Promoting the
QUALITY OF MEDICINES Plus

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

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

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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 ingredient
CFR	case fatality rate
DALY	disability-adjusted life years
GDPPC	per capita gross domestic product
LMIC	low and middle-income countries
OWSA	one-way sensitivity analysis
PCTHE	per capita total expenditure on health
PQM+	Promoting the Quality of Medicines Plus
QALY	quality-adjusted life-years
SF	substandard and falsified
USAID	U.S. Agency for International Development
WHO	World Health Organization

Executive Summary

The U.S. Agency for International Development (USAID)-funded Promoting the Quality of Medicines Plus (PQM+) program[1] developed a substandard and falsified (SF) medicine burden model that stakeholders can use to estimate the burden of using SF medicines on patients, the health care system, and the economy as a whole. PQM+ piloted the model first in Kenya to assess the burden of SF oxytocin. PQM+ then applied the model to estimate the burden of SF amoxicillin for childhood (less than 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 the Southeast Asia region.[2]
2. Provide a model template prepopulated with available data that can be used in the context of any low- and middle-income country (LMIC) or developing region with minimal additional data inputs.

PQM+ identified published data sources for key parameters to estimate the burden of SF amoxicillin in Southeast Asia for the treatment of childhood (less than 5 years old) pneumonia following the World Health Organization (WHO) treatment guidelines. The burden is substantial, likely leading each year to approximately 9,501 cases of severe pneumonia, 1,619 cases of very severe pneumonia, and 211 additional deaths (and life-years lost from those), as well as $14 million in economic costs per 1 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 $22 million per year. The results suggest that the cost of SF amoxicillin to children, society, and the economy in Southeast Asia merits further action.

These preliminary results should be used as a basis for customization of the model in individual countries, both in Southeast Asia 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 – Parameter values and their data sources used for the model template to estimate the burden of SF amoxicillin in Southeast Asia

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

[1] The USAID-funded PQM+ program is led by the U.S. Pharmacopeia. 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 process for using it.
[2] The WHO Southeast Asia Region comprises: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste.

Introduction to the Model

A 2017 WHO study found the aggregate observed failure rate of tested samples of medicines in LMICs is approximately 10.5 percent.[3] 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.[4] 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 USAID-funded PQM+ program[5] developed the SF medicine burden model that stakeholders can use to estimate the burden of using SF medicines on patients, the health care 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 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 use of SF medicines is derived from inadequate active pharmaceutical ingredients (APIs) in the SF medicine to achieve treatment efficacy. Thus, the main driver of health burden is the relationship between the percentage of API in the medicine and medicine efficacy.[6] The SF medicine burden model makes the assumptions about decrements in medicine efficacy based on API content 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 versus those who do not seek care) through the health system[7] and different treatment outcomes, with poor

[3] WHO, 2017
[4] WHO, 2017; McManus, et al., 2020.
[5] The USAID-funded PQM+ program is led by U.S. Pharmacopeia. 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 process for using it.
[6] 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*.
[7] 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.

treatment outcomes experienced by patients who received SF medicine. To account for providers who may increase 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 a SF medicine

Estimating the Burden of SF Amoxicillin for the Treatment of Childhood (under 5 years old) Pneumonia in the Southeast Asia Region

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

In 2019, WHO estimated that 14 percent of all deaths in children under 5 years old were caused by pneumonia, accounting for more than 740,000 deaths annually.[8] 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.[9] These guidelines included an updated classification of pneumonia versus severe pneumonia and recommended the use of oral antibiotics as a treatment. 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 health care facility with an injectable therapy (first-line treatment of parenteral ampicillin/penicillin and gentamicin). However, both oral and injectable amoxicillin are also used in health care facilities for the treatment of severe pneumonia.[10]

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, and the number of cases annually. 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 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 the Southeast Asia region or LMICs globally, depending on data availability. These minimal inputs were used to estimate the burden of SF amoxicillin in the Southeast Asia region per 1 million new cases of childhood

[8] WHO 2014.
[9] WHO 2014.
[10] Lassi, et al., 2013.

