Promoting the
QUALITY OF MEDICINES Plus

Model to Estimate the Burden of Substandard and Falsified Amoxicillin in Treating Childhood Pneumonia

Case Study for Africa and Instructions for Using the Model for Other Regions/Countries

Contact Information

Promoting the Quality of Medicines Plus Program
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852 USA
Tel: +1-301-816-8166
Fax: +1-301-816-8374
Email: PQMplus@USP.org

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About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a six-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

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Contents

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University of Washington:
Sabra Zaraa, PharmD, MPH
Josh J Carlson, PhD, MPH
Andy Stergachis, PhD, BPharm

PQM+:
Amanda Lewin, PhD
Efugbaike Ajayi
Ellie Bahirai, MPH
Leslie Rider-Araki, MA
Souly Phanouvong, PharmD, PhDs
Sultan Ghani, MSc
Uzoamaka Ajene
Waqas Ahmed

Acronyms

API	active pharmaceutical ingredients
CFR	case fatality rate
DALY	disability-adjusted life year
GDPPC	gross domestic product per capita
LMICs	low- and middle-income countries
OWSA	one-way sensitivity analysis
PPB	Pharmacy and Poisons Board
PPH	post-partum hemorrhage
PQM+	Promoting the Quality of Medicines Plus
QALY	quality-adjusted life year
SF	substandard and falsified
TWG	technical working group
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Executive Summary

The USAID-funded Promoting the Quality of Medicines Plus (PQM+) program developed a substandard and falsified (SF) medicine burden model[1] that stakeholders can use to estimate the burden of using SF medicines on patients, the healthcare system, and the economy as a whole. The model was first piloted in Kenya to assess the burden of SF oxytocin. PQM+ then applied the model to estimate the burden of SF amoxicillin for childhood (<5 years old) pneumonia. This report has two primary objectives:

1. Demonstrate use of the model and provide estimates of the burden of SF amoxicillin used as a first-line treatment for childhood pneumonia in Africa.
2. Provide a model template prepopulated with available data that can be used in the context of low- and middle-income countries (LMICs) or developing region with minimal additional data inputs.

PQM+ identified published data sources for key parameters to estimate the burden of SF amoxicillin in Africa for the treatment of childhood (< 5 years old) pneumonia following World Health Organization (WHO) treatment guidelines. The burden is substantial, likely leading each year to an additional 8,063 cases of severe pneumonia, 3,225 cases of very severe pneumonia, and 312 deaths (and life years lost from those deaths), as well as $22.6 million in added economic costs per one million new cases of childhood pneumonia. Given uncertainty in the values for parameters used in the model, the estimated economic burden could be substantially lower or as high as $34 million per year. The results suggest that the cost of SF amoxicillin to children, society, and the economy in Africa merits further action.

These preliminary results should be used as a basis for customization of the model in individual countries, both in Africa and in other developing countries or regions. The results can be used to advocate for increased efforts to reduce the prevalence and availability of SF medicines.

To aid in the adaptation of this model by individual countries or other regions, the following annexes are included with the report:

Annex 1 – Prepopulated model inputs and their data sources used to estimate the burden of SF amoxicillin in Africa

Annex 2 – Description of model template inputs to aid in the adaptation for individual countries

[1] The USAID-funded PQM+ program is led by USP. The School of Pharmacy Global Medicines Program at the University of Washington led development of the model. The Eshelman School of Pharmacy at the University of North Carolina led the associated literature review. PQM+, USAID, the Eshelman School, and the Harvard Pilgrim Healthcare Institute advised on the model and the process for using it.

Introduction to the Model

A study by WHO in 2017 found the aggregate observed failure rate of tested samples of medicines in LMICs to be approximately 10.5% (World Health Organization, 2017). The study acknowledged that, due to limitations in data availability and the non-representative nature of the samples collected, the true burden of poor-quality medicines in LMICs is unknown and likely much higher in some settings (World Health Organization, 2017; McManus & Naughton, 2020). The WHO report also provided estimates of the global burden of using SF medicines for the treatment of two diseases—childhood pneumonia and malaria—while noting that further work was needed to better understand the burden. The PQM+ program developed the SF medicine burden model for stakeholders to estimate the burden of using SF medicines on patients, the healthcare system, and the economy.

The SF medicine burden model can be used to estimate the burden of any medicine. It uses a decision tree structure, comparing two scenarios:

- A real-world scenario with the presence of SF medicines
- An ideal-quality scenario without SF medicines

The model reflects the possible sequences of these scenarios and the outcomes that can occur from each sequence. This approach allows estimation of the incremental burden of the presence and inadvertent use of SF medicines.

The difference between the real-world scenario and the ideal-quality scenario is the presence of SF medicines. The health burden from the use of these medicines comes from active pharmaceutical ingredients (APIs) in the medicines that are inadequate to achieve treatment efficacy. Thus, the main driver of health burden is the relationship between the percentage of APIs in the medicine and medicine efficacy.[2] The SF medicine burden model makes assumptions about decrements in medicine efficacy based on API content as shown in Table 1.

Table 1. Key assumptions about SF medicine efficacy

Medicine quality rating	% of required API	Reduction in efficacy	Medicine efficacy
Standard quality	90 – 110%	0%	100%
Substandard 1 (SS1)	75 – 89%	30%	70%
Substandard 2 (SS2)	50 – 74%	60%	40%
Substandard 3 (SS3)	< 50%	100%	0%

The model's decision tree starts with the eligible population (i.e., the number of people with the disease or health condition of interest). In each scenario, the eligible population follows the care delivery pathway from the first stage of care-seeking behavior (seek care vs. do not seek care) through the health system[3] and different treatment outcomes, with poor treatment outcomes experienced by patients who received SF medicine. To account for providers who may increase

[2] Assumptions about the relationship between API percentage and medicine efficacy, as well as additional explanation of the model, are available in the *Model to Estimate Burden of Use of Substandard and Falsified Medicines: Guidance for Model Users*.
[3] Where there are adequate data on medicine quality in different sectors of care delivery (private vs. public) and treatment location/facility type, users can enter these data to refine the estimate.

the dose of SF medicines to achieve treatment efficacy (i.e., up-dosing), the probability of increasing dosing for SF medicines can be added.

The model estimates two major classes of outcomes:

- **Health outcomes**: life years, disability-adjusted life years (DALYs), quality-adjusted life years (QALYs), death, and disease-specific outcomes
- **Economic/societal outcomes**: cost of retreatment and value of lost productivity from likely failed treatment or complications from treatment with an SF medicine

Estimating the Burden of SF Amoxicillin for the Treatment of Childhood (<5 years old) Pneumonia in Africa

To demonstrate how to use the model and to interpret its results, PQM+ used it to estimate the burden of SF amoxicillin in providing first-line treatment of childhood pneumonia in Africa. The remainder of this report describes that effort and the results.

In 2019, WHO estimated that 14% of all deaths of children under 5 years old were caused by pneumonia, accounting for more than 740,000 deaths annually (World Health Organization, 2022). While pneumonia impacts children worldwide, deaths are most highly concentrated in southern Asia and sub-Saharan Africa.

In 2014, WHO published updated treatment guidelines for pneumonia in children under 5 years old (hereafter referred to as childhood pneumonia) at health facilities (World Health Organization, 2014). These guidelines included an updated classification of pneumonia versus severe pneumonia and recommended treatment with oral antibiotics. Based on the WHO treatment guidelines, pneumonia with fast breathing and/or chest indrawing should be treated with oral amoxicillin in an outpatient setting, whereas severe pneumonia (pneumonia with any general danger sign) should be treated in a healthcare facility with an injectable therapy (first-line treatment of parenteral ampicillin/penicillin and gentamicin). However, both oral and injectable amoxicillin are also used in healthcare facilities for the treatment of severe pneumonia (Lassi, et al., 2013).

The SF medicine burden model requires users to input values for numerous variables, including health outcomes with and without treatment, medicine and other treatment costs, the number of cases annually, and others. It is difficult to find values for some of these variables in the published literature and to triangulate findings from diverse sources. Users will not be able to find consistent, reliable, and current data sources for many variables. To address this, users may enter both the best estimate and ranges for variables. Also, to facilitate use of the model to estimate the burden of SF amoxicillin for childhood pneumonia in other regions or specific countries, PQM+ has identified reliable data sources (global, regional, or country) for many of the variables.

