscitation sets. Table B.19 outlines the total implementation costs in Year 1, and the estimated equivalent annual cost for each oxygen scenario. Capital costs included costs of shipping at 10%, distribution at 5%, and installation with personnel training at 10% of the capital cost for the resuscitation equipment. Operational costs included maintenance of accessories and spare parts at 10% of the capital cost. Additionally, a miscellaneous cost at 10% of both capital and operational expenditure subtotals was factored in.

In total, the implementation cost of resuscitation equipment was estimated at $43,960 for the 'Existing PSA' scenario and $92,573 for the '+Planned PSA' scenario. The equivalent annual cost combined the depreciated capital costs over 3 years of useful life with the yearly operational costs, totalling $15,617 and $32,887 per year for the 'Existing PSA' and '+Planned PSA' scenarios, respectively.

Table B.19 Costing of resuscitation sets in Year 1 (2024) for each oxygen scenarios, and respective equivalent annual cost

	Costs (USD) Year 2024	
Cost category	**Scenario 1**	**Scenario 2**
Resuscitation (adult)	17,735	38,742
Resuscitation (child)	13,185	26,370
Shipping	3,092	6,511
Distribution	1,546	3,256
Installation + Training	3,092	6,511
Miscellaneous	3,865	8,139
CAPEX subtotal	42,515	89,529
Maintenance	1,314	2,767
Miscellaneous	131	277
OPEX subtotal	1,445	3,044
Implementation total (Year 1)	43,960	92,573
Annual cost of capital + operational cost (Year 1)		
Annualised CAPEX (3 years)	14,172	29,843
OPEX (Year 1)	1,445	3,044
Equivalent annual cost	**15,617**	**32,887**

Suction devices

The cost estimation covered 2264 manual and 907 electric suction devices across the facility levels (Table B.11) for the '+Planned PSA' scenario. For the 'Existing PSA' scenario, the total quantity was reduced to 50%, as described earlier. Table B.20 outlines the total implementation costs in Year 1, and the estimated equivalent annual cost for each oxygen scenario. Capital costs included costs of shipping at 10%, distribution at 5%, and installation with personnel training at 10% of the capital expenditure for the devices. Operational costs included the maintenance of accessories and spare parts at 10% of the capital cost of the devices. Additionally, a miscellaneous cost at 10% of both capital and operational expenditure subtotals was factored in.

In total, the implementation cost of suction devices was estimated at $467,921 for scenario 1 and $935,233 for scenario 2. Manual suction device has a 5-lifespan, while the electric suction device has a 3-year lifespan, as indicated in UNICEF Supply Catalogue source. Capital costs were depreciated over the period of their useful life, generating an equivalent annual cost of $155,522 for scenario 1, and $310,810 for scenario 2.

Table B.20 Costing of suction devices in Year 1 (2024) for each oxygen scenarios, and respective equivalent annual cost

	Costs (USD) Year 2024	
Cost category	**Scenario 1**	**Scenario 2**
Suction (manual)	128,505	257,009
Suction (electric)	186,594	372,777
Shipping	31,510	62,979
Distribution	15,755	31,489
Installation + Training	31,510	62,979
Miscellaneous	39,387	78,723
CAPEX subtotal	433,261	865,956
Maintenance	31,510	62,979
Miscellaneous	3,151	6,298
OPEX subtotal	34,661	69,276
Implementation total (Year 1)	467,921	935,233
Annual cost of capital + operational cost (Year 1)		
Annualised CAPEX (5 years)	35,339	70,678
Annualised CAPEX (3 years)	85,522	170,856
OPEX (Year 1)	34,661	69,276
Equivalent annual cost	**155,522**	**310,810**

B.3.3 Oxygen unit cost (L)

From the total equivalent annual cost of Year 1 (Table B.8), the unit cost per litre of oxygen can be estimated, and the cost per treatment for hypoxaemic children with ALRI. To get the unit cost of oxygen (L), the overall equivalent annual cost is divided by the annual oxygen demand that can be met by the oxygen production rate of each scenario.

Scenario 1 – 'Existing PSA' system

For scenario 1 of existing PSA plants, the equivalent annual cost was estimated at $3,051,794 for Year 1 - 2024 (Table B.8).

The annual oxygen demand estimated in the Roadmap was 1,401,065,280 Litres. In scenario 1, with an estimated oxygen coverage of 40% of the national demand, the annual oxygen demand that can be met is 560,426,112 Litres. Therefore, the unit cost of oxygen (L) in 'Existing PSA' scenario equates to $3,051,794 ÷ 560,426,112L = $0.005445

For children under 5 years of age, the average oxygen therapy duration of 3 days with a flow rate of 2L per minute, sums to a total treatment cost of $47.05. For young infants with <2 months of age, the average oxygen therapy duration of 3 days with a flow rate of 1L per minute, sums to a total treatment cost of $23.52.

Scenario 2 – '+Planned PSA' system

For scenario 2 of existing and planned PSA plants, the equivalent annual cost is estimated at $5,884,936 for Year 1 - 2024 (Table B.8).

With a coverage of 80%, the annual oxygen demand that can be met is 1,120,852,224 Litres. Therefore, the unit cost of oxygen (L) in '+Planned PSA' scenario equates to $5,884,936 ÷ 1,120,852,224L = $0.00525.

For children under 5 years of age, the average oxygen therapy duration of 3 days with a flow rate of 2L per minute, sums to a total treatment cost of $45.36. For young infants with <2 months of age, the average oxygen therapy duration of 3 days with a flow rate of 1L per minute, sums to a total treatment cost of $22.68.

Unit cost adjustment

The unit cost calculated for each oxygen scenario represents the cost per case when all patients needing oxygen therapy receive it, while considering the scenario's maximum oxygen service availability. Therefore, this unit cost corresponds to the oxygen scenario with pulse oximetry implemented at all facility levels under optimal conditions, all hypoxaemic cases are identified and oxygen therapy is provided to the scenario's full capacity (coverage).

Conversely, when pulse oximetry is not fully implemented or health system conditions are suboptimal, hypoxaemic case detection is incomplete, resulting in reduced oxygen provision. Since the overall implementation cost remains fixed regardless of hypoxaemia detection rates, the unit cost needs to be adjusted in non-ideal scenarios to maintain consistency with total implementation

expenditure. Without adjusting the unit cost to reflect actual usage rates, cost projections for oxygen therapy in children under-5 with ALRI would be inaccurately lower in scenarios with lower oxygen provision than in scenarios with higher provision rates of the same implementation cost.

Using the model simulation, each scenario outputs the total oxygen volume (in litres), including oxygen used for stabilisation at health centres. Under imperfect health system conditions, where not all available oxygen reaches patients requiring therapy, the outputted total oxygen volume is compared against outputs from perfect conditions (scenarios 1.PO-0 and 2.PO-0 for 'Existing PSA' and '+Planned PSA' coverage scenarios, respectively).

B.3.4 Associated healthcare costs

Additional costs to the health system resulting from increased demand for services and consumables with the implementation of the interventions include antibiotics, outpatient consultation and hospitalisation bed days.

Antibiotics

The costs of antibiotics were sourced from 2015 International Medical Products Price guide by Management Sciences for Health (MSH) [80], and applied an inflation rate, average consumer prices, of 42.4% (World % change from 2015 to 2024, source International Monetary Fund (IMF)), plus handling, shipping [81], and distribution fees of 20% of the drug cost.

Based on the WHO Pocket book of hospital care for children, and the Integrated Management of Childhood Illness (IMCI) guidelines, the dosages were estimated by age group, as TLO demography module does not have weight and height measurements.

The unit cost of the antibiotic after adjusting for handling and shipping fees, and inflation rate, is used to estimate the total cost of a course of treatment. Based on age-dependent dosages, duration of treatment of different pneumonia classifications, and potential switching to second line, the cost of a treatment course differs per those characteristics. Table B.21 shows the unit cost of each antibiotic and respective unit cost by age group.

Table B.21 Antibiotic unit cost, and unit cost by age

Antibiotic	**Unit cost (USD) per tablet/inj**	**+ Inflation (42.4%) + handling & shipping (20%)**	**Unit cost by age-dependent dose**			
			<4 mo	**<1 y**	**1-2 y**	**3-5 y**
Amoxicillin 250mg TAB-CAP	0.016	0.02734	0.02734		0.05468	0.08202
Ampicillin 500mg VIAL (INJ)	0.1507	0.25752	0.10301	0.20602	0.30902	0.51504
Gentamicin Sulphate 10mg/ml AMPOULE (INJ)	0.088	0.15037	0.07519	0.13533	0.203	0.26315
Ceftriaxone 1g VIAL (INJ)	0.398	0.6801	0.20403	0.40801	0.6801	0.95214

For children classified as non-severe pneumonia with fast-breathing only or chest-indrawing, a 3-day or 5-day course of oral amoxicillin is provided, respectively. The total cost of a full course is calculated as the unit cost of age-dependent dosage multiplied by twice daily administration and the length of treatment days. For instance, providing oral amoxicillin to children under 1 year with non-severe hest-indrawing pneumonia incurs a cost the health system of $0.2734; for children aged 1 to 2 years, it costs $0.5468, and for those aged between 3 to 5 years, it amounts to $0.8202.

For severe pneumonia classification, the standard treatment consists of 1st line intravenous antibiotics for 5 days, with ampicillin administration every 6h (or 4 times a day) and gentamicin once a day. The full course of IV antibiotic treatment costs vary based on age groups: for young infants aged less than 4 months, the cost is $2.44; for those aged 4 months to less than 1 year, the cost is $4.80; for age between 1 to 2, the cost is $7.20, and for the older age group between 3 to 5 the cost is $11.62.

In case the 1st line antibiotic treatment fails, a change to ceftriaxone at day 2 revises the total antibiotic treatment cost. Then, the total cost now includes the expenses for the initial 2-day treatment with first-line antibiotics and the subsequent 5-day treatment with the second-line line antibiotic.

Outpatient consultation and inpatient bed days

The cost of outpatient consultation and inpatient bed days were sourced from WHO-CHOICE estimates of cost for inpatient and outpatient health service delivery [82], using the values estimated for Malawi, reported in International Dollars (I$) of 2010 purchasing power parity. Their modelling methods used data from 2008-2010, thus these estimates were first checked for the application of an inflation rate.

WHO-CHOICE 2010 Malawi health system cost per inpatient bed day by hospital level (without drugs) are I$8.81 at tertiary hospital, I$6.81 at secondary hospital, and I$6.53 at primary hospital. Cost per outpatient visit costs I$1.67 at the health centre without bed capacity, I$2.06 at health centre with bed capacity, I$2.35 at primary hospital, I$2.45 at secondary and tertiary hospitals.

Following the methodology proposed by Turner et. al 2019 [83], adjusting the costs with local inflation rate that have been reported in International US$, the outpatient and inpatient heath service delivery were adjusted to reflect current values. Using Malawi GDP Deflator index for 2010 and 2024, sourced from the International Monetary Fund: World Economic Outlook, a % change in this timeline was calculated. The inflation rate = GDP Deflator (current year) - GDP Deflator (base year) / GDP Deflator (base year) * 100.

Inflation = $\frac{248.205 - 29.369}{29.369} * 100 = 745\%$

To adjust for inflation using the local inflation rates, the costs were first converted back to the local currency using the exchange rate relating to the time period the cost data were collected. The costs canthen be inflated and converted back to USD using the exchange rate of the analysis year [83]. The implied PPP conversion rate of the national current per international dollars in 2010 was 70.475 and in 2024 is predicted to be 497.659, sourced from Inter-

national Monetary Fund (IMF). Following the recommended method, the cost of consultation at secondary or tertiary hospital I$2.45 in 2024 is estimated to be I$2.58.

Table B.22 and Table B.23 list respectively, the costs of outpatient consultation and hospital admission per day, as used in the analysis. The cost per facility type reported in the WHO-CHOICE estimates were matched to the TLO facility levels.

Table B.22 Outpatient consultation cost by facility level

Facility level	**Unit cost (I$ 2010)**	**Source**	**Unit cost (I$) in 2024**
Level 3*	2.45	WHO-CHOICE (Tertiary Hospital)	2.58
Level 2	2.45	WHO-CHOICE (Secondary Hospital)	2.58
Level 1b	2.35	WHO-CHOICE (Primary Hospital)	2.47
Level 1a	2.06	WHO-CHOICE (Health Centre (with beds))	2.17
Level 0	1.67	WHO-CHOICE (Health Centre (no beds))	1.76

*Level 3 grouped with Level 2

The cost of outpatient consultation is applied to all individuals receiving outpatient care services and to the follow-up consultations not requiring hospital admission. If an individual requiring inpatient care initiating their first health system contact at a level 0 (village clinics, health posts) or level 1a (health centres), a cost of outpatient consultation is also applied before referral to hospital levels (1b or 2) for further management and associated costs.

Table B.23 Inpatient bed days cost by facility level

Facility level	**Unit cost (I$ 2010)**		**Source**	**Unit cost (I$) in 2024**	**Cost per 5 and 7 days**
Level 3*	8.81	7.526*	WHO-CHOICE (Tertiary Hospital)	7.94	39.7, 55.58
Level 2	6.81		WHO-CHOICE (Secondary Hospital)		
Level 1b	6.53		WHO-CHOICE (Primary Hospital)	6.89	34.44, 48.23

*Average unit cost for facilities level 3 and 2 weighted with the number of beds in each level. A cost of $7.526 per day for hospitalisation at level 2 was used in the analysis

In accordance with the WHO Pocket book of hospital care for children guidelines for the treatment of severe pneumonia, the number of days for hospitalisation is set at 5 days. This extends to 7 days in cases of treatment failure with 1st line IV antibiotics by day 2, switching to 2nd line.

Both outpatient and inpatient service costs include 'costs such as personnel, capital infrastructure and equipment, laboratory, maintenance and other operational costs of the hospital, as well as food costs (...)'[84]

B.4 Modelling limitations

B.4.1 Design of ALRI natural history

Timely progression of disease was not modelled, with all symptoms and complications occurring on the day of disease onset. While this can be a missed opportunity to capture the effect of delayed care seeking, incorporating such timeframe into the model would introduce numerous additional steps, and is further complicated by the lack of data on healthcare-seeking behaviours. Thus, applying this assumption consistently across the entire population simplifies the model, avoiding additional complexity such as differentiating between rural and urban areas, which would require further assumptions.

All-in-one onset is a simplification of what the disease would progress to and the timeline in seeking care, this approach can be justified if the model output is properly calibrated to observed data. There was lack of data to inform the natural progression timeliness, as most data relies on prevalence estimates. Additionally, it is also challenging to model the natural disease progression timeline as ALRI cases must be treated.

While ALRI mortality theoretically involves complex disease states and multiple complications, the current model does not capture all possible ALRI-related complications, and neither is yet integrated with other TLO disease modules for combined mortality risk. Additionally, natural mortality risks in the absence of treatment is unknown, given that recorded cases seen in health facilities must receive treatment. Therefore, our mortality model combines facility-level mortality data, assumptions regarding treatment failure rates and untreated natural mortality, and clinical expert validation of these assumptions and mortality outputs by complication type and disease severity.

B.4.2 Health care provision

The TLO simulation framework does not yet include a central 'oxygen system' within the health system model structure. Therefore, oxygen provision to conditions that require such therapy is modelled at each individual disease module. In the ALRI module, oxygen provision was modelled as a supplementary intervention to inpatient care with IV antibiotics, whereby an effect of such additional treatment is applied to the rate of treatment failure of the antibiotic therapy. The effects of oxygen alone without antibiotic therapy was not modelled, as antibiotic availability is set at 100%, and oxygen alone does not resolve infection.

Oxygen over-use in cases not needing oxygen was not modelled, as monitoring pulse oximetry was included in the oxygen system and used to all severe cases diagnosed (assumption in the model, but key component in oxygen provision and monitoring). Additionally, due to the lack of published data, the quantification of the risk of oxygen overtreatment is uncertain.

The availability of other health care interventions associated with oxygen provision or routine pulse oximetry was assumed to be 100%. This means that the increased demand for health care services and/or consumables with increased diagnosis or treatment requirements (↑inpatient beds, ↑staff time, ↑IV

antibiotics) was assumed to be available. Thus, all required services run and take effect. The constraints of the health system and competing for resource by other disease conditions were not incorporated, as this is an ALRI-focused analysis though even if this analysis was modelled in the TLO health system interaction framework children under-5 years of age are in the priority list to receive available appointments.

Another healthcare provision modelling aspect to note pertains to the accuracy of pulse oximeters. In modelling of effect, pulse oximeters were assumed to have 100% sensitivity and specificity in measuring SpO_2, and therefore in detecting hypoxaemic cases. This assumption was based on the modelling method of hypoxaemia and respective SpO_2 levels in the ALRI module, which was informed by published studies that use pulse oximeter devices with the same level of accuracy in their estimation of hypoxaemia in ALRI cases and SpO_2 measurements. The true level of hypoxaemia and oxygen need is uncertain. Assuming SpO2 as gold standard in clinical practice, and the utilisation of devices meeting current international performance accuracy standards set forth by the US FDA and ISDO regulations, therefore we assume a device accuracy of +/- 2% and that any inaccuracy cancels each other out, with the non-detected or over-diagnosed cases being reflected in the mortality rate (because the studies we use for parameter estimates are also based on use of pulse oximetry of the same accuracy). For the model to truly handle accuracy we would need arterial blood gas measurement data from children in LMICs, which is not available (and is unlikely to ever be for the parameters we need as it's not used in routine clinical practice anywhere in the world) and therefore cannot be incorporated.

B.4.3 Cost estimations

An important component in the continuum of care not modelled in the costing of healthcare provision is the referral transport methods and associated costs of referral. Attributing a unit cost to referrals is challenging due to Malawi's inadequate and fragmented referral system, as well as the mix of referral transport methods available in Malawi [85]. The referral system on its own is a health system bottleneck that needs revising, and investment. The strengthening of referral systems will not only impact the ALRI case management but also other conditions requiring urgent referral and care at the hospital level, including surgical referrals.

The provision of health care services, including oxygen administration and IV antibiotics, require various essential consumables, not listed in the methods. These consumables, such as personal protective equipment (PPE), medication preparation and administration supplies (including sterile saline for injection, IV catheters, syringes, vials or ampoules), and disposables for infection control (disinfectants and sterile gauze), are key in the procedure of delivering safe and effective care. It was assumed that the costs of these basic consumables are already factored into the unit cost of inpatient bed days. However, this assumption may not apply to certain additional consumables specific to the new intervention of oxygen administration. For instance, oxygen masks, nasal cannulas, and tubing, which are essential in oxygen provision, were not in-

cluded in the total expenditure calculation. Although their costs are minimal compared to the rest of the interventions-related components and healthcare service costs, they should be considered when assessing the overall expenses associated with oxygen therapy.

B.4.4 Oxygen coverage estimation

The model assumes a uniform distribution of oxygen supply across the country. The distribution of oxygen supply was not limited by health zones, which in practical context of the country's geographical point, cross-zones distribution might be at a small extent. This consideration is relevant for the 'Existing PSA' scenario, whereby the North health zone has very limited oxygen production capacity.

Given the geographical challenges of oxygen distribution in Malawi, and resulting accessibility equity issues, the relationship between implementation of additional oxygen production capacity and oxygen service availability might follow a saturation curve, never reaching 100%. It is challenging to achieve universal coverage with hard-to-reach facilities in rural locations at greater distances from a production plant. Therefore, the estimated coverage of 80% for the '+Planned PSA' scenario might be optimistic, particularly if the cost of distribution systems and infrastructure is greater than the estimated total cost of 'distribution trucks' and fuel for cylinder distribution, which was used as a proxy calculation.

The Roadmap's calculation of demand by facility type was an average estimation, with no provision of information on facility-specific demand. The Roadmap budgeted for 541 total facilities, though the current number of facilities up to level 1a is greater than the estimated, reported numbers in the HHFA 2018-19 were 101 hospitals and 492 health centres [86].

Considering the multitude of bottlenecks impeding the effective implementation of oxygen systems in Malawi - ranging from inadequate infrastructure for production and storage of oxygen, to insufficient resources for regular maintenance and repairs of production plants, human resources constraints due to shortage of trained personnel, weak supply chains for spare parts and consumables, logistical challenges for oxygen distribution due to poor road infrastructure, and financial burden of operational costs - these issues result in interruptions in oxygen supply. The use of 6 to 8.5 hours of effective production rate per day as a proxy to cover these issues may be an optimistic outlook. However, for some of these bottlenecks the associated costs were incorporated into the costing of oxygen systems. Therefore, if the necessary investments are made, the respective bottleneck can be mitigated or avoided altogether.

Appendix C

Cost-effectiveness analysis of intervention strategies

C.1 Methodology

We ran the model and evaluated the cost-effectiveness of the 15 interventions scenarios defined in Appendix B.

C.1.1 Model simulation

Sample cohort

The model simulation start date is 01/01/2024, with an initial population size of 150,000 children under-5 years of age, representing 5% of Malawi's actual under-5 population. When applying the ALRI incidence model to this initial population, the simulation generated 20,752 pathogen-attributed infections. To create a large representative sample, each infection case was resampled 20 times, with natural disease progression applied in each resample, resulting in a cohort of 415,040 ALRI cases. This expanded cohort represents the expected total ALRI burden for Malawi's under-5 population of 3,000,000 children in 2024.

This ALRI cohort serves as the base for evaluating intervention effects. The model was run separately for each of the 15 intervention scenarios and random variabilty between runs was controlled by maintaining a consistent random seed across simulations. This ensures that any observed variations in outcomes between scenarios and under different health system conditions (in sensitivity analyses) can be directly attributed to the interventions themselves rather than to random variation.

Table C.1 provides a descriptive summary of the ALRI cohort in the simulation. The displayed variables pertain to the disease episode, which are relevant to disease severity, classification, and outcome, along with initial healthcare seeking contact, which is relevant for diagnostic management and subsequently care outcome.