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 Southeast Asia 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 is able replace the Southeast Asia 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 Southeast Asia region. A user can enter values and use the model for countries or regions outside of Southeast Asia; however, some of the prepopulated values will need to be adjusted for the region of interest. Instructions for this are 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 the model and the credibility of its results, both of which may increase the likelihood of follow up to improve medicines 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 the model, 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 directly move 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. This is 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 potential limitations associated with each variable. Limitations associated with specific variables are:

1. *Costs*. The current inputs are generalized based on limited country data.[11] However, costs are significantly impacted by the countries' health care systems, and these inputs would be best replaced by country-specific data. In addition, the aggregate data are from 1998–2013 reports, and health care costs are likely to have increased since then. For this reason, the Southeast Asia results reported here are likely an underestimate.
2. *Proportion of SF amoxicillin*. These inputs are based on a large-scale review including reports of SF medicines from 1992–2020 and are generalized to developing countries.[12] These inputs should be replaced if more recent, reliable data are available for a country. The impact of this on the Southeast Asia model results is indeterminate; depending on the proportion of amoxicillin that is SF, reported results could be an over estimate 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 Southeast Asia. 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 amoxicillin use for severe pneumonia or for other indications. This is because the rates and context for the use of amoxicillin for severe pneumonia is 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.[13] However, it is not well characterized and there are 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 Southeast Asia, country-specific inputs will further increase the relevancy of the outputs to the specific country.

Findings

Findings per 1 million children treated with amoxicillin for pneumonia

This report documents the model's estimates of the SF amoxicillin burden in Southeast Asia per 1 million new cases of children with pneumonia. The model uses a 16 percent prevalence of SF medicines based on Zabala, et al., which is an expansive review study that estimated medicine SF rates in LMICs. The review included 2,208 amoxicillin samples collected between 1992 and 2020. Additional discussion on the prevalence of SF amoxicillin can be found in **Annex 2**.

[11] Zhang, et al.
[12] Zabala, et al.
[13] Cavany, er al.; Zabala, et al.

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

Health burden. The model estimates that in Southeast Asia, per 1 million new cases of pneumonia each year due to use of SF amoxicillin, there are:

- 9,501 additional cases of severe pneumonia
- 1,619 additional cases of very severe pneumonia
- 211 additional deaths
- 5,653 of life-years lost

Economic burden.[14] The additional morbidity and mortality caused by SF amoxicillin results in an economic burden estimated at $14 million (per 1 million new cases of pneumonia in children under 5 years old) from a societal perspective, including approximately:

- $1.1 million in direct costs from the health care sector perspective
- $13 million in productivity losses, including:
  - $575 thousand due to caregivers' missed days of work
  - $12.5 million due to premature death (considering the lifetime productivity of the 211 additional deaths estimated in the given year)

The incremental change in health and economic burdens attributable to use of SF amoxicillin in Southeast Asia per 1 million children under 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 of SF amoxicillin in Southeast Asia (in US$) per 1 million new cases of pneumonia in children under 5 years old: Base case

Burden	Real-world Scenario (SF present)	Ideal Scenario (No SF present)	Burden due to SF amoxicillin
Health Burden			
Cases of severe pneumonia	146,351	136,850	9,501
Cases of very severe pneumonia	24,749	23,130	1,619
Incremental deaths	3,141	2,930	211
Life years lost due to premature deaths	84,102	78,449	5,653
Economic Burden			
Health care sector costs			
Cost of severe pneumonia (from a health care sector perspective)	$8,006,473	$6,992,874	$1,013,599
Cost of very severe pneumonia (from a health care sector perspective)	$902,568	$787,152	$115,416
Total health care sector costs	$8,909,041	$7,780,026	$1,129,015
Productivity losses			
Productivity loss due to missed days at work due to severe pneumonia	$7,118,527	$6,656,384	$462,143