The model template has been prepopulated with data generalized to Africa or LMICs globally, depending on data availability. These minimal inputs were used to estimate the burden of SF amoxicillin in Africa per one million new cases of childhood pneumonia in a year, the results of which are presented in this report. **Annex 1** provides a summary of the data inputs included in the SF burden model to generate the Africa results. **Annex 2** describes each of the model variables, identifies data sources for the variables, and explains how to update the model template to estimate the burden for specific countries or other regions. With the guidance

provided in **Annex 2** and the prepopulated model template file (an Excel spreadsheet that accompanies this report), a user can replace the African data values with country-specific data values, when available, to produce a country-specific SF burden estimate. A user may also include additional data points to further understand the burden of SF amoxicillin in the context of a specific country in the African region. The model template can also be used for countries or regions outside of Africa. However, many of the prepopulated values will need to be adjusted for the region of interest. Instructions for this are also provided in **Annex 2**.

Process for Using the Model

As mentioned above, determining the appropriate value for many variables can be challenging, so it is very helpful to engage experts with detailed knowledge of the variables in the country or region of interest to improve the accuracy of the estimate. Further, the model is intended to raise awareness of the burden of SF medicines. If the estimated burden is substantial, decision makers may seek to understand root causes and decide to take measures to combat poor-quality medicines. Engaging decision makers in using the model increases their understanding of it and the credibility of its results, both of which may increase the likelihood of follow-up to improve medicine quality. Accordingly, there are two approaches for using the model:

- A group of senior stakeholders uses the model via a series of meetings in which they are oriented to the model, consider inputs into it, review results, and decide on follow-up actions. These stakeholders should include experts in clinical care for the medical issue (e.g., pediatrician for childhood pneumonia), the national health system, and medicine quality so that they can provide expert opinions and access current, country-specific data to the extent possible.
- A small group of interested stakeholders populates the model with the best data they can identify to develop a rough estimate of the burden. They then share this rough estimate with experts and senior decision makers to raise awareness and prompt either an effort to refine the values in the model or to move directly to action to address the SF medicine.

Limitations

The data values utilized to prepopulate the model are largely based on large-scale reviews that provide general probabilities. These reviews may compile data from a decade or more of relevant studies. This helps to limit extreme or atypical values that may be reported in an individual study, but it does result in potentially outdated probabilities. Many of the sources that informed data values used in this exercise were published prior to 2015, which may further limit the relevance of the data inputs. However, estimates are still likely to be relevant even as health outcomes or rates of SF medicines have improved because it was a priority to include conservative estimates for the model inputs and factors that improve health outcomes are likely to equally impact values for probabilities associated with treatment and without treatment (e.g., improved access to nutritious food or clean water). **Annex 2** provides a detailed description of each variable and its potential limitations, as applicable. Notable limitations associated with specific variables are:

1. *Costs*. Costs are significantly impacted by the countries' healthcare systems. These inputs would be best replaced by country-specific data. The current input for cost of severe pneumonia management is an average of costs reported for lower-middle income countries, with the averages for low-income and upper-middle income countries used as the range (Adamu, et al., 2022; Batura, et al., 2022; de Broucker, et al., 2020; Ekirapa-

Kiracho, et al.; 2021, Zhang et al., 2016). The current input for cost of very severe pneumonia management is estimated based on limited country data (Zhang, et al., 2016) with data coming exclusively from South Africa, which is classified as an upper-middle income country. To be conservative and more reflective of costs observed in a lower-middle income country, the lowest value reported was used for the model input. However, the cost would still likely be an overestimate for a low-income country.

2. *Proportion of SF amoxicillin*. These inputs are based on a large-scale review, including reports of SF medicines from 1992-2020 and generalized to developing countries (Zabala, et al., 2022). These inputs should be replaced if more recent, reliable data are available for a country. The impact of this on the Africa model results is indeterminate; depending on the proportion of amoxicillin that is SF, reported results could be an over- or an under-estimate. It is useful to consider the results for the range of values for SF amoxicillin to understand their impact on the results.

Other limitations to consider are:

1. *Care-seeking behavior for severe pneumonia.* The model assumes that if a case progresses from pneumonia to severe pneumonia, a patient will seek additional care. The rates of care-seeking behavior for children with severe pneumonia can vary by country and by region within a country. Therefore, PQM+ did not try to adjust the data based on care-seeking behavior for children with severe pneumonia across Africa, and the impact of patients who progress to severe pneumonia and do not seek treatment prior to progressing to very severe pneumonia or death was not captured. If these data are available for a given country, they should be included in the calculation as described in **Annex 2**.

2. *Use of amoxicillin for treatment of severe pneumonia.* The model has been designed to understand the impact of SF amoxicillin as a first-line treatment for pneumonia. It does not model the impact of the use of amoxicillin for severe pneumonia or for other indications. This is because the rates and context for the use of amoxicillin for severe pneumonia are not well characterized.

3. *Impact of SF amoxicillin on antimicrobial resistance.* It is recognized that SF antibiotics may be a contributing factor to antimicrobial resistance (Cavany, et al., 2023; Zabala, et al., 2022). However, it is not well characterized and there is insufficient data available to support development of a model that is able to accurately estimate the burden associated with increased antimicrobial resistance due to the use of SF antibiotics.

While the prepopulated data provide estimates relevant to any LMIC in Africa, country-specific inputs will further increase the relevancy of the outputs to the specific country.

Findings

Findings per one million children treated with amoxicillin for pneumonia

This report documents the model's estimates of the burden of SF amoxicillin in Africa per one million new cases of children with pneumonia. The model uses a 16% prevalence of SF medicines based on Zabala, et al. (2022), which is an expansive study that estimated medicine SF rates in LMICs. The review included a total of 2,208 amoxicillin samples collected between

1992 and 2020. Additional discussion on the prevalence of SF amoxicillin can be found in **Annex 2**.

Base case. The detailed results below reflect the "base case"—the results generated by the model based on the selected likely value for each variable.

Health burden. The model estimates that, due to use of SF amoxicillin in Africa, per one million new cases of pneumonia each year there are:

- 8,063 additional cases of severe pneumonia
- 3,225 additional cases of very severe pneumonia
- 312 additional deaths
- 7,886 life years lost

Economic burden.[4] The additional morbidity and mortality caused by SF amoxicillin results in an economic burden estimated at $22.6 million (per one million new cases of pneumonia in children < 5 years old) from a societal perspective, including approximately:

- $4.8 million in direct costs from the healthcare sector perspective
- $17.8 million in productivity losses including:
  - $471,000 due to caregivers' missed days of work
  - $17.3 million due to premature death (considering the lifetime productivity of the 312 additional deaths estimated in the given year)

The incremental change in health and economic burdens attributable to use of SF amoxicillin in Africa per one million children < 5 years old with pneumonia is presented in Table 2, which compares the ideal scenario (no SF medicine) and the real-world scenario (16% prevalence of SF amoxicillin).

Table 2. Health and economic burden (in US$) of SF amoxicillin in Africa per one million new cases of pneumonia in children < 5 years old: base case

	Real-world scenario (SF present)	Ideal scenario (No SF present)	Burden due to SF amoxicillin
Health burden			
Cases of severe pneumonia	159,013	150,950	8,063
Cases of very severe pneumonia	63,605	60,380	3,225
Incremental deaths	6,252	5,940	312
Life years lost due to pre-mature deaths	157,970	150,084	7,886
Economic burden			
Healthcare sector costs			
Cost of severe pneumonia (from a healthcare sector perspective)	11,991,851	9,904,073	2,087,778
Cost of very severe pneumonia (from a healthcare sector perspective)	15,727,929	12,989,700	2,738,229

[4] All financial figures are presented in United States dollars.