Table C.1 Descriptive of the cohort disease episode characteristics

Properties	N	%
Age		
Median (IQR), years	1.007 (0.364-1.977)	
Mean, years	1.445	
0-11 months	206640	49.79%
12-23 months	107080	25.80%
24-59 months	101320	24.41%
Sex		
Female	204120	49.18%
Male	210920	50.82%
Primary causal pathogens		
Enterobacteriaceae	9840	2.37%
H. influenzae non type-b	15180	3.66%
HMPV	23480	5.66%
H. influenzae type-b	4160	1.00%
Influenza	13220	3.19%
P. jirovecii	6440	1.55%
Parainfluenza	30360	7.32%
RSV	107180	25.82%
Rhinovirus	60520	14.58%
Staphylococcus aureus	13120	3.16%
S. pneumoniae PCV13	4940	1.19%
S. pneumoniae non-PCV13	9740	2.35%
other Streptococci/Enterrococci	3960	0.95%
other bacterial pathogen	40400	9.73%
other viral pathogen	43720	10.53%
other pathogen NoS	28780	6.93%
Secondary bacterial co-infection	29121	7.02%
Disease type		
Other ALRI	265361	63.94%
Pneumonia	149679	36.06%
Duration in days [mean (IQR)]	7 (4-10)	
Acute malnutrition		
Not acutely malnourished	403240	97.16%
Moderate (MAM)	10100	2.43%
Severe (SAM)	1700	0.41%
HIV status		
HIV-	409560	98.68%
HIV+	5480	1.32%
HIV+ not on ART	1780	0.43%
Any complications	121461	29.26%
Hypoxaemia		
$SpO_2 \geq 93$	324569	78.20%
SpO_2=90-92%	46304	11.16%
$SpO_2 < 90\%$	44167	10.64%

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Properties	N	%
Pulmonary complications	31190	7.51%
Pleural effusion	30438	69.54%
Empyema	10158	23.21%
Lung abscess	1578	3.61%
Pneumothorax	1594	3.64%
Bacteraemia	21253	5.12%
First contact facilit level		
Village Clinic (0)	29938	7.21%
Health Centre (1a)	203953	49.14%
Rural/Community/Mission Hospital (1b)	90261	21.75%
District/Central Hospital (2)	90888	21.90%

Treatment effectiveness outputs

Table C.2 presents the natural history mortality rate for each ALRI case type: SpO_2, general danger signs, IMCI symptoms-based classification at first-referral level, and disease type. Also includes the respective treatment effectiveness of oral and parenteral antibiotics with and without oxygen therapy, for each case type.

Table C.2 Risk of death by classification case types and respective treatment effectiveness

Oxygen saturation	General danger signs	IMCI classification	Disease type	Fraction of cases	Probability of death without treatment (%)	Effectiveness IV antibiotics with oxygen (%)	Effectiveness IV antibiotics only (%)	Effectiveness oral antibiotics (%)
>=93%		Cough or cold	Other ALRI	0.0250	2.20	98.16	98.16	92.65
>=93%		Cough or cold	Pneumonia	0.0085	6.37	94.70	94.70	89.19
>=93%		Fast-breathing pneumonia	Other ALRI	0.1783	2.40	98.22	98.22	93.28
>=93%		Fast-breathing pneumonia	Pneumonia	0.0856	7.12	94.80	94.80	90.03
>=93%		Chest-indrawing pneumonia	Other ALRI	0.1711	1.72	98.21	98.21	91.84
>=93%		Chest-indrawing pneumonia	Pneumonia	0.0640	9.62	94.77	94.77	87.91
>=93%	False	Severe pneumonia	Other ALRI	0.0896	2.20	97.77	97.77	88.28
>=93%	False	Severe pneumonia	Pneumonia	0.0524	13.75	93.40	93.40	82.01
>=93%	True	Severe pneumonia	Other ALRI	0.0646	4.59	95.22	95.22	79.44
>=93%	True	Severe pneumonia	Pneumonia	0.0421	24.10	85.72	85.72	68.75
90-92%		Cough or cold	Other ALRI	0.0012	8.17	97.38	97.38	89.95
90-92%		Cough or cold	Pneumonia	0.0007	20.15	92.89	92.89	85.20
90-92%		Fast-breathing pneumonia	Other ALRI	0.0116	8.01	97.46	97.46	90.76
90-92%		Fast-breathing pneumonia	Pneumonia	0.0083	19.63	92.88	92.88	86.18
90-92%		Chest-indrawing pneumonia	Other ALRI	0.0186	8.11	97.67	97.67	88.83
90-92%		Chest-indrawing pneumonia	Pneumonia	0.0163	24.17	93.37	93.37	83.44
90-92%	False	Severe pneumonia	Other ALRI	0.0157	12.94	96.56	96.56	83.54
90-92%	False	Severe pneumonia	Pneumonia	0.0163	37.48	90.74	90.74	75.36
90-92%	True	Severe pneumonia	Other ALRI	0.0093	20.56	93.61	93.61	73.03
90-92%	True	Severe pneumonia	Pneumonia	0.0135	54.75	81.87	81.87	57.76
<90%		Cough or cold	Other ALRI	0.0004	18.49	97.07	91.95	85.86
<90%		Cough or cold	Pneumonia	0.0001	39.19	91.08	79.92	78.68
<90%		Fast-breathing pneumonia	Other ALRI	0.0033	18.85	97.09	91.97	86.86
<90%		Fast-breathing pneumonia	Pneumonia	0.0022	39.15	91.55	80.61	80.71
<90%		Chest-indrawing pneumonia	Other ALRI	0.0151	22.01	97.07	91.93	84.21
<90%		Chest-indrawing pneumonia	Pneumonia	0.0121	47.79	91.43	80.42	76.64
<90%	False	Severe pneumonia	Other ALRI	0.0195	26.91	96.37	90.37	76.56

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Oxygen saturation	**General danger signs**	**IMCI classification**	**Disease type**	**Fraction of cases**	**Probability of death without treatment (%)**	**Effectiveness IV antibiotics with oxygen (%)**	**Effectiveness IV antibiotics only**	**Effectiveness oral antibiotics (%)**
<90%	False	Severe pneumonia	Pneumonia	0.0189	56.91	89.31	76.93	65.14
<90%	True	Severe pneumonia	Other ALRI	0.0167	42.72	92.08	81.69	60.30
<90%	True	Severe pneumonia	Pneumonia	0.0192	75.07	76.37	58.77	39.60

Effectiveness of initial treatment, not applicable to follow-up care, which includes the odds of increased treatment failure if initial treatment fails or not appropriate treatment given at initial appointment.

Health outcomes and costs

We evaluated 15 intervention scenarios of pulse oximetry and oxygen scale-up, as summarised in Table B.1. For each scenario, the simulation outputted key outcomes measures including mortality and DALYs, along with the health-care costs associated with implementation.

The estimation of DALYs is based of years of life lost (YLL) due to premature death, using the health-adjusted life expectancy (HALE) of 54.7 years in 2021 (WHO, latest data year), discounted at 3% rate. In the simulation, each individual death generates a DALY value based on the child's age at time of death and the expected HALE. The years lived with disability (YLD) component of a DALY estimate is not incorporated given the acute nature of the disease (episode duration of a maximum 14 days). For this health economic evaluation, we employed a one-year time horizon and considered only immediate outcomes of a given ALRI episode rather than following children for subsequent outcomes. Thus, we captured health benefits resulting from mortality reduction in that year, assuming those benefiting would live in reasonable states of health for many years on average (according to the HALE estimate).

Beyond health outcomes, the simulation also recorded resource utilisation across each individual's interactions with the health system, which have a cost associated to: usage of pulse oximeters, oxygen provision, antibiotics administration, outpatient consultations, and inpatient hospitalisation days. The simulation also outputs the number of hypoxaemic children seen at primary care facilities 0 and 1a where only stabilisation oxygen can be provided, assumed to be 6 hours of oxygen provision, and the full oxygen therapy provided in hospitals (level 2 and 1b) on average 3 days, at 1 litre per minute for young infants and 2 litres per minute for 2-59 months. Under optimal conditions (100% pulse oximetry use and perfect referral systems), the ALRI cohort would require 362,249,280 litres of oxygen, representing 25.9% of Malawi's total national oxygen demand (1,401,065,280 litres as estimated in the National Oxygen Roadmap). This proportion was used to allocate the appropriate fraction of national oxygen system costs to ALRI treatment in our economic analysis. At an individual level, the unit cost per litre of oxygen was adjusted depending on the full use of oxygen services (Appendix B.3.3), ensuring that the sum of oxygen costs for the cohort accurately reflects the 25.9% allocation of the whole oxygen systems cost.

C.1.2 Cost-effectiveness metrics

Incremental Cost Effectiveness Ratio (ICER)

The cost-effectiveness of each intervention scenario is presented in Incremental Cost-Effectiveness Ratio (ICER) using deaths averted and DALYs averted as the measure of effectiveness, and the cost difference between the baseline scenario and the intervention scenario.

The cost per death or DALY averted is calculated for all scenarios relative to the baseline. Given several scenarios of intervention alternatives, the process to determine the most cost-effective scenario, starts with ranking the

interventions from least costly to most costly. Then, using the DALYs averted of each scenario compared to baseline intervention, the dominated intervention alternatives (those with fewer DALYs averted for the same or higher cost) can be identified. The remaining non-dominated scenarios are compared through ICERs between the most cost-effective scenario identified and the next scenario alternative, as we move along the list sorted by total cost. Thus, identifying the extended dominated scenarios that have an ICER greater than that of the next more effective alternative, and ultimately, the most cost-effective scenario (the scenario with the lowest cost per DALY averted).

Incremental Net Benefit (INB)

In supplementation of the interpretation of cost-effectiveness results of ICERs, the net benefit of interventions were considered in parallel.

The incremental net benefit (INB) puts the costs and health outcomes on the same scale by using a cost-effectiveness threshold, or willingness-to-pay for one unit of health effect. For Malawi, this was estimated to be less or equal to $61 USD per DALY averted in 2016 [87]. To convert the value to 2024 USD terms, the 2016 cost-effectiveness threshold (CET) of $61 was inflated - Table C.3 shows the inflation process. The cost-effectiveness threshold in 2024 is estimated to be $80 USD. With this threshold, the health benefits (DALYs averted) can be converted into a monetary value, and incremental costs can be converted into health benefit value.

Table C.3 Inflation of Malawi's 2016 Cost-Effectiveness Threshold (CET) to 2024 US$ value

Year	US Inflation, average consumer prices (annual %) [Source: International Monetary Fund)	Value in previous year * (100 + inflation rate)/100	
		Value of $1 (base year = 2016)	Value of $61 (base year = 2016)
2016	1.267	1	61
2017	2.131	1.021310	62.30
2018	2.439	1.046220	63.82
2019	1.813	1.065188	64.98
2020	1.249	1.078492	65.79
2021	4.682	1.128987	68.87
2022	7.992	1.219216	74.37
2023	4.128	1.269545	77.44
2024	2.907*	1.306450	**79.69**

*Predicted US inflation in 2024

There are two ways to describe the INB: through the incremental net health benefit (INHB), and the incremental net monetary benefit (INMB).

Using DALYs averted as the health benefit unit, the incremental net health benefit re-scales incremental costs in health effect terms, by diving by the cost-effectiveness threshold and subtracting it from the incremental health effects (DALYs averted):

INHB = DALYs averted - (incremental cost of intervention / CET)

A positive INHB indicates that the overall population health would be

increased as a result of the new intervention being introduced, making it a favourable choice from a cost-effectiveness perspective. Whilst a negative INHB suggests that the intervention may not provide sufficient additional health benefits to justify its costs compared to an alternative health programme (assuming the alternative intervention produces health at or below the cost-effectiveness threshold value, in this case for each $80 spent on the alternative, one DALY is averted).

The incremental net monetary benefit (INMB) re-scales differences in health effects in monetary terms by multiplying it with the cost-effectiveness threshold and then subtracting the cost difference.

INMB = (DALYs averted × CET) - incremental cost of intervention

A positive INMB indicates that the intervention is cost-effective in comparison to the alternative at the specified cost-effectiveness threshold. Whilst a negative INMB suggests that the intervention may not provide sufficient additional monetary benefits to justify its costs compared to the alternative.

C.1.3 Sensitivity analyses

One-way deterministic sensitivity analyses were performed for key health system's configurations, epidemiological parameters, conceptual model assumptions, and costs. By independently modifying each parameter while holding others constant, we assessed how specific uncertainties might influence the cost-effectiveness results.

Health system conditions

1. 'HW Dx Accuracy - 50%' – A reduction in health worker diagnostic accuracy, setting IMCI guideline adherence from 75% (base case) to 50% sensitivity across all health system levels. This analysis reflects documented evidence of poor quality care in Malawi for children under-5 presenting with respiratory symptoms. While positioned as a sensitivity analysis, real-world conditions may more closely align with these parameters, potentially making these results particularly relevant for policy implementation.

2. 'Referral rate - 60%' – Reduce the referral rate success of severe cases seen at health centres and villages clinics, from 85% to 60%. This adjustment reflects documented evidence that Malawi's fragmented referral systems typically achieve only 40-65% completion rates, though these statistics are not specific to severe ALRI cases.

3. 'HW Dx Accuracy - 100%' – Set perfect health workers' adherence to IMCI guidelines, providing an insight into policy efficacy within an otherwise imperfect health system.

4. 'Perfect health system' – The impact of interventions is assessed under optimal health system conditions. This includes health workers' perfect adherence to IMCI guidelines in the delivery of care, 100% consistent

use of pulse oximeter if implemented, and functional referral systems for continuum of care. This analysis evaluates the existing policies in place, projecting the theoretical benefit/impact and associated costs of the interventions at baseline and the interventions in consideration.

Epidemiological parameters

5. 'Reduced incidence' – Reduce ALRI incidence rate by half, from 15 to 7.5 cases per 100 child-years. This adjustment aligns more closely with the Global Burden of Disease estimate for Malawi in 2021, which reported an incidence rate of 7,166.1 (95% CI: 6,209.7 to 8,251.0) cases per 100,000 children [11].

6. 'Reduced mortality' – Reduce the baseline odds of death by half.

7. 'Reduced oxygen effect' – Reduce the effect of oxygen on antibiotic treatment success. Parameter [or_mortality_improved_oxygen_systems] value 0.52 (95% CI: 0.39, 0.70) [72]. Use the inverse of the upper bounds OR=0.70 applied to the parenteral treatment failure.

8. 'Planned PSA - 70% availability' – Reduce the expected oxygen service availability of the 'Planned PSA' scenario from 80% to 70%. Making a closer relationship between increased oxygen production capacity and service coverage. For an overall 70% availability, by facility level it covers 82.1% of Central and District hospitals oxygen demand, 63.0% of Mission, Community and Rural hospitals' oxygen demand, and 60.9% of health centres' oxygen demand.

Conceptual model assumptions

9. 'Remove natural mortality scaling factor' – Remove the conceptual model assumption of a differential baseline mortality rate between treated (observed mortality data) and untreated ALRI (natural history). The mortality model applied an increased risk of death for complicated ALRI and bacterial causes based on calculations derived from simulated natural deaths and treatment failures across disease categories (detailed in Appendix A.2.6).

Intervention-associated costs

10. 'ALRI oxygen consumption - 50%' – Increase the oxygen costs by (nearly) double. Instead of the 25.9% of oxygen system consumption by ALRI, we assume 50% of the service is taken up by ALRI, thus, 50% of the whole oxygen system cost.

11. 'PO unit cost doubled' – Double the unit cost of Pulse Oximetry use.

12. 'Outpatient & Inpatient unit costs doubled' – Double the unit cost of outpatient consultation and inpatient bed days.

C.1.4 Bootstrap analysis

We conducted bootstrap statistical analyses to quantify the uncertainty in the result estimates, whereby the outcomes were resampled by randomly selecting observations with replacement from the original cohort simulation outputs. We conducted 1000 iterations, and in each iteration, we calculated the key metrics for the economic evaluation: difference in costs, deaths averted, DALYs averted, and respective incremental cost-effectiveness ratios (ICERs) and incremental net benefits (INBs) between baseline scenario and intervention scenarios. These were paired comparisons, as we maintained the sampling indices across scenarios within each bootstrap iteration, allowing for direct individual-level comparison of outcomes between the baseline and intervention scenarios while accounting for within-subject correlation. The mean estimate, 2.5 and 97.5 percentiles for the key outcomes are reported.

C.2 Results of the CEA

C.2.1 Main analysis - 'real-world' conditions

The term 'real-world' refers to an attempt to model the conditions characteristic of Malawi's health system. The key parameters include: 75% sensitivity of health workers' IMCI performance, 85% complete referral rate of severe cases seen at health centres, 60% seek follow-up care following oral antibiotics failure, with greater odds of seeking follow-up care with a severe symptom, and pulse oximetry usage rate of 90%. Simulating the effects of interventions and associated costs under such parameters settings provides an evaluation of their effectiveness in practical conditions, and relevant to policy.

Table C.4 lists the simulation outputs of health outcomes and healthcare costs associated with each scenario under 'real-world' conditions, while Table C.5 and Table C.6 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values. To further understand the synergy between oxygen and pulse oximetry and their effects on outcomes, Table C.7 provides an insight into the changes in oxygen need detection and/or oxygen provision with progressive pulse oximetry introduction across facility levels at a consistent usage rate of 90%.

Table C.4 Outcomes and costs outputs of each scenario, under suboptimal 'real-world' conditions

Scenario	Deaths	CFR	DALYs	PO cost	Oxygen cost	Outpatient consultation cost	Oral antibiotics cost	IV antibiotics cost	Inpatient admission cost	Total
Scenario 0	9,485	2.29%	252,392	0	0	895,126	136,970	455,042	3,640,640	5,127,777
0.PO-a	9,255	2.23%	246,270	16,919	0	883,596	135,303	475,826	3,816,026	5,327,670
0.PO-b	8,754	2.11%	232,951	32,400	0	864,041	132,336	513,744	4,069,151	5,611,671
0.PO-c	8,509	2.05%	226,429	49,315	0	859,408	128,263	569,650	4,479,181	6,085,817
0.PO-d	8,498	2.05%	226,135	51,008	0	859,066	127,644	577,626	4,535,353	6,150,698
Scenario 1	9,005	2.17%	239,623	0	789,050	895,113	136,970	455,883	3,625,964	5,902,980
1.PO-a	8,704	2.10%	231,612	16,919	789,050	883,583	135,303	477,023	3,795,586	6,097,465
1.PO-b	8,119	1.96%	216,060	32,399	789,050	864,028	132,336	515,290	4,043,916	6,377,019
1.PO-c	7,678	1.85%	204,329	49,310	789,050	859,350	128,262	571,996	4,439,574	6,837,542
1.PO-d	7,647	1.84%	203,502	51,004	789,050	859,005	127,643	580,101	4,493,683	6,900,486
Scenario 2	8,533	2.06%	227,056	0	1,521,566	895,072	136,968	456,693	3,611,092	6,621,392
2.PO-a	8,191	1.97%	217,951	16,918	1,521,566	883,542	135,301	478,096	3,776,728	6,812,152
2.PO-b	7,524	1.81%	200,216	32,396	1,521,566	863,987	132,334	516,763	4,019,504	7,086,551
2.PO-c	6,879	1.66%	183,060	49,304	1,521,566	859,244	128,258	574,323	4,399,763	7,532,457
2.PO-d	6,816	1.64%	181,384	50,997	1,521,566	858,897	127,639	582,565	4,452,011	7,593,675

CFR: Case Fatality Rate | DALYs: Disability Adjusted Life Years | PO: Pulse Oximetry | IV: Intravenous
Scenario 0 is a null scenario, where children have no access to oxygen or pulse oximetry;
Scenario 1 models 40% oxygen service availability;
Scenario 2 models 80% oxygen service availability;
PO refers to pulse oximetry being available at: a = central and district hospitals only; b = central, district, rural, mission and community hospitals; c= all hospitals and primary health centres; d=all levels of the health system including community health workers.