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

Burden	Real-world Scenario (SF present)	Ideal Scenario (No SF present)	Burden due to SF amoxicillin
Productivity loss due to missed days at work due to very severe pneumonia	$1,730,432	$1,617,250	$113,182
Productivity loss due to premature death	$185,403,356	$172,940,981	$12,462,375
Total productivity loss	$194,252,316	$181,214,615	$13,037,701
Total societal cost (sum of total costs from a health care sector perspective and total productivity losses)	$203,161,356	$188,994,641	$14,166,715

Findings for the entire Southeast Asia region

For additional context, PQM+ estimated the burden based on the number of children in the Southeast Asian region as defined by WHO.[15] The number of children under 5 years in Southeast Asia in 2021 was 169,362,000.[16] Incidence of pneumonia in children under 5 years in South Asia is 0.26 per child year.[17] The total number of children with pneumonia in Southeast Asia per year is estimated to be 44,034,120. Accordingly, the burden of one year's incidence of pneumonia in children under 5 years in Southeast Asia due to use of SF amoxicillin is estimated as follows:

Health burden

- 418,381 additional cases of severe pneumonia
- 71,280 additional cases of very severe pneumonia
- 9,297 additional deaths
- 248,932 of life-years lost

Economic burden. The additional morbidity and mortality caused by SF amoxicillin results in an economic burden estimated at $624 million per year of pneumonia cases from a societal perspective, including approximately:

- $50 million in direct costs from the health care sector perspective
- $574 million in productivity losses, including:
  - $25 million due to missed days of work
  - $549 million due to premature death

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

- **Estimate using Southeast Asian regional values**. Users can calculate the percent of 1 million cases of childhood pneumonia that their country experiences each year (e.g., 500,000 cases of childhood pneumonia each year = 50% of 1 million cases of childhood pneumonia) and multiply this factor by the results listed above for 1 million cases.

- **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

[15] https://www.who.int/countries
[16] The State of the World's Children 2021: Statistical tables - UNICEF DATA, Table 1: Demographics
[17] Walker, et al.

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. In 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 1 million children treated with amoxicillin for pneumonia, the overall ranges of possible results considering all parameters are:

Health Burden

- Additional cases of severe pneumonia: from 3,726 to over 16,500 additional cases
- Additional cases of very severe pneumonia: from 635 to around 2,800 additional cases
- Additional deaths: from 83 to 345 deaths
- Life-years lost: from 2,217 to almost 9,233 life-years lost

Economic Burden – from $5.5 to $22 million in direct costs to the health care 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	9,501 cases	4,575 cases	16,539 cases
Probability of very severe pneumonia without treatment	0.027–0.056	Incremental cases of very severe pneumonia	1,619 cases	774 cases	2,815 cases
Probability of death from pneumonia without treatment	0.0034–0.0069	Economic burden	$14,166,715	$7,520,115	$22,059,553
		Life-years lost	5,653 years	2,638 years	9,233 years
		Death	211 deaths	99 deaths	345 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 Southeast Asia for the treatment of childhood pneumonia following the WHO treatment guidelines.[18] The burden is substantial, even conservatively estimated, likely leading each year to the following results:

- For 1 million cases of childhood pneumonia initially treated with amoxicillin:
  - 9,501 additional cases of severe pneumonia
  - 1,619 additional cases of very severe pneumonia
  - 211 additional deaths (and life-years lost from those)
  - Approximately $14 million in economic costs
- Extrapolated to the estimated 44.03 million cases of childhood pneumonia in Southeast Asia each year:
  - 418,381 additional cases of severe pneumonia
  - 71,280 additional cases of very severe pneumonia
  - 9,297 additional deaths (and life-years lost from those)
  - Approximately $624 million in economic costs
- Ranges for the burden, based on the high and low values input for each parameter used in the model calculations, are:
  - From 3,726 to over 16,500 additional cases of severe pneumonia
  - From 635 to around 2,800 additional cases of very severe pneumonia
  - From 83 to 345 additional deaths (and life-years lost from those)
  - From $5.5 to $22 million in economic costs

The results suggest that the cost of SF amoxicillin to children, societies, and economies in Southeast Asia 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 initiatives to reduce the prevalence and availability of SF medicines include:

- Seeking to understand the root cause of SF amoxicillin in their 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.