	Real-world scenario (SF present)	Ideal scenario (No SF present)	Burden due to SF amoxicillin
Total healthcare sector costs	*27,719,780*	*22,893,773*	*4,826,007*
Productivity losses			
Productivity loss due to missed days at work due to severe pneumonia	5,902,566	5,603,264	299,302
Productivity loss due to missed days at work due to very severe pneumonia	3,393,976	3,221,877	172,099
Productivity loss due to premature death	346,113,326	328,834,564	17,278,762
Total productivity loss	*355,409,868*	*337,659,705*	*17,750,163*
Total societal cost (sum of total costs from a healthcare sector perspective and total productivity losses)	**383,129,647**	**360,553,447**	**22,576,170**

Findings for the entire African region

To provide additional context, PQM+ estimated the burden based on the total number of children < 5 years in Africa in 2021, which was estimated to be 199,751,000.[5] Incidence of pneumonia in children < 5 years in Africa is 0.27 per child year (Walker, et al., 2013). The total number of children with pneumonia in Africa per year is estimated to be 53,932,770. Accordingly, the burden of one year's incidence of pneumonia in children < 5 years in Africa due to use of SF amoxicillin is estimated as follows:

Health burden

- 434,865 additional cases of severe pneumonia
- 173,946 additional cases of very severe pneumonia
- 16,833 additional deaths
- 425,327 of life years lost

Economic burden. The additional morbidity and mortality caused by SF amoxicillin results in an economic burden estimated at $1.2 billion per year from a societal perspective, including approximately:

- $260 million in direct costs from the healthcare sector perspective
- $957 million in productivity losses, including:
  - $25 million due to missed days of work
  - $932 million due to premature death (considering the lifetime productivity of the 16,833 additional deaths estimated in the given year)

Estimates for individual African countries Stakeholders in African countries can estimate the burden of use of SF amoxicillin to treat childhood pneumonia in their country in one of two ways:

- **Estimate using African regional values**. Users can simply calculate the percent of one million cases of childhood pneumonia that their country experiences each year (e.g., 500,000 cases of childhood pneumonia each year = 50% of one million cases of childhood pneumonia) and multiply this factor by the results listed above for one million cases.

[5] UNICEF. The State of the World's Children 2021: Statistical tables, Table 1: Demographics.

- **Estimate using country-specific data**. Users can adjust values used in the model for any parameter for which they have country-specific data, as explained in **Annex 2**. Note that users do not need to enter country-specific values for all parameters; they should use the regional value already in the model for any parameter for which they lack country-specific values.

One-Way Sensitivity Analyses

A one-way sensitivity analysis (OWSA) illustrates the impact of each parameter on the outcome of interest. With an OWSA, one explores the range of results estimated for each health and economic outcome using the high and low values for each parameter, one by one (i.e., parameter by parameter for each outcome). OWSA identifies the parameter that has the greatest impact on each outcome. This helps users interpret results. For example, if there is significant uncertainty about the value of a parameter that has a very large impact on the results, users should take this into consideration when interpreting results. Users can consider the range of results for that outcome based on the range of values for the most influential variable (i.e., the variable that has the greatest impact on that outcome).

Table 3 lists the most influential parameter for each outcome and the range of possible results given the high and low values input for the specific parameter. Per one million children treated with amoxicillin for pneumonia, the overall ranges of possible results considering all parameters were as follows:

Health burden

- Additional cases of severe pneumonia: from 3,162 to over 13,000 additional cases
- Additional cases of very severe pneumonia: from 1,265 to about 5,300 additional cases
- Additional deaths: from 122 to 515 deaths
- Life years lost: from 3,092 to over 13,000 life years lost

Economic burden. From $8.9 to $33.8 million in direct costs to the healthcare system and productivity losses

Table 3. Ranges of outcomes by most influential parameter

Most influential parameter	Range of parameter	Outcome	Base case outcome	Outcome from lowest value for parameter	Outcome from highest value for parameter
Probability of severe pneumonia without treatment	0.16 - 0.33	Incremental cases of severe pneumonia	8,063 cases	4,422 cases	13,265 cases
Probability of very severe pneumonia without treatment	0.064 - 0.132	Incremental cases of very severe pneumonia	3,225 cases	1,769 cases	5,306 cases
Probability of death from pneumonia without treatment	0.0062-0.0129	Economic burden	$22,576,170	$14,512,748	$33,807,365
		Life years lost	7,886 years	4,206 years	13,012 years
		Death	312 deaths	166 deaths	515 deaths

Annex 3 includes tornado diagrams representing the OWSA of the parameters that had the largest effects on each of the health and economic outcomes.

Conclusions and Recommendations

PQM+ identified published data sources for key parameters to estimate the burden of SF amoxicillin in Africa for the treatment of childhood pneumonia following WHO treatment guidelines (World Health Organization, 2014). Even conservatively estimated, the burden is considerable and likely leads each year to the following results:

- For one million cases of childhood pneumonia initially treated with amoxicillin
    - 8,063 additional cases of severe pneumonia
    - 3,225 additional cases of very severe pneumonia
    - 312 additional deaths (and life years lost from those)
    - Approximately $22.6 million in economic costs
- Extrapolated to the estimated 54 million cases of childhood pneumonia in Africa each year
    - 434,865 additional cases of severe pneumonia
    - 173,946 additional cases of very severe pneumonia
    - 16,833 additional deaths (and life years lost from those)
    - Approximately $1.2 billion in economic costs

Ranges for the burden per one million cases of childhood pneumonia, based on the high and low values input for each parameter used in the model calculations, are:

- From 3,162 to over 13,000 additional cases of severe pneumonia
- From 1,265 to about 5,300 additional cases of very severe pneumonia
- From 122 to 515 additional deaths (and life years lost from those deaths)
- From $8.9 to $33.8 million in economic costs

The results suggest that the cost of SF amoxicillin to children, societies, and economies in Africa merits further action. These preliminary results should be used as a basis for customization of the model in individual countries. The country-specific results can be used for advocacy efforts to increase initiatives to reduce the prevalence and availability of SF medicines. Examples of these initiatives include:

- Seeking to understand the root cause(s) of SF amoxicillin in a country
- Strengthening the system for registering quality-assured sources of amoxicillin
- Monitoring the quality of amoxicillin in circulation, including through post-marketing surveillance
- Strengthening medical product quality assurance systems at lower levels of the health system and supply chain, including training, licensing, and inspection

- Increasing funding for post-market surveillance (targeted investments for quality assurance)

The model can also be used to track changes over time in the burden of SF amoxicillin. The initial use of the model will provide a baseline of the results. As new or more recent data are made available, the inputs can be updated. The updated outcomes will provide a long-term perspective of the burden of SF amoxicillin.

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Annex 1: Prepopulated model inputs and their data sources used to estimate of the burden of SF amoxicillin in Africa

#	Parameter	Base case	Range	Source reference
Population and health-seeking behavior				
1	Population eligible	per 1,000,000		Model default
2	Percentage of population that seeks care	51%		WHO data portal* (World Health Organization, 2023)
3	Percentage of population that receives care in the public sector	50%		Model default
4	Percentage of population that receives care in the private sector	50%		
5	Percentage of population that receives care in other sectors	0%		
Medicine quality				
6	Proportion of SF medicines 1 in the real-world scenario	10%	0-15%	Zabala, et al. (2022)
7	Proportion of SF medicines 3 in the real-world scenario	6%	0-8%	
8	Proportion of standard quality medicines in the real-world scenario	84%	77-100%	
SF medicines treatment effect				
9	Treatment effect of SF medicines 1 (API: 75-90%)	60%		Model assumption
10	Treatment effect of SF medicines 2 (API: 50-74%)	30%		
11	Treatment effect of SF medicines 3 (API <50%)	0%		
12	Treatment effect of standard quality medicines (API: 90-110%)	100%		
Health outcomes				
13	Lifetime probability of condition-related death with treatment	0.003	0.0016-0.0059	Addo-Yobo, et al. (2011)*; Ginsberg, et al. (2019)*; Ginsberg, et al. (2020)*;