Table C.5 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), under suboptimal 'real-world' conditions

Scenario	Mortality reduction (%)	Deaths averted	DALYs averted	Incremental cost
Scenario 0				
0.PO-a	2.4 (2.1, 2.8)	230 (197, 264)	6100 (5200, 7000)	200000 (194000, 206000)
0.PO-b	7.7 (7.0, 8.4)	731 (664, 795)	19500 (17600, 21100)	484000 (475000, 493000)
0.PO-c	10.3 (9.3, 11.2)	978 (879, 1066)	26000 (23400, 28300)	958000 (945000, 971000)
0.PO-d	10.4 (9.4, 11.3)	988 (886, 1080)	26300 (23600, 28700)	1023000 (1010000, 1036000)
Scenario 1	5.1 (4.6, 5.5)	480 (441, 523)	12800 (11700, 13900)	775000 (759000, 792000)
1.PO-a	8.2 (7.7, 8.8)	781 (725, 840)	20800 (19300, 22400)	970000 (951000, 987000)
1.PO-b	14.4 (13.6, 15.2)	1366 (1287, 1448)	36400 (34200, 38500)	1250000 (1231000, 1268000)
1.PO-c	19.1 (18.2, 20.0)	1808 (1711, 1908)	48100 (45500, 50700)	1710000 (1690000, 1732000)
1.PO-d	19.4 (18.4, 20.3)	1839 (1736, 1941)	48900 (46200, 51600)	1773000 (1753000, 1795000)
Scenario 2	10.0 (9.4, 10.7)	952 (893, 1017)	25400 (23800, 27100)	1494000 (1470000, 1516000)
2.PO-a	13.6 (13.0, 14.4)	1293 (1225, 1368)	34400 (32600, 36400)	1685000 (1662000, 1708000)
2.PO-b	20.7 (19.8, 21.6)	1961 (1870, 2059)	52200 (49700, 54800)	1959000 (1935000, 1984000)
2.PO-c	27.5 (26.5, 28.5)	2606 (2501, 2717)	69300 (66500, 72300)	2405000 (2380000, 2431000)
2.PO-d	28.1 (27.1, 29.2)	2669 (2561, 2781)	71000 (68100, 74000)	2466000 (2440000, 2492000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.6 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), under suboptimal 'real-world' conditions

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
Scenario 0				
0.PO-a	874 (747, 1019)	33 (28, 38)	3600 (2700, 4600)	290000 (219000, 367000)
0.PO-b	663 (606, 730)	25 (23, 27)	13400 (11600, 15100)	1073000 (930000, 1208000)
0.PO-c	982 (899, 1089)	37 (34, 41)	14000 (11400, 16400)	1124000 (915000, 1313000)
0.PO-d	1037 (950, 1154)	39 (36, 43)	13500 (10800, 15900)	1082000 (861000, 1272000)
Scenario 1	1616 (1485, 1759)	61 (56, 66)	3100 (2000, 4200)	248000 (162000, 336000)
1.PO-a	1243 (1160, 1335)	47 (44, 50)	8700 (7200, 10200)	693000 (577000, 813000)
1.PO-b	915 (864, 969)	34 (32, 36)	20700 (18700, 22800)	1659000 (1493000, 1827000)
1.PO-c	946 (896, 995)	36 (34, 37)	26700 (24200, 29400)	2139000 (1940000, 2348000)
1.PO-d	965 (914, 1019)	36 (34, 38)	26800 (24100, 29400)	2141000 (1931000, 2355000)
Scenario 2	1569 (1474, 1672)	59 (55, 63)	6700 (5100, 8300)	535000 (409000, 665000)
2.PO-a	1303 (1233, 1374)	49 (46, 52)	13400 (11600, 15300)	1071000 (928000, 1227000)
2.PO-b	999 (952, 1047)	38 (36, 39)	27700 (25200, 30200)	2216000 (2019000, 2420000)
2.PO-c	923 (885, 961)	35 (33, 36)	39300 (36500, 42200)	3143000 (2917000, 3378000)
2.PO-d	924 (887, 963)	35 (33, 36)	40200 (37300, 43100)	3215000 (2984000, 3449000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

Table C.7 Change in oxygen need detected and oxygen provision with implementation of routine pulse oximetry at outpatient settings, under suboptimal 'real-world' conditions

Scenario	Oxygen need detected / Oxygen provided	% Increase in oxygen need detected / Oxygen provided	Oxygen provided in litres	Coverage of oxygen provision (%)
Scenario 0	17,515	ref		
0.PO-a	21,502	23%		
0.PO-b	28,365	62%		
0.PO-c	39,947	128%		
0.PO-d	41,556	137%		
Scenario 1	8,024	ref	61234920	18.2 (17.8, 18.5)
1.PO-a	9,879	23%	76082760	22.4 (22.0, 22.7)
1.PO-b	11,978	49%	93410280	27.1 (26.7, 27.5)
1.PO-c	15,709	96%	126973800	35.6 (35.1, 36.0)
1.PO-d	16,219	102%	131627160	36.7 (36.3, 37.2)
Scenario 2	15,328	ref	117073800	34.7 (34.3, 35.1)
2.PO-a	18,518	21%	142734600	41.9 (41.5, 42.4)
2.PO-b	23,171	51%	181087560	52.5 (52.0, 52.9)
2.PO-c	30,697	100%	249529680	69.5 (69.1, 70.0)
2.PO-d	31,768	107%	259307640	71.9 (71.5, 72.4)

Scenario 0 is a null scenario, where children have no access to oxygen or pulse oximetry; Scenario 1 models 40% oxygen service availability; Scenario 2 models 80% oxygen service availability; PO refers to pulse oximetry being available at: a = central and district hospitals only; b = central, district, rural, mission and community hospitals; c= all hospitals and primary health centres; d=all levels of the health system including CHWs.
Column '*Oxygen need detected / Oxygen provided':* for scenarios of antibiotics only with introduction of pulse oximetry, the values apply to the **oxygen need detected**, whereas for scenarios with oxygen implementation, **oxygen provided** values apply. The oxygen need detected refer to the hypoxaemia (SpO_2<90%) cases detected at the facility level where care was first sought.
Column *'% Increase in Oxygen need detected / Oxygen provision'*: for scenario 0, the values pertain to the increase in **oxygen need detected** (SpO_2<90%) with the introduction of pulse oximetry at each additional facility level. Whereas, for each oxygen scenarios 1, and 2 with introduction of pulse oximetry at each additional facility level, the values apply to **the increase in oxygen provision** compared to the respective oxygen scenario without pulse oximetry.
Column '*Coverage of oxygen provision*' applies to oxygen scenarios only. It is the proportion of hypoxaemic cases provided with oxygen therapy among all hypoxaemic cases in the cohort.

C.2.2 Sensitivity analysis: 'HW Dx accuracy - 50%'

An important aspect to consider when analysing the results under 'real-world conditions' is the diagnostic accuracy of health workers, particularly their performance in assessing and classifying ALRI accordingly to the IMCI guidelines. The results presented above were based on the reported health workers' diagnostic accuracy from the HHFA 2018-2019 survey. However, as described earlier, it is imperative to acknowledge that this estimation relied on theoretical examinations of health staff knowledge rather than on exit interviews (re-classification following patient appointment), which may have led to an overestimation of their actual diagnostic performance in practical settings. Further evidence from re-analysis studies using the SPA 2013-2014 survey supports this concern, highlighting poor adherence to IMCI guidelines [62] and the low sensitivity of health workers classification of non-severe pneumonia, with estimates as low as 21% [60]. The low quality of care of patients presenting with cough or difficult breathing is consistent with other smaller scale studies [88]. Given these considerations, presented here is a sensitivity analysis of the cost-effectiveness results of interventions under 'real-world conditions' with a change in the health worker's diagnostic accuracy to an assumed 50% across all facility levels. The antibiotic over-prescription rate remains applicable to the incorrectly classified severe ALRI cases.

Table C.8 lists the simulation outputs of health outcomes and healthcare costs associated with each scenario under 'real-world' health system conditions with a change in health workers' diagnostic accuracy to 50%. Table C.9 and Table C.10 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline under this sensitivity analysis for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values. To further understand the synergy between oxygen and pulse oximetry and their effects on outcomes when quality of care is low, Table C.11 provide an insight into the changes in oxygen need detection and/or oxygen provision with progressive pulse oximetry introduction across facility levels at a consistent usage rate of 90%, in the sensitivity analysis conditions.

Table C.8 Outcomes and costs outputs of each scenario in the sensitivity analysis under suboptimal 'real-world' conditions with health worker's diagnostic accuracy reduced to 50%

Scenario	Deaths	CFR	DALYs	PO cost	Oxygen cost	Outpatient consultation cost	Oral antibiotics cost	IV antibiotics cost	Inpatient admission cost	Total
Scenario 0	12,464	3.00%	331,689	0	0	1,015,867	128,794	300,314	2,325,308	3,770,283
0.PO-a	11,902	2.87%	316,727	16,406	0	995,890	126,220	333,400	2,612,005	4,083,920
0.PO-b	11,065	2.67%	294,473	31,830	0	971,072	123,075	377,456	2,918,128	4,421,560
0.PO-c	10,470	2.52%	278,641	49,422	0	963,919	119,217	439,261	3,383,202	4,955,021
0.PO-d	10,424	2.51%	277,419	51,181	0	963,372	118,590	447,996	3,446,895	5,028,035
Scenario 1	12,150	2.93%	323,334	0	789,050	1,015,858	128,794	300,746	2,317,929	4,552,378
1.PO-a	11,448	2.76%	304,648	16,405	789,050	995,881	126,220	334,380	2,595,432	4,857,368
1.PO-b	10,503	2.53%	279,522	31,829	789,050	971,063	123,075	378,859	2,895,809	5,189,685
1.PO-c	9,664	2.33%	257,206	49,418	789,050	963,865	119,216	441,558	3,344,971	5,708,077
1.PO-d	9,590	2.31%	255,240	51,177	789,050	963,312	118,589	450,419	3,406,388	5,778,935
Scenario 2	11,828	2.85%	314,761	0	1,521,566	1,015,830	128,794	301,151	2,310,403	5,277,745
2.PO-a	11,046	2.66%	293,943	16,404	1,521,566	995,853	126,219	335,180	2,581,586	5,576,809
2.PO-b	9,971	2.40%	265,356	31,827	1,521,566	971,035	123,074	380,150	2,874,976	5,902,628
2.PO-c	8,874	2.14%	236,176	49,411	1,521,566	963,759	119,212	443,813	3,306,403	6,404,164
2.PO-d	8,766	2.11%	233,308	51,170	1,521,566	963,204	118,585	452,828	3,365,716	6,473,069

CFR: Case Fatality Rate | DALYs: Disability Adjusted Life Years | PO: Pulse Oximetry | IV: Intravenous
Scenario 0 is a null scenario, where children have no access to oxygen or pulse oximetry;
Scenario 1 models 40% oxygen service availability;
Scenario 2 models 80% oxygen service availability;
PO refers to pulse oximetry being available at: a = central and district hospitals only; b = central, district, rural, mission and community hospitals; c= all hospitals and primary health centres; d=all levels of the health system including community health workers.

Table C.9 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with health worker's diagnostic accuracy reduced to 50%

Scenario	Mortality reduction (%)	Deaths averted	DALYs averted	Incremental cost
Scenario 0				
0.PO-a	4.5 (4.1, 4.9)	561 (515, 613)	15000 (13700, 16300)	314000 (306000, 321000)
0.PO-b	11.2 (10.6, 11.8)	1399 (1318, 1483)	37200 (35100, 39400)	651000 (641000, 662000)
0.PO-c	16.0 (15.2, 16.8)	1994 (1882, 2096)	53100 (50100, 55800)	1185000 (1170000, 1199000)
0.PO-d	16.4 (15.5, 17.2)	2040 (1922, 2143)	54300 (51200, 57000)	1258000 (1243000, 1272000)
Scenario 1	2.5 (2.3, 2.8)	314 (282, 349)	8400 (7500, 9300)	782000 (762000, 802000)
1.PO-a	8.2 (7.7, 8.6)	1015 (958, 1078)	27000 (25500, 28700)	1087000 (1066000, 1106000)
1.PO-b	15.7 (15.1, 16.4)	1961 (1870, 2052)	52200 (49700, 54600)	1420000 (1399000, 1440000)
1.PO-c	22.5 (21.7, 23.3)	2799 (2686, 2914)	74500 (71500, 77500)	1938000 (1916000, 1961000)
1.PO-d	23.1 (22.3, 23.9)	2873 (2756, 2992)	76400 (73300, 79600)	2009000 (1987000, 2032000)
Scenario 2	5.1 (4.7, 5.5)	636 (590, 687)	16900 (15700, 18300)	1507000 (1480000, 1534000)
2.PO-a	11.4 (10.8, 12.0)	1417 (1346, 1499)	37700 (35800, 39900)	1806000 (1781000, 1833000)
2.PO-b	20.0 (19.3, 20.8)	2492 (2390, 2599)	66300 (63600, 69200)	2133000 (2107000, 2159000)
2.PO-c	28.8 (27.9, 29.7)	3588 (3467, 3712)	95500 (92200, 98800)	2634000 (2607000, 2663000)
2.PO-d	29.7 (28.8, 30.6)	3696 (3572, 3823)	98400 (95000, 101700)	2703000 (2676000, 2730000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.10 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with health worker's diagnostic accuracy reduced to 50%

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
Scenario 0				
0.PO-a	559 (510, 610)	21 (19, 23)	11000 (9800, 12400)	883000 (782000, 993000)
0.PO-b	465 (441, 495)	17 (17, 19)	29100 (26900, 31200)	2326000 (2155000, 2500000)
0.PO-c	594 (565, 629)	22 (21, 24)	38300 (35300, 41000)	3060000 (2823000, 3280000)
0.PO-d	616 (587, 653)	23 (22, 25)	38600 (35500, 41200)	3085000 (2839000, 3299000)
Scenario 1	2492 (2253, 2772)	93 (85, 104)	-1400 (-2268, -539)	-112000 (-181000, -43000)
1.PO-a	1071 (1009, 1134)	40 (38, 43)	13400 (11900, 15100)	1076000 (953000, 1207000)
1.PO-b	724 (692, 758)	27 (26, 28)	34400 (32000, 36800)	2754000 (2561000, 2945000)
1.PO-c	692 (665, 720)	26 (25, 27)	50300 (47300, 53300)	4021000 (3786000, 4264000)
1.PO-d	699 (671, 727)	26 (25, 27)	51300 (48300, 54400)	4107000 (3861000, 4352000)
Scenario 2	2371 (2198, 2546)	89 (83, 96)	-1900 (-3083, -583)	-152000 (-247000, -47000)
2.PO-a	1275 (1208, 1338)	47 (45, 50)	15100 (13300, 17200)	1212000 (1065000, 1379000)
2.PO-b	855 (821, 891)	32 (31, 33)	39700 (37000, 42400)	3173000 (2960000, 3391000)
2.PO-c	734 (710, 759)	27 (27, 29)	62600 (59400, 65900)	5005000 (4751000, 5268000)
2.PO-d	731 (707, 756)	27 (27, 28)	64600 (61300, 67900)	5165000 (4905000, 5432000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

Table C.11 Change in oxygen need detected and oxygen provision with implementation of routine pulse oximetry at outpatient settings, in reduced health workers performance conditions

Scenario	Oxygen need detected / Oxygen provided	% Increase in oxygen need detected / Oxygen provided	Oxygen provided in litres	Coverage of oxygen provision
Scenario 0	11,598	ref		
0.PO-a	18,228	57%		
0.PO-b	26,453	128%		
0.PO-c	39,231	238%		
0.PO-d	40,969	253%		
Scenario 1	5,718	ref	43805520	12.9 (12.6, 13.2)
1.PO-a	8,772	53%	67734000	19.9 (19.5, 20.2)
1.PO-b	11,298	98%	88146000	25.6 (25.1, 26.0)
1.PO-c	15,447	170%	124946280	35.0 (34.5, 35.4)
1.PO-d	16,007	180%	130000680	36.2 (35.8, 36.7)
Scenario 2	10,906	ref	83599200	24.7 (24.3, 25.1)
2.PO-a	16,188	48%	125157600	36.6 (36.2, 37.1)
2.PO-b	21,825	100%	170612640	49.4 (48.9, 49.9)
2.PO-c	30,182	177%	245531160	68.3 (67.9, 68.8)
2.PO-d	31,371	188%	256213800	71.0 (70.6, 71.5)

Description as per Table C.7

C.2.3 Sensitivity analysis: 'Referral rate - 60%'

Malawi's referral systems across care levels are fragmented and do not function optimally [54, 55]. Existing evidence suggests a range of 40-65% [56] completed referrals from health centres, however these are non-specific to severe ALRI cases. In this sensitivity analysis, we examined the impact of suboptimal referral systems by reducing the successful referral rate for severe ALRI cases from health centers and village clinics from 85% to 60%.

Table C.12 lists the simulation outputs of health outcomes and healthcare costs associated with each scenario under 'real-world' health system conditions with a change in referral success rate to 60%, while Table C.13 and Table C.14 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline under this sensitivity analysis for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values. Table C.15 provides an insight into the unmet need of oxygen provision without routine use of pulse oximeters, and changes in oxygen need detection and/or oxygen provision with progressive pulse oximetry introduction across facility levels at a consistent usage rate of 90%, under reduced referral rate completion.

Table C.12 Outcomes and costs outputs of each scenario in the sensitivity analysis under suboptimal 'real-world' conditions with referral completion rate reduced to 60%

Scenario	Deaths	CFR	DALYs	PO cost	Oxygen cost	Outpatient consultation cost	Oral antibiotics cost	IV antibiotics cost	Inpatient admission cost	Total
Scenario 0	9,606	2.31%	255,610	0	0	896,877	139,920	425,352	3,390,706	4,852,856
0.PO-a	9,376	2.26%	249,489	16,439	0	885,347	138,252	446,137	3,566,093	5,052,268
0.PO-b	8,875	2.14%	236,170	31,845	0	865,792	135,285	484,054	3,819,218	5,336,195
0.PO-c	8,657	2.09%	230,368	49,564	0	861,984	132,605	525,587	4,124,612	5,694,351
0.PO-d	8,658	2.09%	230,392	51,319	0	861,722	132,195	531,305	4,165,090	5,741,630
Scenario 1	9,152	2.21%	243,532	0	789,050	896,820	139,915	426,056	3,376,993	5,628,834
1.PO-a	8,851	2.13%	235,521	16,438	789,050	885,290	138,248	447,196	3,546,615	5,822,837
1.PO-b	8,266	1.99%	219,969	31,843	789,050	865,735	135,281	485,463	3,794,944	6,102,316
1.PO-c	7,880	1.90%	209,702	49,556	789,050	861,805	132,585	527,526	4,088,955	6,449,476
1.PO-d	7,859	1.89%	209,140	51,311	789,050	861,537	132,175	533,325	4,127,943	6,495,342
Scenario 2	8,709	2.10%	231,734	0	1,521,566	896,735	139,908	426,732	3,363,312	6,348,254
2.PO-a	8,367	2.02%	222,629	16,436	1,521,566	885,205	138,241	448,135	3,528,948	6,538,532
2.PO-b	7,700	1.86%	204,894	31,839	1,521,566	865,650	135,274	486,801	3,771,724	6,812,855
2.PO-c	7,145	1.72%	190,133	49,546	1,521,566	861,555	132,559	529,320	4,053,639	7,148,185
2.PO-d	7,095	1.71%	188,802	51,300	1,521,566	861,277	132,148	535,211	4,091,179	7,192,682

CFR: Case Fatality Rate | DALYs: Disability Adjusted Life Years | PO: Pulse Oximetry | IV: Intravenous
Scenario 0 is a null scenario, where children have no access to oxygen or pulse oximetry;
Scenario 1 models 40% oxygen service availability;
Scenario 2 models 80% oxygen service availability;
PO refers to pulse oximetry being available at: a = central and district hospitals only; b = central, district, rural, mission and community hospitals; c= all hospitals and primary health centres; d=all levels of the health system including community health workers.

Table C.13 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with referral completion rate reduced to 60%

Scenario	**Mortality reduction**	**Deaths averted**	**DALYs averted**	**Cost difference ($)**
Scenario 0				
0.PO-a	2.4 (2.1, 2.8)	230 (197, 264)	6100 (5200, 7000)	199000 (193000, 206000)
0.PO-b	7.6 (6.9, 8.3)	732 (664, 795)	19500 (17600, 21100)	483000 (475000, 492000)
0.PO-c	9.9 (9.0, 10.8)	951 (857, 1040)	25300 (22800, 27700)	842000 (829000, 853000)
0.PO-d	9.9 (8.9, 10.8)	950 (854, 1041)	25300 (22700, 27700)	889000 (876000, 901000)
Scenario 1	4.7 (4.3, 5.2)	455 (414, 496)	12100 (11000, 13200)	776000 (759000, 793000)
1.PO-a	7.9 (7.3, 8.4)	755 (700, 814)	20100 (18600, 21700)	970000 (951000, 987000)
1.PO-b	14.0 (13.2, 14.8)	1341 (1258, 1422)	35700 (33500, 37800)	1250000 (1230000, 1268000)
1.PO-c	18.0 (17.1, 18.9)	1727 (1631, 1827)	45900 (43400, 48600)	1597000 (1575000, 1618000)
1.PO-d	18.2 (17.3, 19.2)	1748 (1646, 1849)	46500 (43800, 49200)	1643000 (1621000, 1664000)
Scenario 2	9.3 (8.7, 10.0)	898 (838, 954)	23900 (22300, 25400)	1496000 (1471000, 1519000)
2.PO-a	12.9 (12.2, 13.6)	1239 (1171, 1309)	33000 (31200, 34800)	1686000 (1661000, 1710000)
2.PO-b	19.8 (19.0, 20.8)	1906 (1813, 2001)	50700 (48300, 53200)	1960000 (1936000, 1985000)
2.PO-c	25.6 (24.6, 26.6)	2461 (2353, 2570)	65500 (62600, 68400)	2295000 (2269000, 2322000)
2.PO-d	26.1 (25.1, 27.1)	2511 (2400, 2623)	66800 (63800, 69800)	2340000 (2313000, 2366000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.14 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with referral completion rate reduced to 60%

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
Scenario 0				
0.PO-a	872 (746, 1017)	33 (28, 38)	3600 (2700, 4600)	290000 (219000, 368000)
0.PO-b	662 (605, 729)	25 (23, 27)	13400 (11600, 15100)	1073000 (930000, 1208000)
0.PO-c	887 (810, 981)	33 (30, 37)	14800 (12300, 17100)	1182000 (983000, 1369000)
0.PO-d	938 (853, 1040)	35 (32, 39)	14200 (11600, 16600)	1132000 (930000, 1326000)
Scenario 1	1710 (1563, 1867)	64 (59, 70)	2400 (1400, 3500)	192000 (108000, 280000)
1.PO-a	1287 (1201, 1380)	48 (45, 52)	8000 (6600, 9400)	637000 (526000, 753000)
1.PO-b	933 (881, 990)	35 (33, 37)	20000 (17900, 22100)	1603000 (1435000, 1770000)
1.PO-c	925 (875, 976)	35 (33, 37)	26000 (23500, 28600)	2079000 (1881000, 2288000)
1.PO-d	941 (887, 996)	35 (33, 37)	26000 (23400, 28700)	2077000 (1871000, 2293000)
Scenario 2	1668 (1565, 1784)	63 (59, 67)	5200 (3600, 6700)	416000 (290000, 538000)
2.PO-a	1362 (1292, 1442)	51 (49, 54)	11900 (10100, 13700)	952000 (805000, 1097000)
2.PO-b	1029 (981, 1080)	39 (37, 41)	26200 (23800, 28700)	2097000 (1903000, 2293000)
2.PO-c	933 (896, 975)	35 (34, 37)	36800 (33900, 39600)	2943000 (2713000, 3167000)
2.PO-d	932 (893, 974)	35 (34, 37)	37600 (34600, 40400)	3005000 (2770000, 3235000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

Table C.15 Change in oxygen need detected and oxygen provision with implementation of routine pulse oximetry at outpatient settings, with ineffective referral systems

Scenario	Oxygen need detected / Oxygen provided	% Increase in oxygen need detected / Oxygen provided	Oxygen provided in litres	Coverage of oxygen provision
Scenario 0	17,515	ref		
0.PO-a	21,502	23%		
0.PO-b	28,365	62%		
0.PO-c	39,947	128%		
0.PO-d	41,556	137%		
Scenario 1	7,548	ref	57803760	17.1 (16.7, 17.4)
1.PO-a	9,403	25%	72651600	21.3 (20.9, 21.6)
1.PO-b	11,502	52%	89979120	26.0 (25.6, 26.4)
1.PO-c	14,280	89%	115619040	32.3 (31.9, 32.8)
1.PO-d	14,644	94%	119033280	33.2 (32.7, 33.6)
Scenario 2	14,370	ref	110240640	32.5 (32.1, 32.9)
2.PO-a	17,560	22%	135901440	39.8 (39.3, 40.2)
2.PO-b	22,213	55%	174254400	50.3 (49.8, 50.8)
2.PO-c	27,757	93%	226283760	62.8 (62.4, 63.3)
2.PO-d	28,521	98%	233505360	64.6 (64.1, 65.1)

Description as per Table C.7

C.2.4 Sensitivity analysis: 'HW Dx Accuracy - 100%'

Assessing the cost-effectiveness of interventions under full adherence to IMCI guidelines, such evaluation provides an insight on the efficacy of the policies in place under an imperfect health system, namely the Integrate Management of Childhood Illnesses policies - in the form of IMCI Chart booklet in primary care facilities and the extended Hospital pocket book in secondary care facilities.