[18] WHO, 2014

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Annex 1: Prepopulated Model Inputs Their Data Sources Used in This Estimate of the Burden of SF Amoxicillin in Southeast Asia

Table 4. Data Sources for Model Inputs Estimating SF Amoxicillin in Southeast Asia

#	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	69%		WHO Data Portal* (WHO, 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-–5%	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%	
Substandard and Falsified 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	0.002	0.0016–0.0024	Addo-Yobo, et al., 2011*; Hazir, et al., 2011*; McCollum, et al., 2015; Nair, et al., 2013*
14	Lifetime probability of condition-related death without treatment	0.005	0.0034–0.0069	Nair, et al., 2013*; Rudan, et al., 2013
15	Probability of severe pneumonia with treatment	0.095	0.078–0.116	Addo-Yobo, et al., 2011*; Hazir, et al., 2011*; McCollum, et al., 2015
16	Probability of severe pneumonia without treatment	0.23	0.16–0.33	Rudan, et al., 2013

#	Parameter	Base Case	Range	Source Reference #
17	Probability of very severe pneumonia with treatment	0.016	0.013–0.02	Addo-Yobo, et al., 2011*; Hazir, et al., 2011*; McCollum, et al., 2015; Nair, et al., 2013*
18	Probability of very severe pneumonia without treatment	0.039	0.027–0.056	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	106.68	20.30–310.80	Zhang, et al., 2016*
24	Average unit cost of very severe pneumonia management	71.30	61.20–81.30	Zhang, et al., 2016*
25	Median daily wage rate	7.60	3.26–12.32	Estimated for the SE Asia Region* (WorldData.info, 2022)
	Productivity Loss			
26	Life expectancy at birth	71.44		WHO 2019 estimates for Southeast Asia Region* (WHO, n.d.a)
27	Per capita gross domestic product (US$ GDPPC)	2272.50		World Bank 2022 estimates for South Asia* (The World Bank, n.d.)
28	Per capita total expenditure on health (US$ PCTHE)	68		WHO 2012 estimates for Southeast Asia Region* (WHO, 2015)
29	Minimum age for employment	15		International Labour Organization convention, legal minimum age (Ales, et al., 2018)
30	Discount rate	3%		Kirigia, et al., 2015

* Sources with SE Asia Region-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 Southeast Asia region. It provides information on sources and describes how PQM+ made decisions about values for some parameters. These explanations can help future users think about their data and decide what values to use.

In estimating the burden of SF amoxicillin to treat childhood pneumonia in Southeast Asia, PQM+ created a prepopulated model template file (an Excel spreadsheet that accompanies this report). When available, PQM+ used Southeast Asia regional values 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 country-specific estimates, users should replace values already entered into the prepopulated model file with new values specific to the country of interest.

Note that Southeast Asia 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, PQM+ left this input blank and defaulted to estimates per 1,000,000 children under 5 years old with a new case of pneumonia.

When adapting for a specific country, users should enter the total number of children under 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 under 5.

$$Eligible\ Population\ in\ year\ X\ =\ Total\ number\ of\ children < 5\ in\ year\ X\ x\ Incidence\ rate$$

Total number of children under 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.[19] The population of children under 5 can be filtered by country, year, and sex.

Incidence Rates
PQM+ has identified multiple sources that provide incidence rates of pneumonia in children under 5 years.

[19] WHO, n.d.b.

- 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). They also estimate an incidence rate in LMICs of 0.22 (interquartile range of 0.11-0.51) episodes per child per year.