				King, et al. (2015)*; Nair, et al. (2013)*
14	Lifetime probability of condition-related death without treatment	0.009	0.0062-0.0129	Nair, et al. (2013)*; Rudan, et al. (2013)
15	Probability of severe pneumonia with treatment	0.075	0.04-0.15	Addo-Yobo, et al. (2011)*; Ginsberg, et al. (2019)*; Ginsberg, et al. (2020)*; King, et al. (2015)*
16	Probability of severe pneumonia without treatment	0.23	0.16-0.33	Rudan, et al. (2013)
17	Probability of very severe pneumonia with treatment	0.030	0.016-0.06	Addo-Yobo, et al. (2011)*; Ginsberg, et al. (2019)*; Ginsberg, et al. (2020)*; King, et al. (2015)*; Nair, et al. (2013)*
18	Probability of very severe pneumonia without treatment	0.092	0.064-0.132	Nair, et al. (2013)*; Rudan, et al. (2013)
19	Number of sick days due to severe pneumonia with treatment	6.4	4.1-7.1	Zhang, et al. (2016)
20	Number of sick days due to severe pneumonia without treatment	6.4	4.1-7.1	Zhang, et al. (2016)
21	Number of sick days due to very severe pneumonia with treatment	9.2	6.1-12.6	Zhang, et al. (2016)
22	Number of sick days due to very severe pneumonia without treatment	9.2	6.1-12.6	Zhang, et al. (2016)
Costs				
23	Average unit cost of severe pneumonia management	$258.93	$95.23-$963.88	Adamu, et al. (2022); Batura, et al. (2022)*; de Broucker, et al. (2020)*; Ekirapa-Kiracho, et al., (2021)*; Zhang, et al. (2016)*
24	Average unit cost of very severe pneumonia management	$849.00		Zhang, et al. (2016)*
25	Median daily wage rate	$5.80	$0.66-$20.63	Average of African country estimates* (WorldData.info, 2022)

Productivity loss				
26	Life expectancy at birth	64.49		WHO 2019 estimates for Africa* (World Health Organization, n.d.)
27	Gross domestic product per capita (US$ GDPPC)	$2296.00	$259.00-$8820.00	Average of African country 2022 estimates* (The World Bank, n.d.)
28	Per capita total expenditure on health	$105		WHO 2012 estimates for African Region* (World Health Organization, 2015)
29	Minimum age for employment	15		International Labour Organization (ILO) convention legal minimum age (Ales, Bell, Deinert, & Robin-Oliver, 2018)
30	Discount rate	3%		Kirigia, Muthuri, Nabyonga-Orem, & Kirigia (2015)

* Sources with Africa-specific data. All other sources provide data generalized to LMICs or are a model assumption.

Annex 2: Description of model template inputs to aid in the adaptation for individual countries

This section describes the data inputs used in estimating the burden of SF amoxicillin to treat childhood pneumonia in the Africa region. It provides information on sources and describes how decisions about values for some parameters were made. These explanations can help future users consider their data and decide what values to use.

In estimating the burden of SF amoxicillin to treat childhood pneumonia in Africa, PQM+ created a prepopulated model template file (an Excel spreadsheet that accompanies this report). When available, African regional values were used in the prepopulated model; otherwise, values are specific for LMICs. The prepopulated model template can be used as the basis for country-specific estimates. To generate these estimates, users should replace values already entered into the prepopulated model file with new values specific to the country of interest.

Note that Africa regional or LMIC values were either not available or too variable for some optional parameters (e.g., proportion of patients who seek care in different health system levels) so they were left blank in the prepopulated model. If there are country-specific values for any of these optional parameters, they should be entered when developing country-specific estimates.

Note that this annex refers to the Excel file associated with the SF amoxicillin burden model. Input numbers described in this annex correspond to column D in the "Model Input" worksheet of the prepopulated Excel file.

Population and health-seeking behavior inputs

Input 1: Population eligible (mandatory)

For the model template, this input was left blank and defaulted to estimates per one million children < 5 years old with a new case of pneumonia.

When adapting for a specific country, users should enter the total number of children <5 with new cases of pneumonia in the year and country of interest. This can be estimated by multiplying the incidence rate of pneumonia by the total number of children <5.

$$Eligible\ population\ in\ year\ X\ =\ total\ number\ of\ children < 5\ in\ year\ X\ x\ incidence\ rate$$

Total number of children <5

This information is often available from local health agencies but can also be found at WHO's Maternal, Newborn, Child and Adolescent Health and Ageing Data Portal (World Health Organization, n.d.). The population of children <5 can be filtered by country, year, and sex.

Incidence rates

PQM+ has identified multiple sources that provide incidence rates of pneumonia in children <5.

1. Rudan, et al. (2013) utilizes a model to provide estimates of incidence rates of pneumonia by country in 2010-2011 (see Table 1 in Rudan, et al. [2013] to calculate country-specific estimates). Rudan, et al. also estimates an incidence rate in LMICs of 0.22 (interquartile range of 0.11-0.51) episodes per child per year.

2. Walker, et al. (2013) provides estimates of pneumonia in 2010-2011 by region and globally.

Table 1. Incidence of pneumonia (Walker, et al., 2013)

Region	Incidence of pneumonia	
	Base	Range
African Region	0.27	0.14-0.63
Eastern Mediterranean Region	0.23	0.11-0.53
Southeast Asian Region	0.26	0.13-0.61
Western Pacific Region	0.11	0.05-0.24
World	0.19	0.10-0.44

How to modify the input: The prepopulated model template uses the default value of 1,000,000. Therefore, all estimated values are per 1,000,000 eligible people (in this case, children with pneumonia). To adapt for a specific country, this input should be calculated using the equation above with the country's population < 5 years old and the relevant incidence rate for pneumonia.

Inputs 2-5: Care-seeking behavior

- Input 2: Percentage of population that seeks care (mandatory)
- Input 3: Percentage of population that seeks care in the public sector (optional)
- Input 4: Percentage of population that seeks care in the private sector (optional)
- Input 5: Percentage of population that seeks care in other (e.g, faith-based sector) (optional)

Input 2, the percentage of the population that seeks care, is a mandatory input. The model assumes 100% of the population seeks care if no user-defined data is added to the model inputs. WHO reports the care-seeking behavior for children with symptoms of acute respiratory infection by region, country, and year (World Health Organization, 2023).

How to modify the input: The prepopulated model template uses 51%, which is the average of the most recent data reported for each country in the Africa region (note that not all countries have reported data). Country specific data should be entered either from this source or other appropriate sources.

Inputs 3-5 are optional and further categorize input 2 by breaking down where care is received. If values are available for quality of medicine, costs of medicine, and treatment costs in different sectors, percentages of population that seek care in these sectors influence medicine quality and cost estimates. If the quality of medicine, cost of medicine, and treatment costs differ in different sectors, then one should include data on percentage of the population that seeks care in the various sectors to refine the estimates of burden.

How to modify the inputs: Values for these inputs were not included in the prepopulated model template. If country-specific values are available, these inputs can be included.

Inputs 6-10: Proportion of care sites by type and sector (optional)

- Input 6: Proportion of hospitals in public sector
- Input 7: Proportion of public health centers in public sector
- Input 8: Proportion of hospitals in private sector
- Input 9: Proportion of private pharmacies in private sector
- Input 10: Proportion of "other locations" in private sector

This should be data for the proportion of hospitals, public health centers, and other locations in the private and public sectors. These are optional.

How to modify the inputs: Values for these inputs were not included in the prepopulated model template. If country-specific values are available, these inputs can be included.

Medicine quality inputs

Inputs 11-14: Proportion of quality medicines vs SF medicines

- Input 11: Proportion of SF medicines 1 (API: 75-89%) in real-world scenario
- Input 12: Proportion of SF medicines 2 (API: 50-74%) in real-world scenario
- Input 13: Proportion of SF medicines 3 (API <50%) in real-world scenario
- Input 14: Proportion of standard quality medicines (API: 90-110%) in real-world scenario (mandatory)

Inputs 11-14 are the proportion of medicines classified as standard quality or SF. The SF medicines are further divided into three classifications based on API content as established by the model. Input 14 and at least one of the inputs related to SF medicine quality (inputs 11-13) are mandatory.

The prepopulated template model utilized the global estimates from Zabala, et al. (2022), which is an extensive review that included a total of 2,208 amoxicillin samples collected between 1992 and 2020. The study estimated that 16% of amoxicillin is SF in developing countries, which is generally in line with studies in LMICs with larger sample sizes. A subset of the sampled products was tested for API content. Based on these results, we estimate that 10% of products have a content between 75-89% (input 11) and 6% of products have a content < 50% (input 13). The ranges for inputs 11 and 13 are 0-15% and 0-8%, respectively. The base value for input 14 (standard quality) is 84%, with a range of 77-100%. It should be emphasized that this is more reflective of rates in developing countries versus a global estimate that would include rates for more advanced economies. While 16% is higher than averages for SF medicines in general, there are several reports indicating higher rates of SF antibiotics (see Table 2).