This sensitivity analysis provides an insight into the into the impact of health worker's quality of care.

Table C.16 lists the simulation outputs of health outcomes and healthcare costs associated with each scenario under 'real-world' health system conditions with a change in health workers' diagnostic accuracy to 100%, while Table C.17 and Table C.18 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline under this sensitivity analysis for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values. Table C.19 provides an insight into the unmet need of oxygen provision without routine use of pulse oximeters, and changes in oxygen need detection and/or oxygen provision with progressive pulse oximetry introduction across facility levels at a consistent usage rate of 90%, and 100% adherence to IMCI guidelines.

Table C.16 Outcomes and costs outputs of each scenario in the sensitivity analysis under suboptimal 'real-world' conditions with perfect health worker's diagnostic accuracy (100% adherence to IMCI)

Scenario	Deaths	CFR	DALYs	PO cost	Oxygen cost	Outpatient consultation cost	Oral antibiotics cost	IV antibiotics cost	Inpatient admission cost	Total
Scenario 0	6,361	1.53%	169,239	0	0	774,587	145,037	626,494	5,171,200	6,717,319
0.PO-a	6,362	1.53%	169,266	17,495	0	769,644	144,081	637,956	5,250,592	6,819,768
0.PO-b	6,260	1.51%	166,553	33,039	0	756,277	141,347	669,020	5,436,595	7,036,278
0.PO-c	6,416	1.55%	170,694	49,174	0	754,614	137,276	714,890	5,754,115	7,410,070
0.PO-d	6,435	1.55%	171,198	50,807	0	754,444	136,683	721,765	5,800,348	7,464,046
Scenario 1	5,728	1.38%	152,398	0	789,050	774,575	145,037	627,948	5,146,408	7,483,019
1.PO-a	5,714	1.38%	152,026	17,494	789,050	769,632	144,081	639,514	5,224,260	7,584,031
1.PO-b	5,568	1.34%	148,145	33,038	789,050	756,264	141,347	670,792	5,407,562	7,798,054
1.PO-c	5,567	1.34%	148,117	49,170	789,050	754,557	137,275	717,312	5,713,259	8,160,622
1.PO-d	5,571	1.34%	148,221	50,802	789,050	754,382	136,682	724,306	5,757,636	8,212,858
Scenario 2	5,111	1.23%	135,965	0	1,521,566	774,523	145,035	629,375	5,121,107	8,191,607
2.PO-a	5,086	1.23%	135,300	17,493	1,521,566	769,580	144,079	641,019	5,197,847	8,291,584
2.PO-b	4,894	1.18%	130,196	33,035	1,521,566	756,212	141,345	672,553	5,377,841	8,502,553
2.PO-c	4,739	1.14%	126,074	49,163	1,521,566	754,450	137,271	719,734	5,671,906	8,854,090
2.PO-d	4,719	1.14%	125,543	50,795	1,521,566	754,274	136,677	726,839	5,714,823	8,904,975

CFR: Case Fatality Rate | DALYs: Disability Adjusted Life Years | PO: Pulse Oximetry | IV: Intravenous
Scenario 0 is a null scenario, where children have no access to oxygen or pulse oximetry;
Scenario 1 models 40% oxygen service availability;
Scenario 2 models 80% oxygen service availability;
PO refers to pulse oximetry being available at: a = central and district hospitals only; b = central, district, rural, mission and community hospitals; c= all hospitals and primary health centres; d=all levels of the health system including community health workers.

Table C.17 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with perfect health worker's diagnostic accuracy (100% adherence to IMCI)

Scenario	Mortality reduction	Deaths averted	DALYs averted	Cost difference ($)
Scenario 0				
0.PO-a	-0.0 (-0.3, 0.2)	-1 (-16, 15)	-30 (-429, 398)	103000 (99000, 106000)
0.PO-b	1.6 (1.0, 2.2)	102 (61, 141)	2700 (1600, 3800)	319000 (313000, 326000)
0.PO-c	-0.8 (-1.8, 0.2)	-53 (-116, 10)	-1400 (-3090, 278)	693000 (682000, 704000)
0.PO-d	-1.1 (-2.2, -0.1)	-72 (-139, -6)	-1900 (-3682, -148)	747000 (736000, 758000)
Scenario 1	9.9 (9.2, 10.7)	633 (583, 682)	16800 (15500, 18100)	766000 (751000, 780000)
1.PO-a	10.2 (9.4, 11.0)	646 (595, 701)	17200 (15800, 18700)	867000 (851000, 882000)
1.PO-b	12.5 (11.5, 13.4)	793 (728, 860)	21100 (19400, 22900)	1081000 (1064000, 1098000)
1.PO-c	12.5 (11.3, 13.6)	795 (716, 873)	21200 (19000, 23200)	1443000 (1426000, 1462000)
1.PO-d	12.4 (11.2, 13.6)	791 (709, 875)	21000 (18900, 23300)	1496000 (1478000, 1515000)
Scenario 2	19.6 (18.7, 20.6)	1249 (1182, 1317)	33300 (31400, 35100)	1474000 (1454000, 1495000)
2.PO-a	20.0 (19.0, 21.1)	1274 (1203, 1346)	33900 (32000, 35800)	1574000 (1554000, 1595000)
2.PO-b	23.1 (21.9, 24.2)	1467 (1388, 1546)	39000 (36900, 41100)	1785000 (1764000, 1807000)
2.PO-c	25.5 (24.3, 26.7)	1622 (1533, 1705)	43200 (40800, 45400)	2137000 (2114000, 2160000)
2.PO-d	25.8 (24.5, 27.0)	1642 (1553, 1726)	43700 (41300, 45900)	2188000 (2164000, 2210000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.18 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with perfect health worker's diagnostic accuracy (100% adherence to IMCI)

Scenario	**ICER (Deaths)**	**ICER (DALYs)**	**Incremental Net Health Benefit (DALYs averted)**	**Incremental Net Monetary Benefit ($)**
Scenario 0				
0.PO-a	0 (0, 0)	-2463 (-37603, 4391)	-1300 (-1730, -897)	-105000 (-138000, -72000)
0.PO-b	3282 (2267, 5240)	123 (85, 197)	-1300 (-2373, -244)	-103000 (-190000, -20000)
0.PO-c	0 (0, 0)	-423 (-3043, 2450)	-10100 (-11700, -8300)	-805000 (-939000, -667000)
0.PO-d	-11765 (-41217, -4586)	-475 (-1597, -172)	-11300 (-13000, -9500)	-900000 (-1042000, -758000)
Scenario 1	1212 (1126, 1307)	46 (42, 49)	7300 (6000, 8500)	581000 (481000, 683000)
1.PO-a	1343 (1238, 1448)	50 (47, 54)	6400 (5000, 7800)	509000 (404000, 625000)
1.PO-b	1365 (1264, 1483)	51 (48, 56)	7600 (5900, 9300)	607000 (471000, 742000)
1.PO-c	1820 (1652, 2007)	68 (62, 75)	3100 (1100, 5200)	249000 (88000, 415000)
1.PO-d	1896 (1713, 2106)	71 (64, 79)	2300 (193, 4546)	187000 (15000, 364000)
Scenario 2	1181 (1118, 1246)	44 (42, 47)	14800 (13100, 16700)	1186000 (1045000, 1333000)
2.PO-a	1237 (1172, 1307)	46 (44, 49)	14200 (12400, 16100)	1139000 (991000, 1285000)
2.PO-b	1218 (1157, 1284)	46 (43, 48)	16700 (14600, 18700)	1337000 (1171000, 1499000)
2.PO-c	1318 (1253, 1389)	50 (47, 52)	16500 (14200, 18600)	1317000 (1139000, 1492000)
2.PO-d	1333 (1267, 1404)	50 (48, 53)	16300 (14000, 18600)	1308000 (1123000, 1485000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

Table C.19 Change in oxygen need detected and oxygen provision with implementation of routine pulse oximetry at outpatient settings, with 100% sensitivity of health workers diagnostic accuracy as per IMCI guidelines

Scenario	Oxygen need detected / Oxygen provided	% Increase in oxygen need detected / Oxygen provided	Oxygen provided in litres	Coverage of oxygen provision
Scenario 0	23,194	ref		
0.PO-a	25,092	8%		
0.PO-b	30,410	31%		
0.PO-c	40,639	75%		
0.PO-d	42,107	82%		
Scenario 1	10,216	ref	77983920	23.1 (22.8, 23.5)
1.PO-a	11,115	9%	85548240	25.2 (24.8, 25.5)
1.PO-b	12,731	25%	99311760	28.8 (28.4, 29.2)
1.PO-c	15,977	56%	129034080	36.2 (35.7, 36.6)
1.PO-d	16,427	61%	133195320	37.2 (36.7, 37.7)
Scenario 2	19,538	ref	149279040	44.2 (43.8, 44.7)
2.PO-a	21,086	8%	162334080	47.7 (47.3, 48.2)
2.PO-b	24,690	26%	193001760	55.9 (55.4, 56.4)
2.PO-c	31,216	60%	253497240	70.7 (70.2, 71.1)
2.PO-d	32,169	65%	262345680	72.8 (72.4, 73.3)

Description as per Table C.7

C.2.5 Sensitivity analysis: 'Perfect health system'

By examining the cost-effectiveness of each intervention scenario compared to baseline under perfect health system conditions - including quality of care with full adherence to IMCI guidelines, well-established referral systems for continuum of care, and consistent use (100%) of pulse oximetry if implemented - this evaluation examines the theoretical maximum benefit and associated costs of interventions under consideration, when all relevant components of the health system are adequately implemented.

Table C.20 lists the simulation outputs of health outcomes and healthcare costs associated with each scenario under optimal health system conditions, while Table C.21 and Table C.22 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline under this sensitivity analysis for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values. Table C.23 provides an insight into the unmet oxygen need without routine use of pulse oximeters, and changes in oxygen need detection and/or oxygen provision with progressive pulse oximetry introduction across facility levels at a consistent usage rate of 100%.

Table C.20 Outcomes and costs outputs of each scenario, under perfect health system conditions

Scenario	Deaths	CFR	DALYs	PO cost	Oxygen cost	Outpatient consultation cost	Oral antibiotics cost	IV antibiotics cost	Inpatient admission cost	Total
Scenario 0	6,274	1.51%	166,959	0	0	773,542	142,157	656,984	5,431,844	7,004,526
0.PO-a	6,267	1.51%	166,769	17,885	0	768,080	141,103	669,697	5,521,438	7,118,204
0.PO-b	6,163	1.49%	164,016	33,438	0	753,310	138,081	703,877	5,730,702	7,359,407
0.PO-c	6,314	1.52%	168,034	48,863	0	750,994	132,229	770,171	6,184,776	7,887,033
0.PO-d	6,345	1.53%	168,855	50,446	0	750,725	131,373	779,888	6,250,770	7,963,201
Scenario 1	5,591	1.35%	148,786	0	789,050	773,542	142,157	658,711	5,403,490	7,766,949
1.PO-a	5,570	1.34%	148,225	17,885	789,050	768,080	141,103	671,571	5,491,116	7,878,804
1.PO-b	5,420	1.31%	144,245	33,438	789,050	753,310	138,081	705,990	5,697,099	8,116,967
1.PO-c	5,373	1.30%	143,006	48,863	789,050	750,994	132,229	773,460	6,135,272	8,629,868
1.PO-d	5,372	1.29%	142,979	50,446	789,050	750,725	131,373	783,344	6,199,037	8,703,974
Scenario 2	4,943	1.19%	131,540	0	1,521,566	773,542	142,157	660,344	5,377,395	8,475,004
2.PO-a	4,908	1.18%	130,608	17,885	1,521,566	768,080	141,103	673,309	5,463,544	8,585,488
2.PO-b	4,700	1.13%	125,087	33,438	1,521,566	753,310	138,081	708,057	5,665,463	8,819,915
2.PO-c	4,472	1.08%	119,038	48,863	1,521,566	750,994	132,229	776,711	6,088,101	9,318,464
2.PO-d	4,446	1.07%	118,349	50,446	1,521,566	750,725	131,373	786,767	6,149,525	9,390,402

CFR: Case Fatality Rate | DALYs: Disability Adjusted Life Years | PO: Pulse Oximetry | IV: Intravenous
Scenario 0 is a null scenario, where children have no access to oxygen or pulse oximetry;
Scenario 1 models 40% oxygen service availability;
Scenario 2 models 80% oxygen service availability;
PO refers to pulse oximetry being available at: a = central and district hospitals only; b = central, district, rural, mission and community hospitals; c= all hospitals and primary health centres; d=all levels of the health system including community health workers.

Table C.21 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis with perfect health system conditions

Scenario	**Mortality reduction**	**Deaths averted**	**DALYs averted**	**Cost difference ($)**
Scenario 0				
0.PO-a	0.1 (-0.1, 0.4)	7 (-9, 25)	202 (-240, 670)	114000 (110000, 118000)
0.PO-b	1.8 (1.1, 2.4)	111 (72, 150)	2900 (1900, 4000)	355000 (348000, 363000)
0.PO-c	-0.6 (-1.6, 0.3)	-40 (-99, 19)	-1100 (-2630, 510)	883000 (871000, 895000)
0.PO-d	-1.1 (-2.2, -0.1)	-70 (-137, -7)	-1900 (-3651, -179)	959000 (946000, 972000)
Scenario 1	10.9 (10.2, 11.7)	684 (634, 738)	18200 (16900, 19700)	763000 (748000, 776000)
1.PO-a	11.2 (10.5, 12.1)	706 (654, 761)	18800 (17400, 20200)	875000 (859000, 890000)
1.PO-b	13.6 (12.7, 14.7)	855 (794, 923)	22700 (21100, 24600)	1113000 (1096000, 1129000)
1.PO-c	14.4 (13.3, 15.5)	903 (830, 980)	24000 (22100, 26100)	1626000 (1607000, 1645000)
1.PO-d	14.4 (13.3, 15.6)	904 (827, 982)	24000 (22000, 26100)	1700000 (1680000, 1720000)
Scenario 2	21.2 (20.3, 22.2)	1332 (1265, 1402)	35500 (33600, 37300)	1470000 (1450000, 1491000)
2.PO-a	21.8 (20.8, 22.8)	1368 (1297, 1441)	36400 (34500, 38300)	1581000 (1561000, 1602000)
2.PO-b	25.1 (24.1, 26.1)	1575 (1498, 1654)	41900 (39800, 44000)	1815000 (1793000, 1838000)
2.PO-c	28.7 (27.6, 29.9)	1803 (1721, 1891)	48000 (45800, 50300)	2314000 (2291000, 2338000)
2.PO-d	29.2 (28.0, 30.4)	1830 (1746, 1920)	48700 (46400, 51100)	2386000 (2363000, 2410000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.22 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis with perfect health system conditions

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
Scenario 0				
0.PO-a	0 (0, 0)	2380 (-4734, 26261)	-1200 (-1677, -731)	-98000 (-134000, -58000)
0.PO-b	3322 (2372, 4960)	125 (89, 188)	-1500 (-2552, -460)	-120000 (-204000, -37000)
0.PO-c	0 (0, 0)	-1374 (-9518, 5038)	-12100 (-13700, -10500)	-968000 (-1094000, -841000)
0.PO-d	-18295 (-73786, -6350)	-670 (-2685, -238)	-13900 (-15700, -12200)	-1109000 (-1256000, -972000)
Scenario 1	1116 (1035, 1199)	42 (39, 45)	8700 (7400, 10100)	694000 (589000, 806000)
1.PO-a	1241 (1151, 1334)	47 (43, 50)	7800 (6500, 9300)	628000 (519000, 745000)
1.PO-b	1303 (1209, 1397)	49 (45, 52)	8800 (7300, 10600)	706000 (580000, 850000)
1.PO-c	1805 (1660, 1960)	68 (62, 74)	3700 (1700, 5700)	294000 (139000, 458000)
1.PO-d	1884 (1727, 2056)	71 (65, 77)	2800 (730, 4905)	223000 (58000, 392000)
Scenario 2	1104 (1051, 1160)	41 (40, 44)	17100 (15400, 18800)	1366000 (1230000, 1504000)
2.PO-a	1157 (1101, 1216)	43 (41, 46)	16600 (14800, 18500)	1331000 (1185000, 1478000)
2.PO-b	1153 (1101, 1211)	43 (41, 46)	19200 (17200, 21200)	1537000 (1373000, 1693000)
2.PO-c	1284 (1225, 1345)	48 (46, 51)	19000 (16800, 21300)	1522000 (1346000, 1704000)
2.PO-d	1305 (1245, 1369)	49 (47, 51)	18800 (16600, 21200)	1506000 (1325000, 1694000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

Table C.23 Change in oxygen need detected and oxygen provision with implementation of routine pulse oximetry at outpatient settings, under optimal health system conditions

Scenario	Oxygen need detected / Oxygen provided	% Increase in oxygen need detected / Oxygen provided	Oxygen provided in litres	Coverage of oxygen provision
Scenario 0	23,194	ref		
0.PO-a	25,291	9%		
0.PO-b	31,168	34%		
0.PO-c	42,519	83%		
0.PO-d	44,167	90%		
Scenario 1	10,535	ref	80064720	23.9 (23.5, 24.3)
1.PO-a	11,540	10%	88557840	26.1 (25.7, 26.5)
1.PO-b	13,301	26%	103587120	30.1 (29.7, 30.5)
1.PO-c	17,451	66%	141214680	39.5 (39.1, 40.0)
1.PO-d	18,035	71%	146532240	40.8 (40.4, 41.3)
Scenario 2	20,171	ref	153757440	45.7 (45.2, 46.1)
2.PO-a	21,916	9%	168484320	49.6 (49.2, 50.1)
2.PO-b	25,927	29%	202642560	58.7 (58.2, 59.2)
2.PO-c	34,378	70%	279965880	77.8 (77.4, 78.2)
2.PO-d	35,589	76%	291066840	80.6 (80.2, 80.9)

Description as per Table C.7

Even with perfect adherence to IMCI guidelines, the clinical algorithm may overlook up to 47% of hypoxaemic cases. Particularly, the IMCI Chart booklet guidelines used at outpatient departments in primary care facilities, including rural/community hospitals (as modelled), is less comprehensive than that at secondary care facilities, which follow the WHO Hospital pocketbook. The latter incorporates the assessment of respiratory distress symptoms in the classification of severe pneumonia.

C.2.6 Sensitivity analysis: 'Reduced incidence'

In ths sensitivity analysis, ALRI incidence rate was reduced by half, from an overall 15 to 7.5 cases per 100 child-years. This rate aligns more closely with the Global Burden of Disease estimate for Malawi in 2021, which reported an incidence rate of 7,166.1 (95% CI: 6,209.7 to 8,251.0) cases per 100,000 children [11]. In reduced number of cases, the total oxygen need in litres (L) by ALRI outputted in the simulation is 13.2% of the total national demand (184624920L / 1401065280L). Therefore, the total oxygen costs incurred in the ALRI cohort in the 'Existing PSA' system (scenario 1) was $402,149 and in the '+Planned PSA' system (scenario 2) was $775,486.

Table C.24 lists the simulation outputs of outcome and healthcare costs associated with each scenario under the imperfect 'real-world' conditions, while Table C.25 and Table C.26 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline under this sensitivity analysis for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values.

When the number of ALRI incident cases is reduced, the total amount of oxygen incurred by ALRI, and therefore costs is also reduced, as well as, outpatient/inpatient services costs. Hence, the ICERs remains comparable, but the INHB is smaller.

Table C.27 provides an insight into the unmet need of oxygen provision without routine use of pulse oximeters, and changes in oxygen need detection and/or oxygen provision with progressive pulse oximetry introduction across facility levels at a consistent usage rate of 90%, when incidence is reduced by 50%.

Table C.24 Outcomes and costs outputs of each scenario in the sensitivity analysis under suboptimal 'real-world' conditions with ALRI incidence reduced to half

Scenario	Deaths	CFR	DALYs	PO cost	Oxygen cost	Outpatient consultation cost	Oral antibiotics cost	IV antibiotics cost	Inpatient admission cost	Total
Scenario 0	4,821	2.27%	128,280	0	0	458,084	69,667	233,536	1,882,461	2,643,748
0.PO-a	4,676	2.20%	124,419	8,677	0	452,346	68,853	243,730	1,968,801	2,742,407
0.PO-b	4,412	2.07%	117,399	16,631	0	442,286	67,317	262,891	2,099,187	2,888,312
0.PO-c	4,264	2.01%	113,461	25,283	0	439,903	65,240	291,631	2,309,155	3,131,211
0.PO-d	4,246	2.00%	112,980	26,142	0	439,734	64,933	295,605	2,338,086	3,164,500
Scenario 1	4,570	2.15%	121,602	0	402,149	458,075	69,667	234,081	1,873,475	3,037,448
1.PO-a	4,389	2.06%	116,786	8,676	402,149	452,337	68,853	244,451	1,956,957	3,133,423
1.PO-b	4,093	1.92%	108,916	16,631	402,149	442,277	67,317	263,790	2,084,932	3,277,095
1.PO-c	3,837	1.80%	102,109	25,280	402,149	439,873	65,240	292,978	2,287,339	3,512,859
1.PO-d	3,806	1.79%	101,282	26,140	402,149	439,702	64,933	297,021	2,315,236	3,545,181
Scenario 2	4,299	2.02%	114,386	0	775,486	458,066	69,667	234,543	1,865,475	3,403,236
2.PO-a	4,091	1.92%	108,851	8,676	775,486	452,329	68,853	245,055	1,946,875	3,497,273
2.PO-b	3,744	1.76%	99,627	16,630	775,486	442,268	67,317	264,612	2,071,764	3,638,076
2.PO-c	3,376	1.59%	89,840	25,277	775,486	439,825	65,239	294,259	2,265,614	3,865,698
2.PO-d	3,336	1.57%	88,775	26,136	775,486	439,652	64,932	298,372	2,292,426	3,897,004

CFR: Case Fatality Rate | DALYs: Disability Adjusted Life Years | PO: Pulse Oximetry | IV: Intravenous
Scenario 0 is a null scenario, where children have no access to oxygen or pulse oximetry;
Scenario 1 models 40% oxygen service availability;
Scenario 2 models 80% oxygen service availability;
PO refers to pulse oximetry being available at: a = central and district hospitals only; b = central, district, rural, mission and community hospitals; c= all hospitals and primary health centres; d=all levels of the health system including community health workers.