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

Table 5. 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 under 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 at 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 percent of the population seek care if no user-defined data are added to the model inputs. WHO reports the care-seeking behavior for children with symptoms of acute respiratory infection by region, country, and year.[20]

How to modify the input: The prepopulated model template uses 69 percent, which is the average of the most recent data reported for each country in the WHO-defined Southeast Asia region. 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 would want to include data on percentage of the population that seeks care in the various sectors to refine the estimates of burden.

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

- Input 6: Proportion of hospitals in public sector

[20] WHO 2023.

- 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

These should be data for the proportion of hospitals, public health centers, and other locations in the private and public sectors and 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, then these inputs can be included.

Medicine quality inputs

Inputs 11–14: Proportion of quality medicines versus 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,[21] which is an extensive review that included 2,208 amoxicillin samples collected between 1992 and 2020. The study estimated that 16 percent of amoxicillin is SF in developing countries, which is generally in line with studies in LMICs with larger sample sizes. As noted in the publication, subset of the sampled products were tested for API content. Based on these results, the team estimates that 10 percent of SF products have a content between 75–89 percent (input 11), and 6 percent of SF products have a content less than 50 percent (input 13). The ranges for inputs 11 and 13 are 0–15 percent and 0–8 percent respectively. The base value for input 14 (standard quality) is 84 percent, with a range of 77–100 percent. 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 percent is higher than average for SF medicines in general, there are several reports indicating higher rates of SF antibiotics (see Table 5).

How to modify the inputs: The model template includes the estimates discussed above. These 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 results, those results likely exceed the national rate of SF medicines, since risk-based post-marketing surveillance intentionally focuses on higher risk locations and facilities.

Additional sources for SF rates of amoxicillin that were identified are listed in Table 5. Note that studies with fewer than 10 samples were excluded from the list.

[21] Zabala et al., 2022.

Table 6. 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 collection	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, et al. (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, et al. (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, et al. (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 Southeast Asia are more conservative than the above averages (which includes results from many regions). Specifically, the Southeast Asia model uses 10 percent for Input 11 (SF1 quality) and 84 percent for Input 14 (standard quality), versus 23 percent and 73 percent, 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 health care 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 health care 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. These indicate health care provider concern about medicine quality. These inputs affect the treatment cost calculations in the model.

Input 16 is the proportion of health care 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, then 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 a SF medicine and the medicines' 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 3 (API < 50%) = the health outcome without treatment.
- The health outcome of using SF medicine 1 (API: 75–89%) is 60 percent of the health outcome with treatment.
- The health outcome of using SF medicine 2 (PI: 50–74%) is 30 percent of the health outcome with 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, then 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, PQM+ used an alternative approach, described below.

It should be noted that there are limited data available for the overall CFR of pneumonia. However, these estimates do not differentiate between whether patients received treatment. Rudan, et al. (2013) provides estimates of the CFR for pneumonia by country and Walker, et al. (2013) provides estimates by region. Table 7 provides the CFR rates calculated with the regional estimates reported in Walker, et al. (2013).

Table 7. CFR of Pneumonia[22]

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 alternate 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:

[22] Walker, et al., 2023.

$$CFR\ of\ Severe\ Pneumonia =$$

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

Nair et al. (2013) provides an estimate of the severe pneumonia CFR with and without hospital treatment. Because patients' care-seeking behavior with severe pneumonia is variable by country and region, the prepopulated model considers only the CFR of severe pneumonia with hospital treatment. This approach assumes that 100 percent 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 8 are calculated from the data reported in Table 2 (Nair, et al., 2013).

Table 8. CF of severe pneumonia with hospital treatment[23]

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 were calculated using the Southeast Asia specific data: the base rate and range of input 32 multiplied by 0.021. If the data for input 32 are 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 were calculated using the Southeast Asia specific data: base rate and range of input 33 multiplied by 0.021. If the data for input 33 are replaced, the corresponding data for input 31 should also be replaced.