How to modify the inputs: The model template includes the estimates discussed above. This data can be replaced with country-specific values if deemed to be reliable and more reflective of SF rates in the specific context. Please note that if rates of medicine quality are derived from risk-based post-marketing surveillance (RB-PMS) results, those results likely exceed the national rate of SF medicines since RB-PMS intentionally focuses on higher-risk locations and facilities.

Additional sources for SF rates of amoxicillin that were identified are listed in Table 2. Note that studies with fewer than 10 samples were excluded from the list.

Table 2. Results of reports on SF amoxicillin

Country/ region	**Input 11.** SF 1 (%)	**Input 12.** SF 2 (%)	**Input 13.** SF 3 (%)	**Input 14.** standard (%)	**Number of samples**	**Year of sample**	**Additional notes**	**Source**
New Guinea	15			85	190	2018-2019	There is likely overlap in the identity (i.e., product, lot, or batch) of the samples.	Robertson, Hehonah, Mayaune, & Glass (2021)
Cameroon, Chad, Madagascar	8.7		8.7	82.6	23	1995		WHO Action Program on Essential Drugs (1995)
Myanmar, Vietnam	11	3		86	65	1999	This is a conservative estimate as the API ranges reported in this study differ slightly from the model-defined ranges of API amounts.	World Health Organization (1999)
Global	50		8	42	24	2015	This is a conservative estimate as the percent API in the SF products was not reported.	Baratta, Germano, & Brusa (2012)
Indonesia	20			80	20	2006		Hadi, et al. (2010)
Arab Countries	32	3		65	31	2006	18 capsule brands, 4 packs each; 13 suspension brands, 3 samples each; 2006 is an estimate based on a March 2007 submission date.	Kyriacos, Mroueh, Chahine, & Khouzam (2008)
Nigeria	27			73	37	2000	32 capsules, 5 dry syrup	Taylor, et al. (2001)
AVERAGE	**23.4**	**3**	**8.4**	**73.4**				

Note that the values used in the model prepopulated for Africa are more conservative than the above averages (which include results from many regions). Specifically, the Africa model uses 10% for Input 11 (SF1 quality) and 84% for Input 14 (standard quality) versus 23% and 73%, respectively, for these global averages.

Input 15: Proportion of SF medicines adulterated (optional)

Input 15 specifies the proportion of SF medicines that are adulterated. PQM+ did not identify reports of adulteration of amoxicillin products.

How to modify the input: Values for this optional input were not included in the prepopulated model template. If a country-specific value is available, then this input can be included.

Increasing dosing to achieve full effect

Inputs 16-19: Up-dosing behaviors (optional)

- Input 16: Proportion of healthcare providers who increase dose to achieve full effect
- Input 17: Total number of doses after up-dosing for SF medicines 1
- Input 18: Total number of doses after up-dosing for SF medicines 2
- Input 19: Total number of doses after up-dosing for SF medicines 3

In some environments, if healthcare providers do not expect the medicine to be of adequate quality or if they observe that the standard dose is not efficacious, they "up-dose," or prescribe additional doses to achieve efficacy. This indicates healthcare provider concern about medicine quality. These inputs affect the treatment cost calculations in the model.

Input 16 is the proportion of healthcare providers that increase the dose to achieve full effect, and inputs 17-19 specify the increase in doses needed to achieve a full effect based on the API content. PQM+ did not identify reports of dose adjustments of amoxicillin to achieve full effect in response to known issues with amoxicillin quality.

How to modify the inputs: Values for these inputs were not included in the prepopulated model template. If country-specific values are available, these inputs can be included.

Substandard and falsified medicines treatment effect

Inputs 20-23: SF medicines treatment effect (mandatory)

- Input 20: Treatment effect of SF medicines 1 (60%)
- Input 21: Treatment effect of SF medicines 2 (30%)
- Input 22: Treatment effect of SF medicines 3 (0%)
- Input 23: Treatment effect of standard quality medicines 1 (100%)

Inputs 20-23 relate to expected efficacy of standard quality medicines and the three tiers of SF medicines established by the model. The model assumes the relationship between the percent of API in an SF medicine and the medicine's efficacy. Values for these inputs drive calculations of decrements in treatment outcomes.

How to modify the inputs: The standard assumptions were used for the template model. Users might need to adjust the standard assumptions if they change the API ranges for the different medicine quality tiers for inputs 11-14 or if the relationship between the specific medicine efficacy and amount of API differs from the model assumption.

Health outcomes

Inputs 24 – 39 are health outcomes that are impacted by the quality of the medicine used for treatment. For all health outcomes, "with treatment" means the patient received standard quality medicine and care (i.e., first-line treatment with standard quality amoxicillin). "Without treatment" means the patient received no initial medicine or care. The decrements in health outcomes

deriving from use of SF medicine/inadequate API are calculated for any health outcomes defined in the model. Thus,

- The health outcome of using standard quality medicine = the health outcome with treatment.
- The health outcome of using SF medicine 1 (API: 75-89%) is 60% of the health outcome with treatment.
- The health outcome of using SF medicine 2 (PI: 50-74%) is 30% of the health outcome with treatment.
- The health outcome of using SF medicine 3 (API < 50%) = the health outcome without treatment.

Inputs 24-31: General health outcomes (optional)

- Input 24: Life year outcome with treatment
- Input 25: Life year outcome without treatment
- Input 26: QALY outcome with treatment
- Input 27: QALY outcome without treatment
- Input 28: DALY outcome with treatment
- Input 29: DALY outcome without treatment
- Input 30: Lifetime probability of condition-related death with treatment
- Input 31: Lifetime probability of condition-related death without treatment

Inputs 24-29 are the expected life year, QALY, and DALY outcomes with and without treatment.

How to modify the inputs: These values were not included in the prepopulated template model. If country-specific values are identified, these inputs can be included.

Inputs 30-31 are the lifetime mortality estimates of pneumonia with and without amoxicillin treatment.

Determining the case fatality rate (CFR) of pneumonia with amoxicillin treatment is complicated by the fact that treatment is adjusted if a patient is not responsive to amoxicillin. Ideally, this value would be based on controlled studies that examine odds of survival with or without amoxicillin treatment only. However, those trials are unethical and do not reflect standard care. For this reason, CFRs for pneumonia with amoxicillin treatment only are not available (input 30). To determine this value, an alternative approach was used as described below.

It should be noted that there is limited data available for the overall CFR of pneumonia. However, these estimates do not differentiate between whether patients received treatment or not. Rudan, et al. (2013) provides estimates of the CFR for pneumonia by country and Walker, et al. (2013) provides estimates by region. Table 3 provides the CFR rates calculated with the regional estimates reported in Walker, et al. (2013).

Table 3. CFR of pneumonia (Walker, et al., 2013)

Region	CFR estimate for pneumonia	
	Base	Range
African Region	0.015	0.012-0.017
Eastern Mediterranean Region	0.010	0.009-0.013
Southeast Asian Region	0.009	0.007-0.011
World	0.010	0.009-0.012

Alternative Approach

As noted above, an alternative approach for calculating the CFR of pneumonia with or without treatment was developed. While reports for the CFR of pneumonia are limited, there are more reliable estimates for the CFR of severe pneumonia, and it is reasonable to assume that a case of pneumonia first progresses to severe pneumonia prior to resulting in death. Therefore, the alternative approach multiplies the odds of progression to severe pneumonia with and without amoxicillin treatment (see inputs 32 and 33) by the CFR of severe pneumonia, which can be calculated as follows:

$$CFR\ of\ severe\ pneumonia = (CFR\ with\ hospital\ treatment\ x\ \%\ of\ population\ that\ seeks\ care) + (CFR\ without\ hospital\ treatment\ x\ \%\ of\ population\ that\ does\ not\ seek\ care)$$

Nair, et al. (2013) provides an estimate of the CFR of severe pneumonia with and without hospital treatment. Because care-seeking behavior of patients with severe pneumonia is variable by country and region, the prepopulated model only considers the CFR of severe pneumonia with hospital treatment. This approach assumes that 100% of patients that progress to severe pneumonia will seek additional treatment, which is a conservative estimate.