Table C.25 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with ALRI incidence reduced to half

Scenario	Mortality reduction	Deaths averted	DALYs averted	Cost difference ($)
Scenario 0				
0.PO-a	3.0 (2.4, 3.6)	145 (118, 176)	3900 (3100, 4700)	99000 (95000, 103000)
0.PO-b	8.5 (7.5, 9.4)	409 (359, 454)	10900 (9600, 12100)	245000 (238000, 251000)
0.PO-c	11.5 (10.3, 12.7)	556 (490, 616)	14800 (13000, 16400)	487000 (479000, 496000)
0.PO-d	11.9 (10.6, 13.1)	574 (510, 637)	15300 (13600, 16900)	521000 (511000, 531000)
Scenario 1	5.2 (4.6, 5.8)	251 (221, 283)	6700 (5900, 7500)	394000 (382000, 406000)
1.PO-a	9.0 (8.1, 9.8)	432 (390, 474)	11500 (10400, 12600)	490000 (478000, 502000)
1.PO-b	15.1 (14.1, 16.2)	728 (673, 785)	19400 (17900, 20900)	633000 (621000, 646000)
1.PO-c	20.4 (19.1, 21.8)	983 (915, 1052)	26200 (24300, 28000)	869000 (854000, 884000)
1.PO-d	21.1 (19.8, 22.4)	1014 (944, 1082)	27000 (25100, 28800)	901000 (886000, 916000)
Scenario 2	10.8 (9.9, 11.7)	522 (475, 568)	13900 (12600, 15100)	760000 (743000, 777000)
2.PO-a	15.1 (14.1, 16.2)	730 (675, 783)	19400 (18000, 20800)	854000 (837000, 870000)
2.PO-b	22.4 (21.2, 23.6)	1077 (1010, 1144)	28700 (26900, 30500)	994000 (977000, 1011000)
2.PO-c	30.0 (28.6, 31.4)	1444 (1366, 1520)	38400 (36300, 40400)	1222000 (1202000, 1240000)
2.PO-d	30.8 (29.4, 32.2)	1484 (1403, 1565)	39500 (37300, 41600)	1253000 (1234000, 1271000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.26 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with ALRI incidence reduced to half

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
Scenario 0				
0.PO-a	686 (567, 838)	26 (21, 31)	2600 (1900, 3400)	211000 (153000, 276000)
0.PO-b	600 (537, 674)	23 (20, 25)	7800 (6600, 9000)	627000 (524000, 722000)
0.PO-c	879 (791, 992)	33 (30, 37)	8700 (7000, 10300)	697000 (557000, 824000)
0.PO-d	910 (819, 1024)	34 (31, 38)	8800 (7000, 10400)	701000 (562000, 834000)
Scenario 1	1574 (1397, 1780)	59 (52, 67)	1800 (967.0, 2580.0)	141000 (77000, 206000)
1.PO-a	1136 (1037, 1255)	43 (39, 47)	5400 (4300, 6500)	430000 (341000, 516000)
1.PO-b	871 (807, 939)	33 (30, 35)	11500 (10000, 12900)	916000 (801000, 1034000)
1.PO-c	885 (824, 947)	33 (31, 36)	15300 (13500, 17100)	1224000 (1077000, 1370000)
1.PO-d	890 (831, 953)	33 (31, 36)	15700 (13800, 17500)	1257000 (1107000, 1402000)
Scenario 2	1459 (1340, 1593)	55 (50, 60)	4400 (3200, 5600)	351000 (257000, 446000)
2.PO-a	1171 (1092, 1264)	44 (41, 48)	8800 (7300, 10100)	700000 (586000, 810000)
2.PO-b	924 (868, 982)	35 (33, 37)	16200 (14500, 18000)	1298000 (1159000, 1442000)
2.PO-c	847 (804, 892)	32 (30, 34)	23100 (21200, 25200)	1851000 (1694000, 2012000)
2.PO-d	845 (804, 891)	32 (30, 34)	23800 (21700, 25900)	1905000 (1735000, 2071000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

Table C.27 Change in oxygen need detected and oxygen provision with implementation of routine pulse oximetry at outpatient settings, under reduced incidence

Scenario	Oxygen need detected / Oxygen provided	% Increase in oxygen need detected / Oxygen provided	Oxygen provided in litres	Coverage of oxygen provision
Scenario 0	9,149	ref		
0.PO-a	11,111	21%		
0.PO-b	14,629	60%		
0.PO-c	20,491	124%		
0.PO-d	21,300	133%		
Scenario 1	4,291	ref	32485680	19.0 (18.4, 19.5)
1.PO-a	5,236	22%	40028400	23.1 (22.6, 23.7)
1.PO-b	6,340	48%	49061520	28.0 (27.5, 28.6)
1.PO-c	8,215	91%	65882880	36.3 (35.7, 36.9)
1.PO-d	8,505	98%	68524560	37.6 (37.0, 38.2)
Scenario 2	8,111	ref	61454880	35.8 (35.2, 36.5)
2.PO-a	9,713	20%	74242080	42.9 (42.3, 43.6)
2.PO-b	12,146	50%	94079520	53.7 (53.1, 54.3)
2.PO-c	15,892	96%	128181240	70.2 (69.6, 70.8)
2.PO-d	16,441	103%	133230240	72.7 (72.1, 73.3)

Description as per Table C.7

C.2.7 Sensitivity analysis: 'Reduced mortality'

Sensitivity analysis of reduced baseline odds of death by half, given the uncertainty of mortality risk in the absence of care.

Table C.28 lists the simulation outputs of health outcomes and healthcare costs associated with each scenario under 'real-world' health system conditions with a change in baseline odds of death reduced to half, while Table C.29 and Table C.30 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline under this sensitivity analysis for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values.

Table C.28 Outcomes and costs outputs of each scenario, in the sensitivity analysis under suboptimal 'real-world' conditions with with baseline odds of death reduced to half

Scenario	Deaths	CFR	DALYs	PO cost	Oxygen cost	Outpatient consultation cost	Oral antibiotics cost	IV antibiotics cost	Inpatient admission cost	Total
Scenario 0	6,117	1.47%	162,784	0	0	895,126	136,970	455,042	3,640,640	5,127,777
0.PO-a	5,979	1.44%	159,111	16,919	0	883,596	135,303	475,826	3,816,026	5,327,670
0.PO-b	5,648	1.36%	150,314	32,400	0	864,041	132,336	513,744	4,069,151	5,611,671
0.PO-c	5,476	1.32%	145,739	49,315	0	859,408	128,263	569,650	4,479,181	6,085,817
0.PO-d	5,469	1.32%	145,553	51,008	0	859,066	127,644	577,626	4,535,353	6,150,698
Scenario 1	5,795	1.40%	154,216	0	789,050	895,113	136,970	455,883	3,625,964	5,902,980
1.PO-a	5,599	1.35%	148,999	16,919	789,050	883,583	135,303	477,023	3,795,586	6,097,465
1.PO-b	5,208	1.26%	138,606	32,399	789,050	864,028	132,336	515,290	4,043,916	6,377,019
1.PO-c	4,904	1.18%	130,521	49,310	789,050	859,350	128,262	571,996	4,439,574	6,837,542
1.PO-d	4,885	1.18%	130,016	51,004	789,050	859,005	127,643	580,101	4,493,683	6,900,486
Scenario 2	5,478	1.32%	145,778	0	1,521,566	895,072	136,968	456,693	3,611,092	6,621,392
2.PO-a	5,257	1.27%	139,893	16,918	1,521,566	883,542	135,301	478,096	3,776,728	6,812,152
2.PO-b	4,803	1.16%	127,821	32,396	1,521,566	863,987	132,334	516,763	4,019,504	7,086,551
2.PO-c	4,372	1.05%	116,356	49,304	1,521,566	859,244	128,258	574,323	4,399,763	7,532,457
2.PO-d	4,328	1.04%	115,187	50,997	1,521,566	858,897	127,639	582,565	4,452,011	7,593,675

CFR: Case Fatality Rate | DALYs: Disability Adjusted Life Years | PO: Pulse Oximetry | IV: Intravenous
Scenario 0 is a null scenario, where children have no access to oxygen or pulse oximetry;
Scenario 1 models 40% oxygen service availability;
Scenario 2 models 80% oxygen service availability;
PO refers to pulse oximetry being available at: a = central and district hospitals only; b = central, district, rural, mission and community hospitals; c= all hospitals and primary health centres; d=all levels of the health system including community health workers.

Table C.29 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with with baseline odds of death reduced to half

Scenario	Mortality reduction	Deaths averted	DALYs averted	Cost difference ($)
Scenario 0				
0.PO-a	2.3 (1.8, 2.7)	138 (112, 166)	3700 (3000, 4400)	200000 (194000, 206000)
0.PO-b	7.7 (6.8, 8.5)	469 (417, 524)	12500 (11100, 13900)	484000 (475000, 493000)
0.PO-c	10.5 (9.3, 11.5)	643 (566, 710)	17100 (15100, 18900)	958000 (945000, 971000)
0.PO-d	10.6 (9.3, 11.7)	650 (572, 720)	17300 (15200, 19100)	1023000 (1010000, 1036000)
Scenario 1	5.3 (4.7, 5.9)	322 (288, 357)	8600 (7700, 9500)	775000 (759000, 792000)
1.PO-a	8.5 (7.8, 9.2)	518 (473, 564)	13800 (12600, 15000)	970000 (951000, 987000)
1.PO-b	14.9 (13.9, 15.9)	909 (848, 978)	24200 (22500, 26000)	1250000 (1231000, 1268000)
1.PO-c	19.9 (18.7, 21.1)	1215 (1138, 1293)	32300 (30300, 34400)	1710000 (1690000, 1732000)
1.PO-d	20.2 (19.0, 21.4)	1233 (1156, 1312)	32800 (30800, 34900)	1773000 (1753000, 1795000)
Scenario 2	10.5 (9.7, 11.3)	640 (592, 690)	17000 (15700, 18400)	1494000 (1470000, 1516000)
2.PO-a	14.1 (13.2, 15.0)	859 (802, 920)	22900 (21300, 24500)	1685000 (1662000, 1708000)
2.PO-b	21.5 (20.4, 22.7)	1314 (1240, 1392)	35000 (33000, 37000)	1959000 (1935000, 1984000)
2.PO-c	28.5 (27.3, 29.8)	1746 (1660, 1832)	46500 (44200, 48800)	2405000 (2380000, 2431000)
2.PO-d	29.3 (28.0, 30.6)	1790 (1699, 1877)	47600 (45200, 49900)	2466000 (2440000, 2492000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.30 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with with baseline odds of death reduced to half

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
0.PO-a	1467 (1201, 1801)	55 (45, 68)	1200 (464, 1924)	94000 (37000, 154000)
0.PO-b	1034 (925, 1160)	39 (35, 44)	6400 (5100, 7900)	514000 (404000, 631000)
0.PO-c	1494 (1344, 1688)	56 (51, 63)	5100 (3100, 7000)	410000 (248000, 559000)
0.PO-d	1580 (1417, 1796)	59 (53, 68)	4500 (2400, 6400)	359000 (190000, 513000)
Scenario 1	2412 (2176, 2679)	91 (82, 101)	-1100 (-2000, -212)	-89000 (-160000, -17000)
1.PO-a	1878 (1721, 2052)	71 (65, 77)	1700 (458, 2878)	132000 (37000, 230000)
1.PO-b	1376 (1280, 1474)	52 (48, 55)	8600 (7000, 10300)	686000 (556000, 828000)
1.PO-c	1409 (1324, 1504)	53 (50, 57)	10900 (8900, 13000)	874000 (712000, 1040000)
1.PO-d	1439 (1350, 1535)	54 (51, 58)	10600 (8600, 12700)	851000 (687000, 1019000)
Scenario 2	2339 (2170, 2526)	88 (82, 95)	-1700 (-2932, -356)	-132000 (-235000, -29000)
2.PO-a	1962 (1835, 2096)	74 (69, 79)	1800 (339, 3385)	145000 (27000, 271000)
2.PO-b	1492 (1407, 1577)	56 (53, 59)	10500 (8600, 12500)	838000 (685000, 1001000)
2.PO-c	1378 (1312, 1449)	52 (49, 54)	16400 (14100, 18600)	1311000 (1131000, 1492000)
2.PO-d	1379 (1313, 1450)	52 (49, 54)	16800 (14400, 19100)	1343000 (1152000, 1531000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

C.2.8 Sensitivity analysis: 'Reduced oxygen effect'

Sensitivity analysis of reduced effect of oxygen on treatment success, using the upper bounds of the 95% confidence interval from the source [72] of the parameter $[or\_mortality\_improved\_oxygen\_systems] = 0.52$. Reduced to OR=0.70, the inverse is applied to the parenteral treatment failure.

Table C.31 lists the simulation outputs of health outcomes and healthcare costs associated with each scenario under suboptimal 'real-world' conditions with a change in the effect of oxygen in reducing mortality to an OR=0.70, while Table C.32 and Table C.33 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline under this sensitivity analysis for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values.

Table C.31 Outcomes and costs outputs of each scenario in the sensitivity analysis under suboptimal 'real-world' conditions with reduced effect of oxygen on treatment success

Scenario	Deaths	CFR	DALYs	PO cost	Oxygen cost	Outpatient consultation cost	Oral antibiotics cost	IV antibiotics cost	Inpatient admission cost	Total
Scenario 0	8,934	2.15%	237,714	0	0	895,126	136,970	456,006	3,623,754	5,111,856
0.PO-a	8,635	2.08%	229,755	16,919	0	883,596	135,303	477,141	3,793,709	5,306,668
0.PO-b	8,009	1.93%	213,108	32,400	0	864,041	132,336	515,540	4,040,344	5,584,660
0.PO-c	7,618	1.84%	202,700	49,315	0	859,408	128,263	572,115	4,440,691	6,049,791
0.PO-d	7,589	1.83%	201,927	51,008	0	859,066	127,644	580,194	4,495,461	6,113,373
Scenario 1	8,671	2.09%	230,721	0	789,050	895,113	136,970	456,503	3,615,221	5,892,857
1.PO-a	8,342	2.01%	221,962	16,919	789,050	883,583	135,303	477,810	3,782,223	6,084,888
1.PO-b	7,674	1.85%	204,197	32,399	789,050	864,028	132,336	516,380	4,026,349	6,360,543
1.PO-c	7,146	1.72%	190,152	49,310	789,050	859,350	128,262	573,503	4,416,094	6,815,569
1.PO-d	7,101	1.71%	188,954	51,004	789,050	859,005	127,643	581,664	4,469,492	6,877,857
Scenario 2	8,383	2.02%	223,054	0	1,521,566	895,072	136,968	456,990	3,605,576	6,616,173
2.PO-a	8,033	1.94%	213,736	16,918	1,521,566	883,542	135,301	478,431	3,770,514	6,806,273
2.PO-b	7,336	1.77%	195,200	32,396	1,521,566	863,987	132,334	517,211	4,011,733	7,079,228
2.PO-c	6,662	1.61%	177,275	49,304	1,521,566	859,244	128,258	574,915	4,390,022	7,523,309
2.PO-d	6,597	1.59%	175,546	50,997	1,521,566	858,897	127,639	583,176	4,442,044	7,584,319

CFR: Case Fatality Rate | DALYs: Disability Adjusted Life Years | PO: Pulse Oximetry | IV: Intravenous
Scenario 0 is a null scenario, where children have no access to oxygen or pulse oximetry;
Scenario 1 models 40% oxygen service availability;
Scenario 2 models 80% oxygen service availability;
PO refers to pulse oximetry being available at: a = central and district hospitals only; b = central, district, rural, mission and community hospitals; c= all hospitals and primary health centres; d=all levels of the health system including community health workers.

Table C.32 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with reduced effect of oxygen on treatment success

Scenario	Mortality reduction	Deaths averted	DALYs averted	Cost difference ($)
Scenario				
0.PO-a	3.3 (3.0, 3.8)	299 (263, 337)	8000 (7000, 9000)	195000 (189000, 201000)
0.PO-b	10.4 (9.6, 11.1)	925 (859, 993)	24600 (22800, 26400)	473000 (464000, 482000)
0.PO-c	14.7 (13.8, 15.6)	1317 (1226, 1403)	35000 (32600, 37300)	938000 (926000, 950000)
0.PO-d	15.1 (14.1, 16.0)	1346 (1254, 1440)	35800 (33400, 38300)	1002000 (989000, 1014000)
Scenario 1	2.9 (2.6, 3.3)	263 (233, 294)	7000 (6200, 7800)	781000 (765000, 798000)
1.PO-a	6.6 (6.1, 7.2)	592 (543, 645)	15700 (14400, 17200)	973000 (954000, 990000)
1.PO-b	14.1 (13.3, 14.9)	1260 (1185, 1338)	33500 (31500, 35600)	1249000 (1230000, 1268000)
1.PO-c	20.0 (19.1, 20.9)	1789 (1692, 1884)	47600 (45000, 50100)	1704000 (1684000, 1726000)
1.PO-d	20.5 (19.5, 21.4)	1833 (1735, 1929)	48800 (46100, 51300)	1766000 (1746000, 1788000)
Scenario 2	6.2 (5.7, 6.7)	551 (508, 600)	14700 (13500, 16000)	1504000 (1481000, 1527000)
2.PO-a	10.1 (9.5, 10.8)	900 (843, 962)	24000 (22400, 25600)	1695000 (1672000, 1719000)
2.PO-b	17.9 (17.1, 18.8)	1598 (1516, 1685)	42500 (40300, 44800)	1968000 (1944000, 1992000)
2.PO-c	25.4 (24.4, 26.4)	2272 (2169, 2375)	60400 (57700, 63200)	2411000 (2387000, 2438000)
2.PO-d	26.2 (25.2, 27.2)	2336 (2232, 2442)	62100 (59400, 65000)	2472000 (2447000, 2498000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.33 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with reduced effect of oxygen on treatment success

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
0.PO-a	655 (577, 740)	25 (22, 28)	5500 (4600, 6500)	441000 (367000, 523000)
0.PO-b	512 (475, 551)	19 (18, 21)	18700 (16900, 20500)	1496000 (1355000, 1639000)
0.PO-c	713 (667, 765)	27 (25, 29)	23300 (20900, 25600)	1866000 (1671000, 2050000)
0.PO-d	745 (696, 799)	28 (26, 30)	23300 (20900, 25800)	1864000 (1672000, 2065000)
Scenario 1	2979 (2650, 3329)	112 (100, 125)	-2800 (-3500, -1900)	-221000 (-281000, -155000)
1.PO-a	1648 (1520, 1786)	62 (57, 67)	3600 (2300, 4900)	286000 (186000, 392000)
1.PO-b	992 (936, 1054)	37 (35, 40)	17900 (15900, 19900)	1433000 (1275000, 1590000)
1.PO-c	953 (904, 1006)	36 (34, 38)	26300 (23800, 28800)	2103000 (1901000, 2306000)
1.PO-d	964 (916, 1018)	36 (34, 38)	26700 (24100, 29200)	2135000 (1930000, 2340000)
Scenario 2	2735 (2515, 2957)	103 (95, 111)	-4100 (-5300, -2900)	-332000 (-421000, -232000)
2.PO-a	1885 (1768, 2011)	71 (66, 76)	2800 (1200, 4300)	222000 (99000, 345000)
2.PO-b	1232 (1166, 1296)	46 (44, 49)	17900 (15800, 20200)	1433000 (1263000, 1618000)
2.PO-c	1062 (1016, 1112)	40 (38, 42)	30300 (27500, 33000)	2423000 (2203000, 2643000)
2.PO-d	1059 (1013, 1106)	40 (38, 42)	31200 (28500, 34100)	2500000 (2281000, 2726000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

C.2.9 Sensitivity analysis: 'Planned PSA - 70% availability'

By reducing the expected oxygen service availability of the 'Planned PSA' scenario from 80% to 70%, this reflects a saturation curve relationship between increased oxygen production capacity and service coverage. For an overall 70% oxygen availability, by facility level it covers 82.1% of Central and District hospitals oxygen demand, 63.0% of Mission, Community and Rural hospitals' oxygen demand, and 60.9% of health centres' oxygen demand.

Table C.34 lists the simulation outputs of health outcomes and healthcare costs associated with each scenario under 'real-world' health system conditions with a reduction in oxygen service availability to 70% in the '+Planned PSA' system, while Table C.35 and Table C.36 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline under this sensitivity analysis for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values. Table C.37 provides an insight into the unmet need of oxygen provision without routine use of pulse oximeters, and changes in oxygen need detection and/or oxygen provision with progressive pulse oximetry introduction across facility levels at a consistent usage rate of 90%, whereby '+Planned PSA' oxyegn system can reach 70% service availability. The estimates in no oxygen system scenarios and 'Existing PSA' system scenarios remain unchanged.