Additional data

PQM+ has also identified data that provide the CFR of severe pneumonia with amoxicillin treatment that considers both community-based care and hospital treatment.[24] 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

[23] Nair, et al., 2013.
[24] Fox, et al., 2012.

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 36: Probability of other health outcome with treatment
- Input 37: Probability of other health outcome without treatment

PQM+ developed the SF medicine burden model 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.

McCollum, et al. (2015) published a review that included nine studies conducted between 1998 and 2008, seven in Asia (Pakistan and India) and two that include both African and Asian populations. The reported failure rates were between 7.8–22.9 percent for amoxicillin, with an average of 13.1 percent and a median of 11.6 percent. The two most recent studies reported failure rates of 7.8 percent (fast breathing non-severe pneumonia[25]) and 9.2 percent (chest indrawing non-severe pneumonia.[26]). For the latter study, the Asia-specific treatment failure rate was 11.1 percent (9% in Bangladesh and 13.2% in Vietnam).

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 (9.5%) is the average of 7.8 percent as reported in Hazir, et al. (2011) and the Asia-specific data (11.1%) reported in Addo-Yobo, et al. (2011) The range, 7.8–11.6 percent, was based on the failure rates of studies conducted after 2000 as reported in McCollum, et al. (2015) A user may replace these values if more recent or country-specific data are identified.

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,[27] estimated to be 11.5 percent (inter-quartile range of 8–33%) in LMICs. This represents the odds of progression from pneumonia to severe pneumonia in all cases, including cases when the patient received care. To reflect the odds of progression without treatment more accurately, the base rate (11.5%) and the low

[25] Hazir, et al., 2011.
[26] Addo-Yobo, et al., 2011.
[27] Rudan, et al., 2013

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 being doubled and the high estimate remaining unadjusted. Rudan et al. (2013) also include estimates for progression to severe pneumonia for 192 individual countries. Country-specific values can be adjusted as described above if appropriate and the base value included in the prepopulated model replaced when 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 (with general hospital treatment). This follows the WHO treatment guideline and assumes that a patient who progresses to severe pneumonia will seek additional treatment.

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. They estimate 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 9 are calculated from the data reported in Table 2 by dividing the incidence rate of very severe pneumonia by the combined incidence rates of severe pneumonia and very severe pneumonia.

Table 9. Odds of progression from severe pneumonia to very severe pneumonia with treatment[28]

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 were calculated using the Southeast Asia-specific data: the base rate and range of input 32 (probability of severe pneumonia with treatment) multiplied by 0.17. 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.

How to modify the input: The model template data were calculated using the Southeast Asia-specific data: the base rate and range of input 33 (probability of severe pneumonia without

[28] Nair, et al., 2013.

treatment) multiplied by 0.17. 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. conducted a comprehensive review of pneumonia treatment and reports the median length of hospital stay in LMICs as 6.4 days (inter-quartile range of 4.1–7.1) for severe pneumonia and 9.2 days (inter-quartile 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.[29] 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, then these inputs can be included.

[29] Zhang, et al., 2016.

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, so adding data for the cost per dose does not impact the model. The model considers only additional costs from up-dosing and does not take into account 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 are identified, then 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. Zhang, et al., 2016 reported the cost per episode of severe and very severe pneumonia for LMICs. For the Southeast Asia region, the average in-patient cost of care was $106.68 ($23.90–$310.80; n = 5) for severe pneumonia and $71.30 ($61.20–$81.30; n = 2) for very severe pneumonia. The authors did not provide an explanation for the lower cost associated with hospital treatment of very severe pneumonia compared to severe pneumonia in the Southeast Asia region. However, this could be due to the limited data available for the cost of very severe pneumonia in the region, the variability of treatment costs in the region, or may reflect a shorter hospital stay for very severe pneumonia cases due to the higher observed CFR.