For input 30, the data for input 32 (odds of progression to severe pneumonia with treatment) should be multiplied by the CFR of severe pneumonia calculated with data reported in Nair, et al. (2013). This study reviewed global data and utilized relevant data to estimate CFRs of children admitted to a hospital with severe pneumonia by region. The values in Table 4 are calculated from the data reported in Table 2 of Nair, et al. (2013).

Table 4. CFR of severe pneumonia with hospital treatment (Nair, et al., 2013)

Region	CFR probability
African Region	0.039
Americas	0.013
Eastern Mediterranean Region	0.076
SE Asia Region	0.021
Western Pacific Region	0.023
Developing	0.023
Global	0.021

How to modify the input: The template model data was calculated using the Africa specific data: the base rate and range of input 32 multiplied by 0.039. If the data for input 32 is replaced, the corresponding data for input 34 should also be replaced.

For input 31, the alternative approach described above provided a more conservative estimate of the CFR of pneumonia without amoxicillin treatment compared to the data provided by Walker, et al. (2013) and was therefore used in the prepopulated model. To calculate the value for input 31, the data for input 33 (odds of progression to severe pneumonia without treatment) should be multiplied by the CFR of severe pneumonia calculated with data reported in Nair, et al. (2013).

How to modify the input: The template model data was calculated using the Africa specific data: base rate and range of input 33 multiplied by 0.039. If the data for input 33 is replaced, the corresponding data for input 31 should also be replaced.

Additional Data

PQM+ has also identified data that provides the CFR of severe pneumonia with amoxicillin treatment that considers both community-based care and hospital treatment (Fox, et al., 2012). The CFR of severe pneumonia with and without amoxicillin treatment could be used in the model to estimate the increased burden of deaths due to SF amoxicillin. This would be applicable in a country that utilizes amoxicillin as a common or first-line treatment for severe pneumonia, and the model could be adjusted to provide estimates specific to amoxicillin for treatment of severe pneumonia

Inputs 32-39: Specific health outcomes (optional)

- Input 32: Probability of severe pneumonia with treatment
- Input 33: Probability of severe pneumonia without treatment
- Input 34: Probability of very severe pneumonia with treatment
- Input 35: Probability of very severe pneumonia without treatment
- Input 36: Probability of other health outcome with treatment
- Input 37: Probability of other health outcome without treatment
- Input 38: Probability of other health outcome with treatment
- Input 39: Probability of other health outcome without treatment

The SF medicine burden model was developed to be used with any medicine for any disease. Each disease will have its own disease-specific health outcomes. The model allows users to enter values for health outcomes with and without treatment for up to four health outcomes. In the case of childhood pneumonia, the template model includes two health outcomes: severe pneumonia and very severe pneumonia.

Probability of severe pneumonia

Probability of severe pneumonia with treatment was based on reported treatment failure rates for amoxicillin. Table 5 provides data identified for the African region.

Table 5. Treatment failure rates of amoxicillin in Africa

Country	Failure rate	Year of study	Source

Egypt	8.6%	2005-2008	Addo-Yobo, et al., 2011
Ghana	6.4%		
Malawi (chest-indrawing)	5.9% (3-day treatment)	2016-2019	Ginsberg, et al., 2020
	5.2% (5-day treatment)		
Malawi (fast breathing)	4%	2016-2017	Ginsberg, et al., 2019
Malawi	15%	2013-2014	King, et al., 2015

A user should try to identify recent clinical reports studying amoxicillin efficacy in the country of interest. However, the model template inputs may be used if country-specific data cannot be identified.

How to modify the input: The base rate included in the model template (7.5%) is the average of the studies listed in Table 5, with the highest and lowest reported values used as the range (4-15%). Country-specific rates can replace these values if available.

We could not find data on the probability of severe pneumonia without any treatment. Instead, the value used for input 33 (probability of severe pneumonia without treatment) was estimated based on the odds of progression to severe pneumonia reported in Rudan, et al. (2013) which was estimated to be 11.5% (interquartile range of 8-33%) in LMICs. This is the odds of progression from pneumonia to severe pneumonia in all cases, including cases where the patient received care. To reflect the odds of progression without treatment more accurately, the base rate (11.5%) and the low estimate (8%) were doubled. The high estimate was not adjusted as it was assumed to be more reflective of countries with lower care-seeking behavior and therefore includes a higher portion of cases where treatment was not received.

How to modify the input: The overall estimates of progression to severe pneumonia for LMICs reported by Rudan, et al. (2013) are included in the model template with the base value and low estimates doubled and the high estimate unadjusted. Rudan, et al. (2013) also includes estimates for progression to severe pneumonia for 192 individual countries. Country-specific values can be adjusted as described above if appropriate and can replace the base value included in the prepopulated model, where relevant.

Probability of very severe pneumonia

The data used for inputs 34 and 35 are calculated based on the odds of progression from pneumonia to severe pneumonia (with and without amoxicillin treatment) multiplied by the odds of progression from severe pneumonia to very severe pneumonia. If a user has data to support care-seeking behavior for children with severe pneumonia, the odds of progression to very severe pneumonia can be calculated as follows:

$$Odds\ of\ progression\ to\ very\ severe\ pneumonia =$$
$$(odds\ of\ progression\ \boldsymbol{with}\ hospital\ treatment\ x\ \%\ of\ population\ that\ \boldsymbol{seeks\ care})$$
$$+\ (odds\ of\ progression\ \boldsymbol{without}\ hospital\ treatment\ x\ \%\ of\ population\ that\ \boldsymbol{does\ not\ seek\ care})$$

As already noted, care-seeking behavior of patients with severe pneumonia is variable by country and region. Therefore, the prepopulated model only considers odds of progression to very severe pneumonia with hospital treatment. This approach follows the WHO treatment

guideline and assumes that 100% of patients that progress to severe pneumonia will seek additional treatment, which is a conservative estimate.

For input 34, the data for input 32 (probability of severe pneumonia with treatment) should be multiplied by odds of progression from severe pneumonia to very severe pneumonia based on data reported in Nair, et al. (2013). This study reviewed global data to determine rates of severe pneumonia and very severe pneumonia by region. It estimates the incidence and number of episodes of severe pneumonia and very severe pneumonia in hospitals in 2010 based on studies conducted in the specific region. The values in Table 6 are calculated from the data reported in Table 1 of Nair, et al. (2013) by dividing the incidence rate of very severe pneumonia by the combined incidence rates of severe pneumonia and very severe pneumonia.

Table 6. Odds of progression from severe pneumonia to very severe pneumonia with treatment (Nair, et al., 2013)

Region	Progression probability
African Region	0.40
Americas	0.13
Eastern Mediterranean Region	Not available
Southeast Asia Region	0.17
Western Pacific Region	0.27
Developing Countries	0.21

How to modify the input: The model template data was calculated using the Africa specific data: the base rate and range of input 32 (probability of severe pneumonia with treatment) multiplied by 0.40. If the value for input 32 is replaced, the corresponding value for input 34 should also be replaced.

For input 35 (probability of very severe pneumonia without treatment), the data for input 33 (probability of severe pneumonia without treatment) should be multiplied by odds of progression from severe pneumonia to very severe pneumonia based on data reported in Nair, et al. (2013), Table 6.

How to modify the input: The model template data was calculated using the Africa specific data: the base rate and range of input 33 (probability of severe pneumonia without treatment) multiplied by 0.40. If the value for input 33 is replaced, the corresponding value for input 35 should also be replaced.

Inputs 40-47: Productivity loss (optional)

- Input 40: Number of sick days due to severe pneumonia with treatment
- Input 41: Number of sick days due to severe pneumonia without treatment
- Input 42: Number of sick days due to very severe pneumonia with treatment
- Input 43: Number of sick days due to very severe pneumonia without treatment
- Input 44: Number of sick days due to custom health outcome 3 with treatment
- Input 45: Number of sick days due to custom health outcome 3 without treatment
- Input 46: Number of sick days due to custom health outcome 4 with treatment

- Input 47: Number of sick days due to custom health outcome 4 without treatment

The model allows users to input the number of sick days associated with each health outcome. In the case of childhood pneumonia, these values would inform the calculation of productivity losses for the caretaker who cares for the hospitalized child.