Table C.34 Outcomes and costs outputs of each scenario in the sensitivity analysis under suboptimal 'real-world' conditions with Planned PSA (scenario 2) reaching 70% service availability

Scenario	Deaths	CFR	DALYs	PO cost	Oxygen cost	Outpatient consultation cost	Oral antibiotics cost	IV antibiotics cost	Inpatient admission cost	Total
Scenario 0	9,485	2.29%	252,392	0	0	895,126	136,970	455,042	3,640,640	5,127,777
0.PO-a	9,255	2.23%	246,270	16,919	0	883,596	135,303	475,826	3,816,026	5,327,670
0.PO-b	8,754	2.11%	232,951	32,400	0	864,041	132,336	513,744	4,069,151	5,611,671
0.PO-c	8,509	2.05%	226,429	49,315	0	859,408	128,263	569,650	4,479,181	6,085,817
0.PO-d	8,498	2.05%	226,135	51,008	0	859,066	127,644	577,626	4,535,353	6,150,698
Scenario 1	9,005	2.17%	239,623	0	789,050	895,113	136,970	455,883	3,625,964	5,902,980
1.PO-a	8,704	2.10%	231,612	16,919	789,050	883,583	135,303	477,023	3,795,586	6,097,465
1.PO-b	8,119	1.96%	216,060	32,399	789,050	864,028	132,336	515,290	4,043,916	6,377,019
1.PO-c	7,678	1.85%	204,329	49,310	789,050	859,350	128,262	571,996	4,439,574	6,837,542
1.PO-d	7,647	1.84%	203,502	51,004	789,050	859,005	127,643	580,101	4,493,683	6,900,486
Scenario 2	8,646	2.08%	230,064	0	1,521,566	895,087	136,968	456,508	3,614,926	6,625,057
2.PO-a	8,314	2.00%	221,227	16,918	1,521,566	883,557	135,301	477,866	3,781,214	6,816,423
2.PO-b	7,682	1.85%	204,426	32,397	1,521,566	864,002	132,334	516,425	4,025,574	7,092,300
2.PO-c	7,087	1.71%	188,602	49,307	1,521,566	859,285	128,259	573,771	4,410,360	7,542,547
2.PO-d	7,031	1.69%	187,112	51,000	1,521,566	858,940	127,640	581,979	4,463,058	7,604,183

CFR: Case Fatality Rate | DALYs: Disability Adjusted Life Years | PO: Pulse Oximetry | IV: Intravenous
Scenario 0 is a null scenario, where children have no access to oxygen or pulse oximetry;
Scenario 1 models 40% oxygen service availability;
Scenario 2 models 70% oxygen service availability;
PO refers to pulse oximetry being available at: a = central and district hospitals only; b = central, district, rural, mission and community hospitals; c= all hospitals and primary health centres; d=all levels of the health system including community health workers.

Table C.35 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with Planned PSA (scenario 2) reaching 70% service availability

Scenario	Mortality reduction (%)	Deaths averted	DALYs averted	Incremental cost
Scenario 0				
0.PO-a	2.4 (2.1, 2.8)	230 (197, 264)	6100 (5200, 7000)	200000 (194000, 206000)
0.PO-b	7.7 (7.0, 8.4)	732 (664, 795)	19500 (17600, 21100)	484000 (475000, 493000)
0.PO-c	10.3 (9.3, 11.2)	978 (879, 1066)	26000 (23400, 28300)	958000 (945000, 971000)
0.PO-d	10.4 (9.4, 11.3)	989 (886, 1080)	26300 (23600, 28700)	1023000 (1010000, 1036000)
Scenario 1	5.1 (4.6, 5.5)	481 (441, 523)	12800 (11700, 13900)	775000 (759000, 792000)
1.PO-a	8.2 (7.7, 8.8)	781 (725, 840)	20800 (19300, 22400)	970000 (951000, 987000)
1.PO-b	14.4 (13.6, 15.2)	1367 (1287, 1448)	36400 (34200, 38500)	1250000 (1231000, 1268000)
1.PO-c	19.1 (18.2, 20.0)	1809 (1711, 1908)	48100 (45500, 50700)	1710000 (1690000, 1732000)
1.PO-d	19.4 (18.4, 20.3)	1839 (1736, 1941)	48900 (46200, 51600)	1773000 (1753000, 1795000)
Scenario 2	8.9 (8.3, 9.4)	839 (784, 899)	22300 (20900, 23900)	1497000 (1473000, 1522000)
2.PO-a	12.3 (11.7, 13.1)	1171 (1106, 1242)	31200 (29400, 33000)	1689000 (1664000, 1714000)
2.PO-b	19.0 (18.2, 19.9)	1803 (1713, 1896)	48000 (45600, 50400)	1965000 (1940000, 1990000)
2.PO-c	25.3 (24.3, 26.3)	2398 (2290, 2507)	63800 (60900, 66700)	2415000 (2389000, 2443000)
2.PO-d	25.9 (24.9, 26.9)	2454 (2339, 2568)	65300 (62200, 68300)	2476000 (2451000, 2504000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.36 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with Planned PSA (scenario 2) reaching 70% service availability

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
Scenario 0				
0.PO-a	874 (747, 1019)	33 (28, 38)	3600 (2700, 4600)	290000 (219000, 367000)
0.PO-b	663 (606, 730)	25 (23, 27)	13400 (11600, 15100)	1073000 (930000, 1208000)
0.PO-c	982 (899, 1089)	37 (34, 41)	14000 (11400, 16400)	1124000 (915000, 1313000)
0.PO-d	1037 (950, 1154)	39 (36, 43)	13500 (10800, 15900)	1082000 (861000, 1272000)
Scenario 1	1616 (1485, 1759)	61 (56, 66)	3100 (2000, 4200)	248000 (162000, 336000)
1.PO-a	1243 (1160, 1335)	47 (44, 50)	8700 (7200, 10200)	693000 (577000, 813000)
1.PO-b	915 (864, 969)	34 (32, 36)	20700 (18700, 22800)	1659000 (1493000, 1827000)
1.PO-c	946 (896, 995)	36 (34, 37)	26700 (24200, 29400)	2139000 (1940000, 2348000)
1.PO-d	965 (914, 1019)	36 (34, 38)	26800 (24100, 29400)	2141000 (1931000, 2355000)
Scenario 2	1786 (1670, 1903)	67 (63, 72)	3600 (2200, 5200)	290000 (178000, 414000)
2.PO-a	1444 (1365, 1529)	54 (51, 57)	10000 (8300, 11900)	803000 (667000, 951000)
2.PO-b	1090 (1039, 1145)	41 (39, 43)	23400 (21000, 25800)	1873000 (1680000, 2065000)
2.PO-c	1007 (964, 1054)	38 (36, 40)	33600 (30800, 36500)	2689000 (2463000, 2919000)
2.PO-d	1010 (967, 1056)	38 (36, 40)	34300 (31400, 37200)	2746000 (2512000, 2979000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

Table C.37 Change in oxygen need detected and oxygen provision with implementation of routine pulse oximetry at outpatient settings, with '+Planned PSA' oxygen system reaching 70% service availability

Scenario	Oxygen need detected / Oxygen provided	% Increase in oxygen need detected / Oxygen provided	Oxygen provided in litres	Coverage of oxygen provision
Scenario 0	17,515	ref		
0.PO-a	21,502	23%		
0.PO-b	28,365	62%		
0.PO-c	39,947	128%		
0.PO-d	41,556	137%		
Scenario 1	8,024	ref	61234920	18.2 (17.8, 18.5)
1.PO-a	9,879	23%	76082760	22.4 (22.0, 22.7)
1.PO-b	11,978	49%	93410280	27.1 (26.7, 27.5)
1.PO-c	15,709	96%	126973800	35.6 (35.1, 36.0)
1.PO-d	16,219	102%	131627160	36.7 (36.3, 37.2)
Scenario 2	13,687	ref	104605920	31.0 (30.6, 31.4)
2.PO-a	16,633	22%	128275200	37.7 (37.2, 38.1)
2.PO-b	20,512	50%	160256160	46.4 (46.0, 46.9)
2.PO-c	27,097	98%	219868920	61.3 (60.9, 61.8)
2.PO-d	28,034	105%	228387600	63.5 (63.0, 63.9)

Description as per Table C.7

C.2.10 Sensitivity analysis: 'Remove natural mortality scaling factor'

Parameter values for mortality rates and associated risk factors were derived from published studies using observed mortality data from healthcare settings. However, modelling the natural history of disease presented challenges due to the limited data on untreated ALRI mortality. Therefore, we incorporated a theoretical assumption regarding the natural risk of death, applying higher rates for complicated ALRI and bacterial causes. The values were estimated based on the simulation outputted number of deaths and treatment failures across different disease and treatment categories (detailed in appendix A.2.6). This sensitivity analysis examines intervention effects under the highly unlikely alternative assumption where baseline mortality risks remain equivalent between cases with and without antibiotic treatment across disease severity.

In the unlikely scenario where we may have overestimated natural mortality by 3.55-fold, we conducted a sensitivity analysis by setting parameters [scaling_factor_base_odds_death_uncomplicated_ALRI_if_bacterial_cause], [scaling_factor_base_odds_death_if_complicated_ALRI_viral_cause], and [scaling_factor_death_complicated_ALRI_if_bacterial_cause] to 0. Even under this extreme assumption, the full-implementation strategy returned an ICER=75$/DALY, remaining below Malawi's cost-effectiveness threshold.

Table C.38 Outcomes and costs outputs of each scenario in the sensitivity analysis under suboptimal 'real-world' conditions without the scaling factor of increased natural (untreated) mortality for ALRI with complications and/or bacterial causes

Scenario	Deaths	CFR	DALYs	PO cost	Oxygen cost	Outpatient consultation cost	Oral antibiotics cost	IV antibiotics cost	Inpatient admission cost	Total
Scenario 0	4,663	1.12%	124,112	0	0	895,126	136,970	455,042	3,640,640	5,127,777
0.PO-a	4,580	1.10%	121,904	16,919	0	883,596	135,303	475,826	3,816,026	5,327,670
0.PO-b	4,339	1.05%	115,497	32,400	0	864,041	132,336	513,744	4,069,151	5,611,671
0.PO-c	4,243	1.02%	112,944	49,315	0	859,408	128,263	569,650	4,479,181	6,085,817
0.PO-d	4,234	1.02%	112,706	51,008	0	859,066	127,644	577,626	4,535,353	6,150,698
Scenario 1	4,430	1.07%	117,912	0	789,050	895,113	136,970	455,883	3,625,964	5,902,980
1.PO-a	4,305	1.04%	114,584	16,919	789,050	883,583	135,303	477,023	3,795,586	6,097,465
1.PO-b	4,018	0.97%	106,953	32,399	789,050	864,028	132,336	515,290	4,043,916	6,377,019
1.PO-c	3,828	0.92%	101,899	49,310	789,050	859,350	128,262	571,996	4,439,574	6,837,542
1.PO-d	3,808	0.92%	101,368	51,004	789,050	859,005	127,643	580,101	4,493,683	6,900,486
Scenario 2	4,215	1.02%	112,187	0	1,521,566	895,072	136,968	456,693	3,611,092	6,621,392
2.PO-a	4,070	0.98%	108,325	16,918	1,521,566	883,542	135,301	478,096	3,776,728	6,812,152
2.PO-b	3,735	0.90%	99,413	32,396	1,521,566	863,987	132,334	516,763	4,019,504	7,086,551
2.PO-c	3,457	0.83%	92,016	49,304	1,521,566	859,244	128,258	574,323	4,399,763	7,532,457
2.PO-d	3,421	0.82%	91,060	50,997	1,521,566	858,897	127,639	582,565	4,452,011	7,593,675

CFR: Case Fatality Rate | DALYs: Disability Adjusted Life Years | PO: Pulse Oximetry | IV: Intravenous
Scenario 0 is a null scenario, where children have no access to oxygen or pulse oximetry;
Scenario 1 models 40% oxygen service availability;
Scenario 2 models 80% oxygen service availability;
PO refers to pulse oximetry being available at: a = central and district hospitals only; b = central, district, rural, mission and community hospitals; c= all hospitals and primary health centres; d=all levels of the health system including community health workers.

Table C.39 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions without the scaling factor of increased natural (untreated) mortality for ALRI with complications and/or bacterial causes

Scenario	Mortality reduction (%)	Deaths averted	DALYs averted	Incremental cost
Scenario 0				
0.PO-a	1.8 (1.3, 2.3)	83 (62, 105)	2200 (1600, 2800)	200000 (194000, 206000)
0.PO-b	6.9 (6.1, 7.8)	324 (282, 368)	8600 (7500, 9800)	484000 (475000, 493000)
0.PO-c	9.0 (7.8, 10.2)	421 (361, 483)	11200 (9600, 12900)	958000 (945000, 971000)
0.PO-d	9.2 (7.9, 10.4)	430 (367, 491)	11400 (9800, 13100)	1023000 (1010000, 1036000)
Scenario 1	5.0 (4.4, 5.6)	233 (205, 265)	6200 (5500, 7000)	775000 (759000, 792000)
1.PO-a	7.7 (6.9, 8.5)	357 (319, 396)	9500 (8500, 10500)	970000 (951000, 987000)
1.PO-b	13.8 (12.8, 15.0)	645 (592, 702)	17200 (15700, 18700)	1250000 (1231000, 1268000)
1.PO-c	17.9 (16.7, 19.2)	836 (768, 902)	22200 (20400, 24000)	1710000 (1690000, 1732000)
1.PO-d	18.3 (17.0, 19.7)	855 (786, 925)	22800 (20900, 24600)	1773000 (1753000, 1795000)
Scenario 2	9.6 (8.8, 10.5)	448 (407, 490)	11900 (10800, 13000)	1494000 (1470000, 1516000)
2.PO-a	12.7 (11.8, 13.7)	592 (543, 641)	15800 (14500, 17100)	1685000 (1662000, 1708000)
2.PO-b	19.9 (18.7, 21.1)	928 (867, 990)	24700 (23100, 26300)	1959000 (1935000, 1984000)
2.PO-c	25.9 (24.5, 27.2)	1206 (1134, 1279)	32100 (30200, 34000)	2405000 (2380000, 2431000)
2.PO-d	26.6 (25.2, 28.0)	1242 (1166, 1313)	33000 (31000, 34900)	2466000 (2440000, 2492000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.40 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions without the scaling factor of increased natural (untreated) mortality for ALRI with complications and/or bacterial causes

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
Scenario 0				
0.PO-a	2466 (1906, 3234)	93 (72, 122)	-300 (-870, 289)	-24000 (-70000, 23000)
0.PO-b	1501 (1310, 1712)	56 (49, 64)	2600 (1500, 3800)	205000 (118000, 301000)
0.PO-c	2289 (1980, 2655)	86 (74, 100)	-788 (-2405, 879)	-63000 (-192000, 70000)
0.PO-d	2394 (2075, 2794)	90 (78, 105)	-1400 (-3053, 317)	-109000 (-244000, 25000)
Scenario 1	3337 (2943, 3782)	125 (111, 142)	-3500 (-4200, -2700)	-279000 (-339000, -216000)
1.PO-a	2721 (2448, 3021)	102 (92, 113)	-2600 (-3600, -1600)	-209000 (-285000, -126000)
1.PO-b	1941 (1784, 2112)	73 (67, 79)	1500 (118, 3019)	123000 (9457, 241553)
1.PO-c	2050 (1893, 2222)	77 (71, 84)	853 (-912, 2651)	68000 (-73000, 212000)
1.PO-d	2076 (1916, 2257)	78 (72, 85)	592 (-1200, 2500)	47000 (-100000, 197000)
Scenario 2	3340 (3053, 3670)	125 (115, 138)	-6700 (-7800, -5700)	-540000 (-628000, -453000)
2.PO-a	2849 (2629, 3092)	107 (99, 116)	-5300 (-6500, -4000)	-423000 (-523000, -321000)
2.PO-b	2114 (1978, 2257)	79 (74, 85)	198 (-1400, 1900)	16000 (-111000, 150000)
2.PO-c	1996 (1881, 2123)	75 (71, 80)	2000 (101, 3971)	163000 (8094, 317713)
2.PO-d	1988 (1878, 2114)	75 (71, 79)	2200 (222, 4100)	178000 (18000, 328000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

C.2.11 Sensitivity analysis: 'ALRI oxygen consumption - 50% '

In this sensitivity analysis, we assumed ALRI oxygen consumption takes up 50% of the oxygen system service availability, equivalent to half of the total oxygen system cost. Therefore, the total oxygen costs incurred in the cohort in the 'Existing PSA' system (scenario 1) was $1,525,897 and in the '+Planned PSA' system (scenario 2) was $2,942,468. The health outcomes and other healthcare costs remain the same as per the main analysis results Table C.4.

Table C.41 and Table C.42 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline under this sensitivity analysis for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values.

Table C.41 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with ALRI oxygen consumption taking up 50% of the systems' cost

Scenario	Mortality reduction (%)	Deaths averted	DALYs averted	Incremental cost
Scenario 0				
0.PO-a	2.4 (2.1, 2.8)	230 (197, 264)	6100 (5200, 7000)	200000 (194000, 206000)
0.PO-b	7.7 (7.0, 8.4)	732 (664, 795)	19500 (17600, 21100)	484000 (475000, 493000)
0.PO-c	10.3 (9.3, 11.2)	978 (879, 1066)	26000 (23400, 28300)	958000 (945000, 971000)
0.PO-d	10.4 (9.4, 11.3)	989 (886, 1080)	26300 (23600, 28700)	1023000 (1010000, 1036000)
Scenario 1	5.1 (4.6, 5.5)	481 (441, 523)	12800 (11700, 13900)	1512000 (1480000, 1545000)
1.PO-a	8.2 (7.7, 8.8)	781 (725, 840)	20800 (19300, 22400)	1707000 (1674000, 1738000)
1.PO-b	14.4 (13.6, 15.2)	1367 (1287, 1448)	36400 (34200, 38500)	1987000 (1955000, 2016000)
1.PO-c	19.1 (18.2, 20.0)	1809 (1711, 1908)	48100 (45500, 50700)	2447000 (2418000, 2478000)
1.PO-d	19.4 (18.4, 20.3)	1839 (1736, 1941)	48900 (46200, 51600)	2510000 (2480000, 2541000)
Scenario 2	10.0 (9.4, 10.7)	953 (893, 1017)	25400 (23800, 27100)	2915000 (2869000, 2958000)
2.PO-a	13.6 (13.0, 14.4)	1294 (1225, 1368)	34400 (32600, 36400)	3106000 (3063000, 3149000)
2.PO-b	20.7 (19.8, 21.6)	1962 (1870, 2059)	52200 (49700, 54800)	3380000 (3339000, 3421000)
2.PO-c	27.5 (26.5, 28.5)	2607 (2501, 2717)	69300 (66500, 72300)	3825000 (3787000, 3867000)
2.PO-d	28.1 (27.1, 29.2)	2669 (2561, 2781)	71000 (68100, 74000)	3887000 (3848000, 3926000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.42 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with ALRI oxygen consumption taking up 50% of the systems' cost

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
Scenario 0				
0.PO-a	874 (747, 1019)	33 (28, 38)	3600 (2700, 4600)	290000 (219000, 367000)
0.PO-b	663 (606, 730)	25 (23, 27)	13400 (11600, 15100)	1073000 (930000, 1208000)
0.PO-c	982 (899, 1089)	37 (34, 41)	14000 (11400, 16400)	1124000 (915000, 1313000)
0.PO-d	1037 (950, 1154)	39 (36, 43)	13500 (10800, 15900)	1082000 (861000, 1272000)
Scenario 1	3152 (2897, 3431)	118 (109, 129)	-6100 (-7200, -5000)	-489000 (-576000, -397000)
1.PO-a	2188 (2045, 2348)	82 (77, 88)	-554 (-2000, 880)	-44000 (-160000, 70000)
1.PO-b	1455 (1374, 1540)	55 (52, 58)	11500 (9500, 13600)	922000 (758000, 1090000)
1.PO-c	1354 (1283, 1426)	51 (48, 54)	17500 (15000, 20100)	1402000 (1202000, 1609000)
1.PO-d	1366 (1295, 1443)	51 (49, 54)	17500 (14900, 20200)	1404000 (1196000, 1618000)
Scenario 2	3062 (2875, 3262)	115 (108, 123)	-11100 (-12700, -9400)	-886000 (-1014000, -754000)
2.PO-a	2402 (2274, 2532)	90 (85, 95)	-4400 (-6200, -2500)	-351000 (-500000, -196000)
2.PO-b	1724 (1643, 1804)	65 (62, 68)	9900 (7500, 12500)	795000 (603000, 997000)
2.PO-c	1468 (1409, 1530)	55 (53, 58)	21500 (18700, 24400)	1722000 (1497000, 1952000)
2.PO-d	1457 (1399, 1518)	55 (53, 57)	22400 (19600, 25300)	1795000 (1566000, 2023000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

C.2.12 Sensitivity analysis: 'PO unit cost doubled'

In this sensitivity analysis we doubled the unit cost pulse oximeter usage. The health outcomes and other healthcare costs remain the same as per the main analysis results Table C.4.

Table C.43 and Table C.44 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline under this sensitivity analysis for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values.