How to modify the inputs: The prepopulated model template has included the data reported by Zhang, et al. (2016) for the Southeast Asia region*. 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 averaged available data from LMICs in the South and Southeast Asia region from the source noted above (average of $7.60 per day with a range of $3.26–$12.32). 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, then 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 (US$ PCTHE)
- 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 lost and productivity lost due to premature death is based on the estimate described in Kirigia, et al. 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 PCTHE (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[30] provides estimated life expectancies that can be sorted by region, country, year, and sex. Table 10 lists the life expectance at birth sorted by region for the year 2019.

Table 10. Life Expectancy at Birth[31]

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 Southeast Asia. The data source above can be used for country-specific values or other available reliable values.

Input 150 is the gross domestic product per capita in US$. The values by region and country are available from the World Bank [32] Table 11 lists the GDPPC in current US$ by region for the year 2022, which is the most recent data reported.

Table 11. Gross domestic product per capita

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

[30] World Health Organization, n.d.a.
[31] World Health Organization, n.d.a.
[32] The World Bank, n.d.

How to modify the input: The model template used the GDPPC for South Asia, which is in line with estimates for lower middle-income countries. The data source above can be used for country-specific values or other available reliable values may be used.

Input 151 is the per capita total expenditure on health (PCTHE). WHO's World Health Statistics Report[33] provided the 2012 per total expenditure on health in US$ using the average exchange rate. The data by region is provided in Table 12.

Table 12. Per capita total expenditure on health

Region	PCTHE (US$ 2012)
African Region	105
America	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 PCTHE for the Southeast Asia region. The data source above can be used for country-specific values or other available reliable values may be used.

Input 152 is the minimum age for employment. As cited in Kirigia,[34] according to Article 2 of the International Labour Organization convention, the legal minimum age for employment is 15 years old.[35]

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, et al.[36] used a discount rate of 3 percent.

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

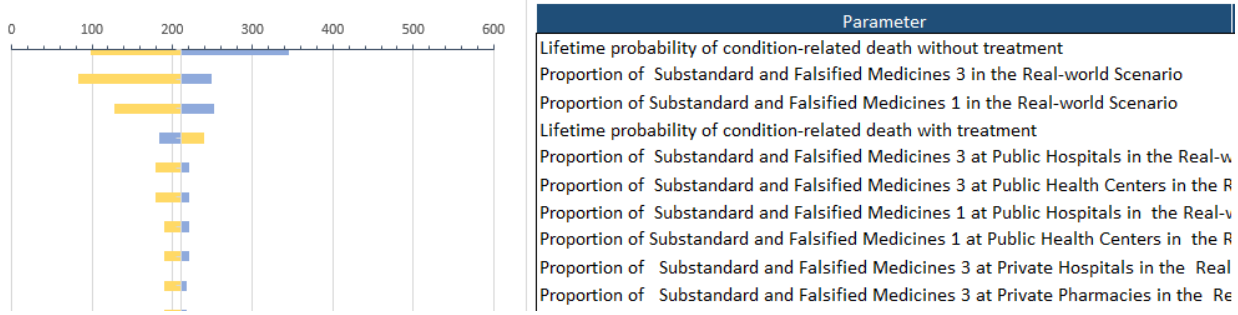
[33] World Health Organization, 2015.
[34] Kirigia, et al., 2015.
[35] Ales, et al., 2018.
[36] Kirigia, et al., 2015.

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, with the widest bars demonstrating 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 whether 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:

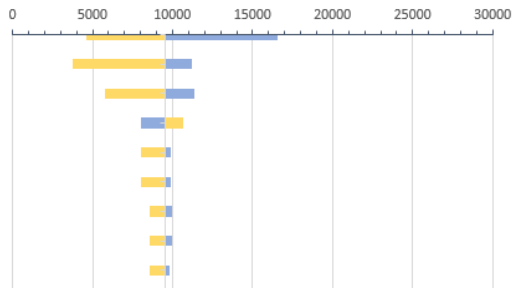
- The parameter that has the greatest impact on incremental deaths associated with use of SF amoxicillin is the lifetime probability of death from pneumonia without treatment.
- At the lowest value in the range used for lifetime probability of death from pneumonia without treatment (i.e., 0.0034), the incremental number of deaths is 99. The yellow bar in the tornado diagram shows the difference between the number of incremental deaths calculated with the base input (i.e., 211) 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., 0.0069), the incremental number of deaths is 345. The blue bar in the tornado diagram shows the difference between the number of incremental deaths calculated with the base input (i.e., 211) versus the number of incremental deaths calculated with the highest value in the range.

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



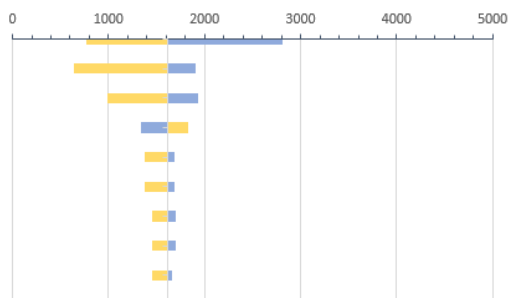
Tornado diagrams for impact of parameter ranges on incremental cases of severe pneumonia, incremental cases of very severe pneumonia, incremental life-years lost, and incremental costs are provided in Figures 2–5.

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



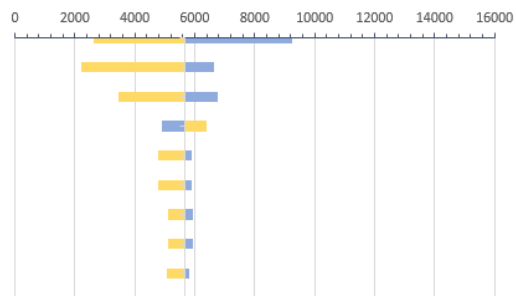
Parameter
Probability of severe pneumonia without treatment
Proportion of Substandard and Falsified Medicines 3 in the Real-world Scenario
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Probability of severe pneumonia with treatment
Proportion of Substandard and Falsified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

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



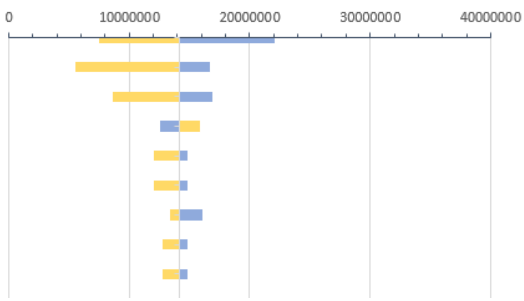
Parameter
Probability of very severe pneumonia without treatment
Proportion of Substandard and Falsified Medicines 3 in the Real-world Scenario
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Probability of very severe pneumonia with treatment
Proportion of Substandard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

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
Proportion of Substandard and Falsified Medicines 1 in the Real-world Scenario
Lifetime probability of condition-related death with treatment
Proportion of Substandard and Falsified Medicines 3 at Public Hospitals in the Real-w
Proportion of Substandard and Falsified Medicines 3 at Public Health Centers in the R
Proportion of Substandard and Falsified Medicines 1 at Public Hospitals in the Real-v
Proportion of Substandard and Falsified Medicines 1 at Public Health Centers in the R
Proportion of Substandard and Falsified Medicines 3 at Private Hospitals in the Real
Proportion of Substandard and Falsified Medicines 3 at Private Pharmacies in the Re

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
Proportion of Substandard and Falsified Medicines 3 at Public Hospitals in the Real-w
Proportion of Substandard and Falsified Medicines 3 at Public Health Centers in the R
Average Unit Cost of severe pneumonia Management
Proportion of Substandard and Falsified Medicines 1 at Public Hospitals in the Real-v
Proportion of Substandard and Falsified Medicines 1 at Public Health Centers in the R
Probability of severe pneumonia without treatment