Inputs 40-47 are the expected number of sick days associated with progression of disease. Zhang, et al. (2016) conducted a comprehensive review of pneumonia treatment and reports the median length of hospital stay in LMICs as 6.4 days (interquartile range of 4.1-7.1) for severe pneumonia and 9.2 days (interquartile range 6.1-12.6) for very severe pneumonia.

How to modify the inputs: The model template includes the median treatment days reported for LMICs in general (Zhang, et al., 2016). If country-specific values are identified, the model template inputs may be replaced.

Inputs 48-55: Health decrements due to adulterated medicines (optional)

- Input 48: Health decrement in life years due to adulterated medicine
- Input 49: Health decrement in QALYs due to adulterated medicine
- Input 50: Health decrement in DALYs due to adulterated medicine
- Input 51: Health decrement in lifetime probability of condition-related death due to adulterated medicine
- Input 52: Health decrement in severe pneumonia due to adulterated medicine
- Input 53: Health decrement in very severe pneumonia due to adulterated medicine
- Input 54: Health decrement in custom health outcome 3 due to adulterated medicine
- Input 55: Health decrement in custom health outcome 4 due to adulterated medicine

Inputs 48-55 involve decrements in life year, QALY, DALY, mortality, and specific health outcomes due to adulterated medicine. PQM+ did not identify reports of use of adulterated amoxicillin or of health decrements due to use of adulterated amoxicillin products.

How to modify the inputs: These values were not included in the model templates. If country-specific values are identified, these inputs can be included.

Costs

Inputs 56-60: Costs associated with treatment

- Input 56: Average drug cost per dose
- Input 57: Average unit cost of severe pneumonia management
- Input 58: Average unit cost of very severe pneumonia management
- Input 59: Average unit cost of custom health outcome 3 management
- Input 60: Average unit cost of custom health outcome 4 management

Input 56 is the cost per dose of amoxicillin in the country. The dose of amoxicillin is not reported to be increased in response to SF rates. Therefore, adding data for the cost per dose does not

impact the model. The model only considers additional costs from up-dosing and does not consider wasted resources associated with procuring SF medicines.

How to modify the input: These data were not included in the model templates. If country-specific data is identified, these inputs can be included. However, there will not be a change in the model output unless increased dosing in response to SF amoxicillin is added to the model via inputs 16-19.

Inputs 57-60 are the costs of managing specific health outcomes.

Severe pneumonia

The cost per episode of severe pneumonia was reported by Zhang, et al. (2016) for LMICs. For the Africa region, the average inpatient cost of care was $470.73 ($89.50-$1553.20; n=10) for severe pneumonia, including data from Guinea, Kenya, South Africa, and Zambia. Additional studies were identified that determined costs associated with pneumonia treatment in general but did not specify severity. However, distinctions were made between outpatient care and hospitalization. Therefore, costs for hospitalized treatment were assumed to be reflective of costs associated with treatment of severe pneumonia. The data reported in these sources were averaged based on country classification (low-income, lower-middle income, or upper-middle income countries[6])(see Table 7).

Table 7. Costs of severe pneumonia by country classification

Country Classification	Average (n)	Range	Country (source)
Low-income	$95.23 (8)	$5.9 - $236.8	Gambia (de Broucker, et al., 2020)
			Guinea and Kenya* (Zhang, et al., 2016)
			Mozambique and Uganda (Batura, et al., 2022)
			Uganda (Ekirapa-Kiracho, et al., 2021)
Lower-middle income	$258.93 (4)	$249.7 - $285.60	Kenya* and Zambia (de Broucker, et al., 2020)
			Nigeria (Adamu, et al., 2022)
			Zambia (Zhang, et al., 2016)
Upper-middle income	$963.88 (6)	$110.00 - $1924.66	South Africa (Zhang, et al., 2016; de Broucker, et al., 2020)

*Kenya was classified as low-income until 2014 and lower-middle income from 2014 until present.

How to modify the inputs: The prepopulated model template has included the averages listed in Table 7. The base value used was the average cost of severe pneumonia treatment for lower-middle income countries in Africa. The low and high range values were the average costs for low-income countries and upper-middle income countries, respectively. Country-specific values should be obtained and included in the model if possible.

Very severe pneumonia

[6] World Bank. Country Classification (based on gross national income). https://datahelpdesk.worldbank.org/knowledgebase/topics/19280-country-classification. Classification was determined based on the specific year associated with the cost estimate.

Zhang, et al. (2016) also reported the inpatient cost of care for very severe pneumonia (average: $7,446.87; range: $849.00-$14,795.40, n=3). However, all the estimates are from South Africa, which is categorized as an upper-middle income country. No additional estimates specific to costs of very severe pneumonia treatment in Africa were identified. Because the average costs reported in Zhang, et al. (2016) are not a reasonable estimate of average costs across African countries, the lowest value reported was used for the model, though this may still be an overestimate of average costs observed in Africa.

How to modify the inputs: The prepopulated model template has included the lowest cost reported by Zhang, et al. (2016) as the base value ($849). Country-specific values should be obtained and included in the model if possible.

Input 61: Median daily wage rate (required)

Input 61 is the estimated median daily wage rate. This is used to calculate the cost of productivity losses. Various sources provide estimates for daily or monthly wage rates, including WorldData.info (2022).

How to modify the input: The model template used the average of the available data from countries in the Africa region from the source noted above (average of $5.80 per day with a range of $0.66-$20.63). The data source above can be used for country-specific data or other reliable data may be used.

Detailed data

Inputs 62–148: Medicine quality per treatment location, portions of adulterated medicines, costs per treatment location, and up-dosing behavior per treatment location (optional)

Inputs 62-148 may be used if values for the above inputs are available for specific treatment locations (e.g., public hospital, private hospital). These more granular data improve the accuracy of the estimate but are not required.

How to modify the inputs: Values for specific treatment locations were not available and were not included in the prepopulated model template. If country-specific values are identified, these inputs can be included.

Mortality cost calculation

Inputs 149–153: Inputs associated with mortality (required)

- Input 149: Life expectancy at birth
- Input 150: Gross domestic product per capita (current US$ GDPPC)
- Input 151: Per capital total expenditure on health
- Input 152: Minimum age for employment
- Input 153: Discount rate

These inputs support estimation of the economic cost of mortality. The calculation for life years and productivity lost due to premature death is based on the estimate described in Kirigia,

Muthuri, Nabyonga-Orem, & Kirigia (2015). Productivity loss due to premature deaths is calculated with the following equation:

$$NHGDPLoss_{\square} = \sum_{t=1}^{n} [1-(1-r)^t]\ x\ [NHGDPPCUS\$] x\ [total\ child\ deaths]$$

The number of life years lost due to premature deaths is calculated with the following equation:

$$Life\ years\ lost_{\square} = \sum_{t=1}^{n} [1-(1-r)^t]\ x\ [total\ child\ deaths]$$

In these equations, n represents the number of productive years remaining after an individual's death and is calculated using life expectancy at birth (input 149), average age at death (the model used 2.5 years), and minimum age for employment (input 152) with the following equation

$$n = [life\ expectancy\ at\ birth - average\ age\ at\ death - (age\ of\ employment - 1)]$$

The first term in each equation $(1-(1-r)^t)$ is the discount factor where r is the discount rate (input 153).

The second term in the first equation (NHGDPPCUS$) is the per-capita non-health gross domestic product in US dollars and is calculated by subtracting per capital total expenditure on health (input 151) from GDPPC (input 150).

The total number of child deaths is calculated by the model.

The data sources for these calculations (inputs 149-153) are described below.

Input 149 is the life expectancy at birth. The Global Health Observatory (World Health Organization, n.d.) provides estimated life expectancies that can be sorted by region, country, year, and sex. Table 8 lists the life expectancy at birth sorted by region for the year 2019.

Table 8. Life expectancy at birth (WHO, n.d.)

Life expectancy at birth in years (2019 estimates)	
WHO Global	73.31
Africa	64.49
Americas	77.16
Southeast Asia	71.44
Europe	78.24
Eastern Mediterranean	69.74
Western Pacific	77.66

How to modify the input: The model template used the estimate for Africa. The data source above can be used for country-specific values, or other reliable values available may be used.