Table C.43 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with the unit cost of pulse oximetry usage doubled

Scenario	Mortality reduction (%)	Deaths averted	DALYs averted	Incremental cost
Scenario 0				
0.PO-a	2.4 (2.1, 2.8)	230 (197, 264)	6100 (5200, 7000)	217000 (211000, 223000)
0.PO-b	7.7 (7.0, 8.4)	732 (664, 795)	19500 (17600, 21100)	516000 (508000, 525000)
0.PO-c	10.3 (9.3, 11.2)	978 (879, 1066)	26000 (23400, 28300)	1007000 (995000, 1020000)
0.PO-d	10.4 (9.4, 11.3)	989 (886, 1080)	26300 (23600, 28700)	1074000 (1061000, 1087000)
Scenario 1	5.1 (4.6, 5.5)	481 (441, 523)	12800 (11700, 13900)	775000 (759000, 792000)
1.PO-a	8.2 (7.7, 8.8)	781 (725, 840)	20800 (19300, 22400)	987000 (968000, 1004000)
1.PO-b	14.4 (13.6, 15.2)	1367 (1287, 1448)	36400 (34200, 38500)	1282000 (1263000, 1301000)
1.PO-c	19.1 (18.2, 20.0)	1809 (1711, 1908)	48100 (45500, 50700)	1759000 (1739000, 1781000)
1.PO-d	19.4 (18.4, 20.3)	1839 (1736, 1941)	48900 (46200, 51600)	1824000 (1804000, 1846000)
Scenario 2	10.0 (9.4, 10.7)	953 (893, 1017)	25400 (23800, 27100)	1494000 (1470000, 1516000)
2.PO-a	13.6 (13.0, 14.4)	1294 (1225, 1368)	34400 (32600, 36400)	1701000 (1679000, 1725000)
2.PO-b	20.7 (19.8, 21.6)	1962 (1870, 2059)	52200 (49700, 54800)	1991000 (1968000, 2016000)
2.PO-c	27.5 (26.5, 28.5)	2607 (2501, 2717)	69300 (66500, 72300)	2454000 (2429000, 2481000)
2.PO-d	28.1 (27.1, 29.2)	2669 (2561, 2781)	71000 (68100, 74000)	2517000 (2491000, 2543000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.44 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with the unit cost of pulse oximetry usage doubled

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
Scenario 0				
0.PO-a	948 (811, 1106)	36 (30, 41)	3400 (2500, 4400)	273000 (202000, 350000)
0.PO-b	707 (647, 779)	27 (24, 29)	13000 (11200, 14700)	1040000 (897000, 1175000)
0.PO-c	1032 (945, 1145)	39 (36, 43)	13400 (10800, 15800)	1074000 (866000, 1263000)
0.PO-d	1089 (997, 1212)	41 (37, 46)	12900 (10100, 15300)	1031000 (810000, 1221000)
Scenario 1	1616 (1485, 1759)	61 (56, 66)	3100 (2000, 4200)	248000 (162000, 336000)
1.PO-a	1265 (1180, 1359)	48 (44, 51)	8400 (7000, 9900)	676000 (560000, 796000)
1.PO-b	939 (887, 994)	35 (33, 37)	20300 (18300, 22400)	1627000 (1461000, 1794000)
1.PO-c	973 (921, 1024)	37 (35, 39)	26100 (23600, 28700)	2089000 (1890000, 2299000)
1.PO-d	992 (940, 1048)	37 (35, 39)	26100 (23500, 28800)	2090000 (1880000, 2304000)
Scenario 2	1569 (1474, 1672)	59 (55, 63)	6700 (5100, 8300)	535000 (409000, 665000)
2.PO-a	1316 (1246, 1388)	49 (47, 52)	13200 (11400, 15100)	1054000 (911000, 1210000)
2.PO-b	1016 (968, 1064)	38 (36, 40)	27300 (24800, 29800)	2184000 (1987000, 2387000)
2.PO-c	942 (903, 981)	35 (34, 37)	38700 (35800, 41600)	3094000 (2868000, 3328000)
2.PO-d	943 (906, 983)	35 (34, 37)	39600 (36700, 42500)	3164000 (2933000, 3398000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

C.2.13 Sensitivity analysis: 'Outpatient & Inpatient costs doubled'

In this sensitivity analysis we doubled the unit costs of outpatient consultation and inpatient bed days. The health outcomes and other healthcare costs remain the same as per the main analysis results Table C.4.

Table C.45 and Table C.46 list the mean estimate and uncertainty intervals resulting from the bootstrap iteration comparing intervention scenario to the baseline under this sensitivity analysis for the key metrics: the cost difference and health benefits, and the respective ICERs and INB values.

Table C.45 Incremental effect in deaths and DALYs averted, and incremental costs of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with the unit cost of outpatient consultation and inpatient bed days doubled

Scenario	Mortality reduction (%)	Deaths averted	DALYs averted	Incremental cost
Scenario 0				
0.PO-a	2.4 (2.1, 2.8)	230 (197, 264)	6100 (5200, 7000)	364000 (352000, 376000)
0.PO-b	7.7 (7.0, 8.4)	732 (664, 795)	19500 (17600, 21100)	882000 (866000, 898000)
0.PO-c	10.3 (9.3, 11.2)	978 (879, 1066)	26000 (23400, 28300)	1761000 (1737000, 1785000)
0.PO-d	10.4 (9.4, 11.3)	989 (886, 1080)	26300 (23600, 28700)	1882000 (1857000, 1906000)
Scenario 1	5.1 (4.6, 5.5)	481 (441, 523)	12800 (11700, 13900)	761000 (744000, 777000)
1.PO-a	8.2 (7.7, 8.8)	781 (725, 840)	20800 (19300, 22400)	1113000 (1091000, 1135000)
1.PO-b	14.4 (13.6, 15.2)	1367 (1287, 1448)	36400 (34200, 38500)	1622000 (1597000, 1647000)
1.PO-c	19.1 (18.2, 20.0)	1809 (1711, 1908)	48100 (45500, 50700)	2473000 (2443000, 2505000)
1.PO-d	19.4 (18.4, 20.3)	1839 (1736, 1941)	48900 (46200, 51600)	2590000 (2559000, 2622000)
Scenario 2	10.0 (9.4, 10.7)	953 (893, 1017)	25400 (23800, 27100)	1464000 (1441000, 1486000)
2.PO-a	13.6 (13.0, 14.4)	1294 (1225, 1368)	34400 (32600, 36400)	1809000 (1782000, 1835000)
2.PO-b	20.7 (19.8, 21.6)	1962 (1870, 2059)	52200 (49700, 54800)	2307000 (2279000, 2338000)
2.PO-c	27.5 (26.5, 28.5)	2607 (2501, 2717)	69300 (66500, 72300)	3128000 (3093000, 3165000)
2.PO-d	28.1 (27.1, 29.2)	2669 (2561, 2781)	71000 (68100, 74000)	3241000 (3205000, 3277000)

DALYs averted rounded to the nearest 100
Incremental cost values rounded to the nearest 1000

Table C.46 Incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) of each intervention scenario compared to baseline (Scenario 0), in the sensitivity analysis under suboptimal 'real-world' conditions with the unit cost of outpatient consultation and inpatient bed days doubled

Scenario	ICER (Deaths)	ICER (DALYs)	Incremental Net Health Benefit (DALYs averted)	Incremental Net Monetary Benefit ($)
Scenario 0				
0.PO-a	1591 (1360, 1854)	60 (51, 70)	1600 (681, 2544)	126000 (54000, 203000)
0.PO-b	1207 (1102, 1330)	45 (41, 50)	8400 (6600, 10200)	675000 (531000, 812000)
0.PO-c	1804 (1652, 2001)	68 (62, 75)	4000 (1400, 6400)	321000 (111000, 508000)
0.PO-d	1907 (1746, 2124)	72 (66, 80)	2800 (48, 5112)	223000 (3802, 408971)
Scenario 1	1585 (1456, 1727)	60 (55, 65)	3300 (2200, 4400)	262000 (176000, 351000)
1.PO-a	1427 (1333, 1534)	54 (50, 58)	6900 (5400, 8300)	549000 (434000, 668000)
1.PO-b	1187 (1122, 1258)	45 (42, 47)	16100 (14000, 18200)	1287000 (1124000, 1453000)
1.PO-c	1368 (1294, 1440)	51 (49, 54)	17200 (14700, 19900)	1375000 (1177000, 1590000)
1.PO-d	1409 (1333, 1488)	53 (50, 56)	16600 (13900, 19300)	1324000 (1114000, 1543000)
Scenario 2	1538 (1444, 1640)	58 (54, 62)	7100 (5500, 8700)	565000 (438000, 695000)
2.PO-a	1399 (1324, 1478)	53 (50, 56)	11800 (10000, 13800)	946000 (802000, 1101000)
2.PO-b	1177 (1121, 1233)	44 (42, 46)	23400 (20900, 25900)	1868000 (1673000, 2073000)
2.PO-c	1201 (1152, 1250)	45 (43, 47)	30200 (27400, 33200)	2420000 (2194000, 2655000)
2.PO-d	1215 (1165, 1267)	46 (44, 48)	30500 (27600, 33400)	2440000 (2209000, 2675000)

ICER: Incremental Cost Effectiveness Ratio (cost per Death or DALY averted)
Incremental Net Health Benefit values rounded to the nearest 100
Incremental Net Monetary Benefit values rounded to the nearest 1000

Bibliography

[1] Li Liu, Shefali Oza, Dan Hogan, Yue Chu, Jamie Perin, Jun Zhu, Joy E. Lawn, Simon Cousens, Colin Mathers, and Robert E. Black. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *The Lancet*, 388(10063):3027–3035, 12 2016. ISSN 1474547X. doi: 10.1016/S0140-6736(16)31593-8.

[2] Grant Mackenzie. The definition and classification of pneumonia. *Pneumonia*, 8(1):14, 12 2016. ISSN 2200-6133. doi: 10.1186/s41479-016-0012-z.

[3] Daniel R Feikin, Laura L Hammitt, David R Murdoch, Katherine L O'brien, J Anthony, and G Scott. The Enduring Challenge of Determining Pneumonia Etiology in Children: Considerations for Future Research Priorities. *Clinical Infectious Diseases*, 2017. doi: 10.1093/cid/cix143.

[4] Igor Rudan, Lana Tomaskovic, Cynthia Boschi-Pinto, and Harry Campbell. Global estimate of the incidence of clinical pneumonia among children under five years of age. *Bulletin of the World Health Organization*, 82(12):895–903, 12 2004. ISSN 00429686. doi: /S0042-96862004001200005.

[5] World Health Organization. *Integrated Management of Childhood Illness: Chart Booklet*. 2014. ISBN 978 92 4 150682 3.

[6] Trevor Duke. What the PERCH study means for future pneumonia strategies. *The Lancet*, 394(10200):714–716, 8 2019. ISSN 1474547X. doi: 10.1016/S0140-6736(19)31512-0.

[7] Stewart Jackson, Kyle H. Mathews, Dražen Pulanić, Rachel Falconer, Igor Rudan, Harry Campbell, and Harish Nair. Risk factors for severe acute lower respiratory infections in children - a systematic review and meta-analysis. *Croatian Medical Journal*, 54(2):110–121, 4 2013. ISSN 03539504. doi: 10.3325/cmj.2013.54.110.

[8] Christa L Fischer Walker, Igor Rudan, Li Liu, Harish Nair, Evropi Theodoratou, Zulfiqar A Bhutta, Katherine L O'Brien, Harry Campbell, and Robert E Black. Global burden of childhood pneumonia and diarrhoea. *Lancet (London, England)*, 381(9875):1405–1416, 4 2013. ISSN 1474-547X. doi: 10.1016/S0140-6736(13)60222-6.

[9] Eric D. McCollum, Bejoy Nambiar, Rashid Deula, Beatiwel Zadutsa, Austin Bondo, Carina King, James Beard, Harry Liyaya, Limangeni Mankhambo, Marzia Lazzerini, Charles Makwenda, Gibson Masache, Naor Bar-Zeev, Peter N. Kazembe, Charles Mwansambo, Norman Lufesi, Anthony Costello, Ben Armstrong, and Tim Colbourn. Impact of the 13-Valent Pneumococcal Conjugate Vaccine on Clinical and Hypoxemic Childhood Pneumonia over Three Years in Central Malawi: An Observational Study. *PLOS ONE*, 12(1):e0168209, 1 2017. ISSN 1932-6203. doi: 10.1371/journal.pone.0168209.

[10] Taneli Puumalainen, Beatriz Quiambao, Erma Abucejo-Ladesma, Socorro Lupisan, Tarja Heiskanen-Kosma, Petri Ruutu, Marilla G. Lucero, Hanna Nohynek, Eric A.F. Simoes, and Ian Riley. Clinical case review: A method to improve identification of true

clinical and radiographic pneumonia in children meeting the World Health Organization definition for pneumonia. *BMC Infectious Diseases*, 8:95, 7 2008. ISSN 14712334. doi: 10.1186/1471-2334-8-95.

[11] GBD 2021 Lower Respiratory Infections and Antimicrobial Resistance Collaborators. Global, regional, and national incidence and mortality burden of non-COVID-19 lower respiratory infections and aetiologies, 1990–2021: a systematic analysis from the Global Burden of Disease Study 2021. *The Lancet Infectious Diseases*, 24(9):974–1002, 9 2024. ISSN 14744457.

[12] David A. McAllister, Li Liu, Ting Shi, Yue Chu, Craig Reed, John Burrows, Davies Adeloye, Igor Rudan, Robert E. Black, Harry Campbell, and Harish Nair. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. *The Lancet Global Health*, 7(1):e47–e57, 1 2019. ISSN 2214109X. doi: 10.1016/S2214-109X(18)30408-X.

[13] Stephanie D. Kovacs, Kim Mullholland, Julia Bosch, Harry Campbell, Mohammad H. Forouzanfar, Ibrahim Khalil, Stephen Lim, Li Liu, Stephen N. Maley, Colin D. Mathers, Alastair Matheson, Ali H. Mokdad, Kate O'Brien, Umesh Parashar, Torin T. Schaafsma, Duncan Steele, Stephen E. Hawes, and John T. Grove. Deconstructing the differences: A comparison of GBD 2010 and CHERG's approach to estimating the mortality burden of diarrhea, pneumonia, and their etiologies. *BMC Infectious Diseases*, 15(1):1–15, 1 2015. ISSN 14712334. doi: 10.1186/S12879-014-0728-4.

[14] Kerry-Ann F. O'Grady, Paul J. Torzillo, Kieran Frawley, and Anne B. Chang. The radiological diagnosis of pneumonia in children. *Pneumonia 2014 5:1*, 5(1):38–51, 12 2014. ISSN 2200-6133. doi: 10.15172/pneu.2014.5/482.

[15] Susan C Lipsett, Michael C Monuteaux, Richard G Bachur, Nicole Finn, and Mark I Neuman. Negative Chest Radiography and Risk of Pneumonia. *Pediatrics*, 142(3), 9 2018. ISSN 1098-4275. doi: 10.1542/peds.2018-0236.

[16] The Pneumonia Etiology Research for Child Health (PERCH) Study Group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. *The Lancet*, 394 (10200):757–779, 8 2019. doi: 10.1016/S0140-6736(19)30721-4.

[17] A Begom, A M Choudhury, M N Islam, M A Ali, M A Hossain, M A Hoque, S I Miah, and K J Bhuiyan. Clinical and Radiological Evaluation of Children Aged 2 Months to 5 Years with Severe Pneumonia According to WHO Guideline. *Mymensingh medical journal : MMJ*, 27(4):702–709, 10 2018. ISSN 2408-8757.

[18] Tabish Hazir, Yasir Bin Nisar, Shamim A. Qazi, Shazia F. Khan, Mujahid Raza, Shehla Zameer, and Syed Asif Masood. Chest radiography in children aged 2-59 months diagnosed with non-severe pneumonia as defined by World Health Organization: Descriptive multicentre study in Pakistan. *British Medical Journal*, 333(7569):629–631, 9 2006. ISSN 09598146. doi: 10.1136/bmj.38915.673322.80.

[19] Daniel S. Balk, Christine Lee, Jesse Schafer, Jeremy Welwarth, John Hardin, Victor Novack, Shaked Yarza, and Beatrice Hoffmann. Lung ultrasound compared to chest X-ray for diagnosis of pediatric pneumonia: A meta-analysis. *Pediatric Pulmonology*, 53(8):1130–1139, 8 2018. ISSN 87556863. doi: 10.1002/ppul.24020.

[20] Grant A. Mackenzie, Philip C. Hill, David J. Jeffries, Ilias Hossain, Uchendu Uchendu, David Ameh, Malick Ndiaye, Oyedeji Adeyemi, Jayani Pathirana, Yekini Olatunji, Bade Abatan, Bilquees S. Muhammad, Augustin E. Fombah, Debasish Saha, Ian Plumb, Aliu Akano, Bernard Ebruke, Readon C. Ideh, Bankole Kuti, Peter Githua, Emmanuel Olutunde, Ogochukwu Ofordile, Edward Green, Effua Usuf, Henry Badji, Usman N.A. Ikumapayi, Ahmad Manjang, Rasheed Salaudeen, E. David Nsekpong, Sheikh Jarju, Martin Antonio, Sana Sambou, Lamin Ceesay, Yamundow Lowe-Jallow, Momodou

Jasseh, Kim Mulholland, Maria Knoll, Orin S. Levine, Stephen R. Howie, Richard A. Adegbola, Brian M. Greenwood, and Tumani Corrah. Effect of the introduction of pneumococcal conjugate vaccination on invasive pneumococcal disease in The Gambia: a population-based surveillance study. *The Lancet Infectious Diseases*, 16(6):703–711, 2016. ISSN 14744457. doi: 10.1016/S1473-3099(16)00054-2.

[21] Charles O. Obonyo and Joseph TF. Lau. Efficacy of Haemophilus influenzae type b vaccination of children: A meta-analysis. *European Journal of Clinical Microbiology and Infectious Diseases*, 25(2), 2006. ISSN 09349723. doi: 10.1007/s10096-006-0092-4.

[22] Eili Y. Klein, Bradley Monteforte, Alisha Gupta, Wendi Jiang, Larissa May, Yu Hsiang Hsieh, and Andrea Dugas. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. *Influenza and other respiratory viruses*, 10(5): 394–403, 9 2016. ISSN 1750-2659. doi: 10.1111/IRV.12398. URL `https://pubmed.ncbi.nlm.nih.gov/27232677/`.

[23] Steven J. Siegel and Jeffrey N. Weiser. Mechanisms of Bacterial Colonization of the Respiratory Tract. *Annual Review of Microbiology*, 69(1):425–444, 10 2015. ISSN 0066-4227. doi: 10.1146/annurev-micro-091014-104209.

[24] World Health Organization. *Pocket book of hospital care for children (Second edition)*. 2013. ISBN 9789241548373.

[25] WHO. ICD-11 International Classification of Diseases 11th Revision, 2023. URL `https://icd.who.int/browse11/l-m/en`.

[26] MSD Manual Consumer Version, 2023. URL `https://www.msdmanuals.com/en-pt/home`.

[27] Massimo Resti, Maria Moriondo, Martina Cortimiglia, Giuseppe Indolfi, Clementina Canessa, Laura Becciolini, Elisa Bartolini, Fernando Maria De Benedictis, Maurizio De Martino, and Chiara Azzari. Community-acquired bacteremic pneumococcal pneumonia in children: Diagnosis and serotyping by real-time polymerase chain reaction using blood samples. *Clinical Infectious Diseases*, 51(9), 2010. ISSN 10584838. doi: 10.1086/656579.

[28] Ahmed Ehsanur Rahman, Aniqa Tasnim Hossain, Harish Nair, Mohammod Jobayer Chisti, David Dockrell, Shams El Arifeen, and Harry Campbell. Prevalence of hypoxaemia in children with pneumonia in low-income and middle-income countries: a systematic review and meta-analysis. *The Lancet Global Health*, 10(3):e348–e359, 3 2022. ISSN 2214109X. doi: 10.1016/S2214-109X(21)00586-6.

[29] Eric D. McCollum, Erica Bjornstad, Geoffrey A. Preidis, Mina C. Hosseinipour, and Norman Lufesi. Multicenter study of hypoxemia prevalence and quality of oxygen treatment for hospitalized Malawian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 107(5), 2013. ISSN 00359203. doi: 10.1093/trstmh/trt017.

[30] Eric D. McCollum, Tisungane Mvalo, Michelle Eckerle, Andrew G. Smith, Davie Kondowe, Don Makonokaya, Dhananjay Vaidya, Veena Billioux, Alfred Chalira, Norman Lufesi, Innocent Mofolo, and Mina Hosseinipour. Bubble continuous positive airway pressure for children with high-risk conditions and severe pneumonia in Malawi: an open label, randomised, controlled trial. *The Lancet Respiratory Medicine*, 7(11), 2019. ISSN 22132619. doi: 10.1016/S2213-2600(19)30243-7.

[31] Jennifer L. Lenahan, Evangelyn Nkwopara, Melda Phiri, Tisungane Mvalo, Mari T. Couasnon, Kali Turner, Chifundo Ndamala, Eric D. McCollum, Susanne May, and Amy Sarah Ginsburg. Repeat assessment of examination signs among children in Malawi with fast-breathing pneumonia. *ERJ Open Research*, 6(2), 2020. ISSN 23120541. doi: 10.1183/23120541.00275-2019.

[32] Eric D Mccollum, Carina King, Rashid Deula, Beatiwel Zadutsa, Limangeni Mankhambo, Bejoy Nambiar, Charles Makwenda, Gibson Masache, Norman Lufesi, Charles Mwansambo, Anthony Costello, and Tim Colbourn. Pulse oximetry for children with pneumonia treated as outpatients in rural Malawi. *Bull World Health Organ*, 2016. doi: 10.2471/BLT.16.173401.

[33] Shubhada Hooli, Carina King, Beatiwel Zadutsa, Bejoy Nambiar, Charles Makwenda, Gibson Masache, Norman Lufesi, Charles Mwansambo, Lucas Malla, Anthony Costello, Tim Colbourn, and Eric D. McCollum. The Epidemiology of Hypoxemic Pneumonia among Young Infants in Malawi. *The American Journal of Tropical Medicine and Hygiene*, 102(3):676, 2020. ISSN 00029637. doi: 10.4269/AJTMH.19-0516.

[34] Nicholas Fancourt, Maria Deloria Knoll, Henry C. Baggett, W. Abdullah Brooks, Daniel R. Feikin, Laura L. Hammitt, Stephen R.C. Howie, Karen L. Kotloff, Orin S. Levine, Shabir A. Madhi, David R. Murdoch, J. Anthony G. Scott, Donald M. Thea, Juliet O. Awori, Breanna Barger-Kamate, James Chipeta, Andrea N. DeLuca, Mahamadou Diallo, Amanda J. Driscoll, Bernard E. Ebruke, Melissa M. Higdon, Yasmin Jahan, Ruth A. Karron, Nasreen Mahomed, David P. Moore, Kamrun Nahar, Sathapana Naorat, Micah Silaba Ominde, Daniel E. Park, Christine Prosperi, Somwe Wa Somwe, Somsak Thamthitiwat, Syed M.A. Zaman, Scott L. Zeger, Katherine L. O'Brien, Wei Fu, E. Wangeci Kagucia, Mengying Li, Zhenke Wu, Nora L. Watson, Jane Crawley, Hubert P. Endtz, Khalequ Zaman, Doli Goswami, Lokman Hossain, Hasan Ashraf, Martin Antonio, Jessica McLellan, Eunice Machuka, Arifin Shamsul, Grant Mackenzie, Susan C. Morpeth, Alice Kamau, Sidi Kazungu, Milagritos D. Tapia, Samba O. Sow, Mamadou Sylla, Boubou Tamboura, Uma Onwuchekwa, Nana Kourouma, Aliou Toure, Peter V. Adrian, Vicky L. Baillie, Locadiah Kuwanda, Azwifarwi Mudau, Michelle J. Groome, Susan A. Maloney, Charatdao Bunthi, Julia Rhodes, Pongpun Sawatwong, Pasakorn Akarasewi, Lawrence Mwananyanda, Phil Seidenberg, James Mwansa, and Geoffrey Kwenda. Chest radiograph findings in childhood pneumonia cases from the multisite PERCH study. *Clinical Infectious Diseases*, 64(suppl_3): S262–S270, 2017. ISSN 15376591. doi: 10.1093/cid/cix089.