Input 150 is the gross domestic product per capita in US$. The values by region and country are available from the World Bank (The World Bank, n.d.). Table 9 lists the GDPPC in current US$ by region for the year 2022, which is the most recent data reported.

Table 9. Gross domestic product per capita (The World Bank, n.d.)

Region	GDPPC (US$)
Sub-Saharan Africa (excluding high income)	1,689
Sub-Saharan Africa	1,690
Middle East & North Africa	8,949
Middle East & North Africa (excluding high income)	3,952
East Asia & Pacific (excluding high income)	9,952
East Asia & Pacific	21,907
South Asia	2,273
Europe & Central Asia (excluding high income)	10,377
Europe & Central Asia	27,364
Latin America & Caribbean (excluding high income)	8,885
Latin America & Caribbean	9,475
Least developed countries: UN classification	1,259
Low-income	741
Lower-middle income	2,542
Low & middle income	5,793
Middle income	6,388

How to modify the input: The model template used the average GDPPC for all countries (if available, excluding Mauritius and Seychelles) in Africa (average: $2296, range: $259-8820), which is in line with estimates for lower middle-income countries and sub-Saharan Africa. The data source above can be used for country-specific values, or other reliable values available may be used.

Input 151 is the per capita total expenditure on health (PCTHE). WHO's World Health Statistics Report (World Health Organization, 2015) provided the 2012 per total expenditure on health in US$ using the average exchange rate. The data by region is provided in Table 10.

Table 10. Per capita total expenditure on health (WHO, 2015)

Region	PCTHE (US$ 2012)
African Region	105
Americas	3,599

Southeast Asia Region	68
European Region	2,270
Eastern Mediterranean Region	245
Western Pacific Region	730

How to modify the input: The model template used the per capital total expenditure on health for the African region. The data source above can be used for country-specific values, or other reliable values available may be used.

Input 152 is the minimum age for employment. As cited in Kirigia, Muthuri, Nabyonga-Orem, & Kirigia (2015), according to Article 2 of the International Labour Organization (ILO) convention, the legal minimum age for employment is 15 years old (Ales, Bell, Deinert, & Robin-Oliver, 2018).

How to modify the input: The model template used a minimum age of employment of 15 years old. If the legal minimum age for employment is different in the specific country or a more appropriate age is identified for the specific country or region, this data input can be updated.

Input 153 is the discount rate which is used to calculate the discount factor applied to the GDPPC losses of different years. Kirigia, Muthuri, Nabyonga-Orem, & Kirigia (2015) used a discount rate of 3%.

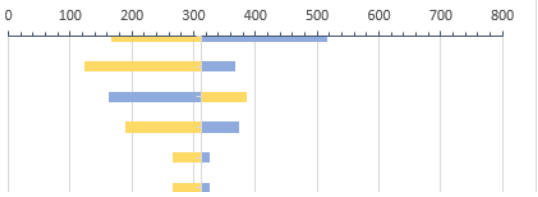
How to modify the input: The model template used a discount rate of 3%. If an alternate discount rate is identified, it can be used.

Annex 3: OWSA tornado diagrams of the parameters with the largest effects on health and economic outcomes

Figures 1-5 provide tornado diagrams that show which parameters have the greatest impact on the outcome of interest. Outcomes of interest are the health outcomes and the economic burden (i.e., incremental costs). The width of the bars in the tornado diagram demonstrates this—the widest bars demonstrate the greatest impact. These figures also depict the impact of the range of values for those parameters on the outcome of interest. The color of the bar identifies if the value was calculated using the lowest value in the range (yellow bar) or the highest value in the range (blue bar). As an example, Figure 1 demonstrates the following:

- The parameter that has the greatest impact on incremental deaths associated with use of SF amoxicillin is the lifetime probability of death from pneumonia without treatment.
- At the lowest value in the range used for lifetime probability of death from pneumonia without treatment (i.e., 0.0062), the incremental number of deaths is 166. The yellow bar in the tornado diagram shows the difference between the number of incremental deaths calculated with the base input (i.e., 312) versus the number of incremental deaths calculated with the lowest value in the range.
- At the highest value in the range used for lifetime probability of death from pneumonia without treatment (i.e., 0.0129), the incremental number of deaths is 515. The blue bar in the tornado diagram shows the difference between the number of incremental deaths calculated with the base input (i.e., 312) versus the number of incremental deaths calculated with the highest value in the range.

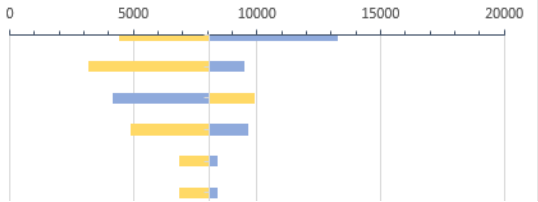
Figure 1. OWSA – Impact of parameter ranges on incremental deaths



Parameter
Lifetime probability of condition-related death without treatment
Proportion of Substandard and Falsified Medicines 3 in the Real-world Scenario
Lifetime probability of condition-related death with treatment
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Proportion of Substandard and Falsified Medicines 3 at Public Hospitals in the Real-world Scenario
Proportion of Substandard and Falsified Medicines 3 at Public Health Centers in the Real-world Scenario

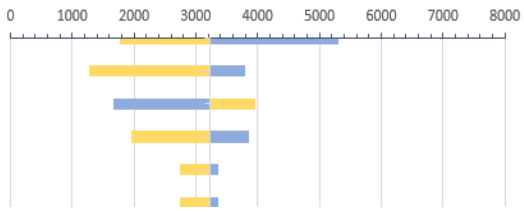
Tornado diagrams for impact of parameter ranges on incremental cases of severe pneumonia, incremental cases of very severe pneumonia, incremental life years lost, and incremental costs are provided in Figures 2-5.

Figure 2. OWSA – Impact of parameter ranges on incremental cases of severe pneumonia



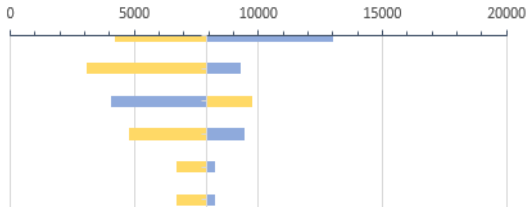
Parameter
Probability of severe pneumonia without treatment
Proportion of Substandard and Falsified Medicines 3 in the Real-world Scenario
Probability of severe pneumonia with treatment
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Proportion of Substandard and Falsified Medicines 3 at Public Hospitals in the Real-world Scenario
Proportion of Substandard and Falsified Medicines 3 at Public Health Centers in the Real-world Scenario

Figure 3. OWSA – Impact of parameter ranges on incremental cases of very severe pneumonia



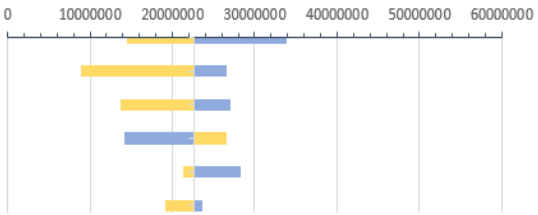
Parameter
Probability of very severe pneumonia without treatment
Proportion of Substandard and Falsified Medicines 3 in the Real-world Scenario
Probability of very severe pneumonia with treatment
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Proportion of Substandard and Falsified Medicines 3 at Public Hospitals in the Real-world Scenario
Proportion of Substandard and Falsified Medicines 3 at Public Health Centers in the Real-world Scenario

Figure 4. OWSA – Impact of parameter ranges on incremental life years lost



Parameter
Lifetime probability of condition-related death without treatment
Proportion of Substandard and Falsified Medicines 3 in the Real-world Scenario
Lifetime probability of condition-related death with treatment
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Proportion of Substandard and Falsified Medicines 3 at Public Hospitals in the Real-world Scenario
Proportion of Substandard and Falsified Medicines 3 at Public Health Centers in the Real-world Scenario

Figure 5. OWSA – Impact of parameter ranges on incremental costs



Parameter
Lifetime probability of condition-related death without treatment
Proportion of Substandard and Falsified Medicines 3 in the Real-world Scenario
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Lifetime probability of condition-related death with treatment
Average Unit Cost of severe pneumonia Management
Proportion of Substandard and Falsified Medicines 3 at Public Health Centers in the Real-world Scenario