[35] Chris A Rees, Sudha Basnet, Angela Gentile, Bradford D Gessner, Cissy B Kartasasmita, Marilla Lucero, Luis Martinez, Kerry-Ann F O'Grady, Raul O Ruvinsky, Claudia Turner, Harry Campbell, Harish Nair, Jennifer Falconer, Linda J Williams, Margaret Horne, Tor Strand, Yasir B Nisar, Shamim A Qazi, and Mark I Neuman. An analysis of clinical predictive values for radiographic pneumonia in children. *BMJ Global Health*, 5(8):e002708, 2020. ISSN 2059-7908. doi: 10.1136/BMJGH-2020-002708.

[36] Pui Ying Iroh Tam, Ethan Bernstein, Xiaoye Ma, and Patricia Ferrieri. Blood Culture in Evaluation of Pediatric Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. *Hospital pediatrics*, 5(6), 2015. ISSN 21541663. doi: 10.1542/hpeds.2014-0138.

[37] Betuel Sigaúque, Anna Roca, Inácio Mandomando, Luís Morais, Llorenç Quintó, Jahit Sacarlal, Eusébio MacEte, Tacilta Nhamposa, Sónia MacHevo, Pedro Aide, Quique Bassat, Azucena Bardají, Delino Nhalungo, Montse Soriano-Gabarró, Brendan Flannery, Clara Menendez, Myron M. Levine, and Pedro L. Alonso. Community-acquired bacteremia among children admitted to a rural hospital in Mozambique. *Pediatric Infectious Disease Journal*, 28(2):108–113, 2009. ISSN 15320987. doi: 10.1097/INF.0B013E318187A87D.

[38] F. Ferrero, C. M. Nascimento-Carvalho, M. R. Cardoso, P. Camargos, M. F.P. March, E. Berezin, R. Ruvinsky, C. Sant'Anna, J. Feris-Iglesias, R. Maggi, Y. Benguigui, and CARIBE group. Radiographic findings among children hospitalized with severe community-acquired pneumonia. *Pediatric pulmonology*, 45(10), 2010. ISSN 10990496. doi: 10.1002/ppul.21287.

[39] Kamal Masarweh, Michal Gur, Yazeed Toukan, Ronen Bar-Yoseph, Imad Kassis, Guy Gut, Fahed Hakim, Vered Nir, and Lea Bentur. Factors associated with complicated

pneumonia in children. *Pediatric Pulmonology*, 56(8), 2021. ISSN 10990496. doi: 10.1002/ppul.25468.

[40] Chris A Rees, Tim Colbourn, Shubhada Hooli, Carina King, Norman Lufesi, Eric D Mccollum, Charles Mwansambo, Clare Cutland, Shabir Ahmed Madhi, Marta Nunes, Joseph L Mathew, Emmanuel Addo-Yobo, Noel Chisaka, Mumtaz Hassan, Patricia L Hibberd, Prakash M Jeena, Juan M Lozano, William B Macleod, Archana Patel, Donald M Thea, Ngoc Tuong, Vy Nguyen, Cissy B Kartasasmita, Marilla Lucero, Shally Awasthi, Ashish Bavdekar, Monidarin Chou, Pagbajabyn Nymadawa, Jean-William Pape, Glaucia Paranhos-Baccala, Valentina S Picot, Mala Rakoto-Andrianarivelo, Vanessa Rouzier, Graciela Russomando, Mariam Sylla, Philippe Vanhems, Jianwei Wang, Rai Asghar, Salem Banajeh, Imran Iqbal, Irene Maulen-Radovan, Greta Mino-Leon, Samir K Saha, Mathuram Santosham, Sunit Singhi, Sudha Basnet, Tor A Strand, Shinjini Bhatnagar, Nitya Wadhwa, Rakesh Lodha, Satinder Aneja, Alexey W Clara, Harry Campbell, Harish Nair, Jennifer Falconer, Shamim A Qazi, and Yasir B Nisar. Derivation and validation of a novel risk assessment tool to identify children aged 2-59 months at risk of hospitalised pneumonia-related mortality in 20 countries Mark I Neuman, 48 On behalf of the World Health Organization PREPARE study group. *BMJ Global Health*, 7(4), 2022. doi: 10.1136/bmjgh-2021-008143.

[41] Marzia Lazzerini, Nadine Seward, Norman Lufesi, Rosina Banda, Sophie Sinyeka, Gibson Masache, Bejoy Nambiar, Charles Makwenda, Anthony Costello, Eric D. McCollum, and Tim Colbourn. Mortality and its risk factors in Malawian children admitted to hospital with clinical pneumonia, 2001-12: A retrospective observational study. *The Lancet Global Health*, 2016. ISSN 2214109X. doi: 10.1016/S2214-109X(15)00215-6.

[42] Penelope M. Enarson, Robert P. Gie, Charles C. Mwansambo, Alfred E. Chalira, Norman N. Lufesi, Ellubey R. Maganga, Donald A. Enarson, Neil A. Cameron, and Stephen M. Graham. Potentially Modifiable Factors Associated with Death of Infants and Children with Severe Pneumonia Routinely Managed in District Hospitals in Malawi. *PLOS ONE*, 10(8), 8 2015. ISSN 1932-6203. doi: 10.1371/journal.pone.0133365.

[43] Todd A. Florin, Lilliam Ambroggio, Douglas Lorenz, Andrea Kachelmeyer, Richard M. Ruddy, Nathan Kuppermann, and Samir S. Shah. Development and Internal Validation of a Prediction Model to Risk Stratify Children With Suspected Community-Acquired Pneumonia. *Clinical Infectious Diseases*, 73(9):e2713–e2721, 11 2021. ISSN 1058-4838. doi: 10.1093/CID/CIAA1690.

[44] Chris Wilkes, Mohamed Bava, Hamish R. Graham, and Trevor Duke. What are the risk factors for death among children with pneumonia in low and middle-income countries? A systematic review. *Journal of Global Health*, 13, 2023. ISSN 20472986. doi: 10.7189/jogh.13.05003.

[45] Wei Shan, Ting Shi, Kaile Chen, Jian Xue, Yin Wang, Jia Yu, Genming Zhao, Jianmei Tian, and Tao Zhang. Risk Factors for Severe Community-aquired Pneumonia among Children Hospitalized with CAP Younger Than 5 Years of Age. *Pediatric Infectious Disease Journal*, 38(3):224–229, 3 2019. ISSN 15320987. doi: 10.1097/INF.0000000000002098.

[46] C. Suresh Kumar, Sreeram Subramanian, Srinivas Murki, J. V. Rao, Meera Bai, Sarguna Penagaram, Himabindu Singh, Nirupama Padmaja Bondili, Alimelu Madireddy, Swapna Lingaldinna, Srikanth Bhat, and Bharadwaj Namala. Predictors of Mortality in Neonatal Pneumonia: An INCLEN Childhood Pneumonia Study. *Indian Pediatrics*, 58(11):1040–1045, 11 2021. ISSN 09747559. doi: 10.1007/S13312-021-2370-8.

[47] Rakesh Lodha, Sushil K. Kabra, and Ravindra M. Pandey. Antibiotics for community-acquired pneumonia in children. *Cochrane Database of Systematic Reviews*, (6), 6 2013. ISSN 1465-1858. doi: 10.1002/14651858.CD004874.pub4.

[48] Zohra S. Lassi, Jai K. Das, Syed Waqas Haider, Rehana A. Salam, Shamim A. Qazi, and Zulfiqar A. Bhutta. Systematic review on antibiotic therapy for pneumonia in children between 2 and 59 months of age. *Archives of Disease in Childhood*, 99(7): 687–693, 7 2014. doi: 10.1136/archdischild-2013-304023.

[49] Zohra S. Lassi, Aamer Imdad, and Zulfiqar A. Bhutta. Short-course versus long-course intravenous therapy with the same antibiotic for severe community-acquired pneumonia in children aged two months to 59 months. *Cochrane Database of Systematic Reviews*, 2015(6), 6 2015. ISSN 14651858. doi: 10.1002/14651858.CD008032.pub2.

[50] Batool A. Haider, Muhammad Ammad Saeed, and Zulfiqar A. Bhutta. Short-course versus long-course antibiotic therapy for nonsevere community-acquired pneumonia in children aged 2 months to 59 months. *Cochrane Database of Systematic Reviews*, (2), 2008. ISSN 1469493X. doi: 10.1002/14651858.CD005976.pub2.

[51] Wingston Ng'ambi, Tara Mangal, Andrew Phillips, Tim Colbourn, Joseph Mfutso-Bengo, Paul Revill, and Timothy B. Hallett. Factors associated with healthcare seeking behaviour for children in Malawi: 2016. *Tropical Medicine and International Health*, 25(12):1486–1495, 2020. ISSN 13653156. doi: 10.1111/tmi.13499.

[52] National Statistical Office/Malawi and ICF. Malawi Demographic and Health Survey 2015-16. Technical report, National Statistical Office and ICF, Zomba, Malawi, 2017.

[53] Ministry of Health (MOH) [Malawi] and ICF International. Malawi Service Provision Assessment (MSPA) 2013-14. Technical report, Ministry of Health and ICF International, Lilongwe, Malawi, and Rockville, Maryland, USA, 2014.

[54] Rele Ologunde, Mahiben Maruthappu, Kumaran Shanmugarajah, and Joseph Shalhoub. Surgical care in low and middle-income countries: Burden and barriers. *International Journal of Surgery*, 12(8):858–863, 2014. doi: 10.1016/j.ijsu.2014.07.009.

[55] Chiara Pittalis, Ruairí Brugha, Leon Bijlmakers, Frances Cunningham, Gerald Mwapasa, Morgane Clarke, Henk Broekhuizen, Martilord Ifeanyichi, Eric Borgstein, and Jakub Gajewski. Using Network and Complexity Theories to Understand the Functionality of Referral Systems for Surgical Patients in Resource-Limited Settings, the Case of Malawi. *International Journal of Health Policy and Management*, 11(11), 2022. ISSN 23225939. doi: 10.34172/ijhpm.2021.175.

[56] Carina King, Beatiwel Zadutsa, Lumbani Banda, Everlisto Phiri, Eric D. McCollum, Josephine Langton, Nicola Desmond, Shamim Ahmad Qazi, Yasir Bin Nisar, Charles Makwenda, and Helena Hildenwall. Prospective cohort study of referred Malawian children and their survival by hypoxaemia and hypoglycaemia status. *Bulletin of the World Health Organization*, 100(5), 2022. ISSN 15640604. doi: 10.2471/BLT.21.287265.

[57] Government of the Republic of Malawi and Ministry of Health. Malawi National Medical Oxygen Ecosystem Roadmap 2021-2026. Technical report, Government of the Republic of Malawi, Ministry of Health, Lilongwe, Malawi, 2021.

[58] Edgar Arnold Lungu, Catherine Darker, and Regien Biesma. Determinants of healthcare seeking for childhood illnesses among caregivers of under-five children in urban slums in Malawi: A population-based cross-sectional study. *BMC Pediatrics*, 20(1): 1–13, 1 2020. ISSN 14712431. doi: 10.1186/S12887-020-1913-9/TABLES/2.

[59] Duyen Thi Kim Nguyen, Karen K. Leung, Lynn McIntyre, William A. Ghali, and Reg Sauve. Does Integrated Management of Childhood Illness (IMCI) Training Improve the Skills of Health Workers? A Systematic Review and Meta-Analysis. *PLoS ONE*, 8(6): e66030, 6 2013. doi: 10.1371/journal.pone.0066030.

[60] Omolara T Uwemedimo, Todd P Lewis, Elsie A Essien, Grace J Chan, Humphreys Nsona, Margaret E Kruk, and Hannah H Leslie. Distribution and determinants of pneumonia diagnosis using Integrated Management of Childhood Illness guidelines: a nationally representative study in Malawi. *BMJ global health*, 3(2):e000506, 4 2018. ISSN 2059-7908. doi: 10.1136/bmjgh-2017-000506.

[61] World Health Organization. WHO Recommendations on the Management of Diarrhoea and Pneumonia in HIV-Infected Infants and Children: Integrated Management of Childhood Illness (IMCI). Technical report, Geneva, 2010.

[62] Emily White Johansson, Humphreys Nsona, Liliana Carvajal-Aguirre, Agbessi Amouzou, and Helena Hildenwall. Determinants of Integrated Management of hildhood Illness (IMCI) non-severe pneumonia classification and care in Malawi health facilities: Analysis of a national facility census. *Journal of Global Health*, 7(2), 11 2017. ISSN 20472986. doi: 10.7189/jogh.07.020408.

[63] Emily White Johansson, Katarina Ekholm Selling, Humphreys Nsona, Bonnie Mappin, Peter W. Gething, Max Petzold, Stefan Swartling Peterson, and Helena Hildenwall. Integrated paediatric fever management and antibiotic over-treatment in Malawi health facilities: data mining a national facility census. *Malaria Journal*, 15(1):396, 12 2016. ISSN 1475-2875. doi: 10.1186/s12936-016-1439-7.

[64] Restituta Phabian Muro, Tulla Sylvester Masoza, Godfrey Kasanga, Neema Kayange, and Benson R. Kidenya. Predictors and outcome of first line treatment failure among under-five children with community acquired severe pneumonia at Bugando Medical Centre, Mwanza, Tanzania: A prospective cohort study. *PloS ONE*, 15(12), 12 2020. ISSN 1932-6203. doi: 10.1371/journal.pone.0243636.

[65] Amy Sarah Ginsburg, Tisungane Mvalo, Evangelyn Nkwopara, Eric D. McCollum, Chifundo B. Ndamala, Robert Schmicker, Ajib Phiri, Norman Lufesi, Rasa Izadnegahdar, and Susanne May. Placebo vs Amoxicillin for Nonsevere Fast-Breathing Pneumonia in Malawian Children Aged 2 to 59 Months: A Double-blind, Randomized Clinical Noninferiority Trial. *JAMA Pediatrics*, 173(1):21–28, 1 2019. ISSN 2168-6203. doi: 10.1001/jamapediatrics.2018.3407Abstract.

[66] Amy-Sarah Ginsburg, Tisungane Mvalo, Evangelyn Nkwopara, Eric D. McCollum, Melda Phiri, Robert Schmicker, Jun Hwang, Chifundo B. Ndamala, Ajib Phiri, Norman Lufesi, and Susanne May. Amoxicillin for 3 or 5 Days for Chest-Indrawing Pneumonia in Malawian Children. *The New England journal of medicine*, 383(1):13–23, 7 2020. ISSN 1533-4406. doi: 10.1056/NEJMoa1912400.

[67] Enhanced Management of Pneumonia in Community (EMPIC) Study. Community-based amoxicillin treatment for fast breathing pneumonia in young infants 7-59 days old: a cluster randomised trial in rural Bangladesh, Ethiopia, India and Malawi. *BMJ Global Health*, 6(8):e006578, 8 2021. ISSN 2059-7908. doi: 10.1136/bmjgh-2021-006578.

[68] Eric D. McCollum, Carina King, Robert Hollowell, Janet Zhou, Tim Colbourn, Bejoy Nambiar, David Mukanga, and Deborah C.Hay Burgess. Predictors of treatment failure for non-severe childhood pneumonia in developing countries – systematic literature review and expert survey – the first step towards a community focused mHealth risk-assessment tool? *BMC Pediatrics*, 15(1), 7 2015. ISSN 14712431. doi: 10.1186/S12887-015-0392-X.

[69] A. Patel, M. Mamtani, P. L. Hibberd, T. A. Tuan, P. Jeena, N. Chisaka, M. Hassan, I. Maulen-Radovan, D. M. Thea, S. Qazi, and H. Kulkarni. Value of chest radiography in predicting treatment response in children aged 3-59 months with severe pneumonia. *Int J Tuberc Lung Dis*, 12(11):1320–1326, 9 2008.

[70] Carina King, Tim Colbourn, Limangeni Mankhambo, James Beard, Debbie C. Hay Burgess, Anthony Costello, Rasa Izadnegahdar, Norman Lufesi, Charles Mwansambo, Bejoy Nambiar, Eric S. Johnson, Robert W. Platt, David Mukanga, and Eric D. McCollum. Non-treatment of children with community health worker-diagnosed fast-breathing pneumonia in rural Malawi: exploratory subanalysis of a prospective cohort study. *BMJ Open*, 6(11):e011636, 11 2016.

[71] Tisungane Mvalo, Andrew G. Smith, Michelle Eckerle, Mina C. Hosseinipour, Davie Kondowe, Dhananjay Vaidya, Yisi Liu, Kelly Corbett, Dan Nansongole, Takondwa A. Mtimaukanena, Norman Lufesi, and Eric D. McCollum. Antibiotic treatment failure in children aged 1 to 59 months with World Health Organization-defined severe pneumonia in Malawi: A CPAP IMPACT trial secondary analysis. *PLoS ONE*, 17(12):e0278938, 2022. ISSN 19326203. doi: 10.1371/journal.pone.0278938.

[72] Felix Lam, Angela Stegmuller, Victoria B. Chou, and Hamish R. Graham. Oxygen systems strengthening as an intervention to prevent childhood deaths due to pneumonia in low-resource settings: systematic review, meta-analysis and cost-effectiveness. *BMJ Global Health*, 6(12):e007468, 12 2021. ISSN 2059-7908. doi: 10.1136/BMJGH-2021-007468.

[73] Alberto Gregori. An overview of Covid-19 in Malawi: Scotland-Malawi Oxygen Supply Coordination Group. Technical report, 2 2021. URL `https://www.scotland-malawipartnership.org/assets/documents/SMP_Oxygen_group_Full_Summary_v3_1.pdf`.

[74] Food and Agriculture Organization of the United Nations. Food Price Monitoring and Analysis (FPMA): Malawi national currency devalued, 2023. URL `https://www.fao.org/giews/food-prices/food-policies/detail/en/c/1667165/`.

[75] Victoria Smith, Alana Changoor, Chloe McDonald, David Barash, Bernard Olayo, Steve Adudans, Tyler Nelson, Cheri Reynolds, Monica Cainer, and James Stunkel. A Comprehensive Approach to Medical Oxygen Ecosystem Building: An Implementation Case Study in Kenya, Rwanda, and Ethiopia. *Global Health Science and Practice*, 10 (6), 2022. ISSN 2169575X. doi: 10.9745/GHSP-D-21-00781.

[76] M. Itimu, C. Chilikutali, P. Bango, A. Mhone, A. Nkhata, and S. Brandstetter. P0272 / #739: THE FIRST PEADIATRIC SURGERY AND INTENSIVE CARE CENTRE IN MALAWI: A SITUATIONAL ANALYSIS OF MERCY JAMES CENTRE FOR PAEDIATRIC SURGERY AND INTENSIVE CARE. In *Pediatric Critical Care Medicine*, volume 22, 2021. doi: 10.1097/01.pcc.0000739428.48054.77.

[77] PATH and Clinton Health Access Initiative (CHAI). COVID-19 Respiratory Care Response Coordination project- Oxygen Generation and Storage. Technical report, PATH | CLINTON HEALTH ACCESS INITIATIVE, 2021.

[78] Institute for Transformative Technologies (ITT) and Oxygen Hub. Closing the medical oxygen gap in sub-Saharan Africa: A case for a decentralized hub-spoke network of pressure swing adsorption plants. Technical report, 2021. URL `https://oxygenhub.org/wp-content/uploads/2021/01/ClosingO2GapinSSA.pdf`.

[79] PATH. Biomedical Equipment for COVID-19 Case Management Malawi Facility Survey Report. Technical report, PATH, Seatle: PATH, 2021.

[80] MSH (Management Sciences for Health). International Medical Products Price Guide, 2015 Edition. Technical report, MSH (Management Sciences for Health), Medford, Mass.: MSH, 2016.

[81] Handling fees | UNICEF Supply Division. URL `https://www.unicef.org/supply/handling-fees`.

[82] Economic Analysis and Evaluation Team and Department of Health Systems Governance and Financing. WHO-CHOICE estimates of cost for inpatient and outpatient health service delivery. Technical report, World Health Organization, 2021.

[83] Hugo C. Turner, Jeremy A. Lauer, Bach Xuan Tran, Yot Teerawattananon, and Mark Jit. Adjusting for Inflation and Currency Changes Within Health Economic Studies. *Value in health: International Society for Pharmacoeconomics and Outcomes Research*, 22(9):1026–1032, 9 2019. ISSN 1524-4733. doi: 10.1016/j.jval.2019.03.021.

[84] Karin Stenberg, Jeremy A. Lauer, Georgios Gkountouras, Christopher Fitzpatrick, and Anderson Stanciole. Econometric estimation of WHO-CHOICE country-specific costs for inpatient and outpatient health service delivery. *Cost Effectiveness and Resource Allocation*, 16(1), 2018. ISSN 14787547. doi: 10.1186/s12962-018-0095-x.

[85] Carlos Varela, Sven Young, Nyengo Mkandawire, Reinou S. Groen, Leonard Banza, and Asgaut Viste. TRANSPORTATION BARRIERS TO ACCESS HEALTH CARE FOR SURGICAL CONDITIONS IN MALAWI a cross sectional nationwide household survey. *BMC Public Health*, 19(1), 2019. ISSN 14712458. doi: 10.1186/s12889-019-6577-8.

[86] Government of Malawi. Harmonised Health Facility Assessment (HHFA) 2018-2019. Technical report, Government of Malawi, Ministry of Health and Population, 2019.

[87] Jessica Ochalek, Paul Revill, Gerald Manthalu, Finn McGuire, Dominic Nkhoma, Alexandra Rollinger, Mark Sculpher, and Karl Claxton. Supporting the development of a health benefits package in Malawi. *BMJ Global Health*, 3(2):e000607, 4 2018.

[88] Erica Bjornstad, Geoffrey A. Preidis, Norman Lufesi, Dan Olson, Portia Kamthunzi, Mina C. Hosseinipour, and Eric D. McCollum. Determining the quality of IMCI pneumonia care in Malawian children. *Paediatrics and International Child Health*, 34(1): 29–36, 2 2014. ISSN 2046-9047. doi: 10.1179/2046905513Y.0000000070.