

# Supplementary Information

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## Existing evidence on the economic burden of GAS infections

This section describes the search outcomes of the economic burden of diseases caused by group A *Streptococcus* (GAS). The search outcomes were presented by disease manifestation: pharyngitis, impetigo, cellulitis, invasive and toxin mediated diseases, acute rheumatic fever (ARF), rheumatic heart disease (RHD), severe RHD (such as congestive heart failure, cardiac surgery, etc.). The primary focus of the search was to identify any costs associated with GAS and extract further details including healthcare descriptions, treatment items, and the unit of measure if available. More details are available at Cannon et al., “Modalities of group A streptococcal prevention and treatment and their economic justification” (currently under review by npj Vaccines).

Considering that each study reported the economic burden of a disease associated with GAS in various formats, the search outcomes were manually reviewed and categorized into direct medical cost (DMC), direct non-medical cost (DNMC), and indirect cost (IC) based on healthcare descriptions and treatment items for the purpose of the current economic burden analysis.

### Pharyngitis

A total of 24 articles met the inclusion criteria and reported the three types (DMC, DNMC, or IC) of costs associated with pharyngitis or tonsillitis, or tonsillectomy. Given the limited number of data, the costs of pharyngitis and tonsillitis were considered to be in the same disease group.

Supplementary Table 1.1 shows the number of studies from which cost data were extracted for pharyngitis and tonsillectomy. As indicated in the table, a majority of the costs were observed in high-income country settings. Regarding the cost type, it appeared that DMC was the most commonly reported form followed by IC and DNMC. The number of studies was significantly lower in other income settings than in the high-income group, and there was no study available for the low-income group. In fact, Manji et al. targeted developing countries for their cost-effectiveness analysis mentioning sub-Saharan African in their paper [1], but this study was excluded because the source of costing data was not clearly indicated, and they reported annual costs rather than cost per episode or cost per patient. The economic burden of tonsillectomy was only available from high-income country settings.

**Supplementary Table 1.1 Number of studies for pharyngitis**

Income group	Cost type	Disease type	Source
		Pharyngitis (or tonsillitis)	
High income	DMC	21	[2-22]
	DNMC	2	[3, 20]
	DMC&DNMC	-	
	IC	5	[3, 6, 15, 20, 22]
Upper-middle income	DMC	2	[23, 24]
	DNMC	-	
	DMC&DNMC	-	
	IC	-	
	DMC	1	[25]

Lower-middle income	DNMC	1	[25]
	DMC&DNMC	-	
	IC	-	
Low income	DMC	-	
	DNMC	-	
	DMC&DNMC	-	
	IC	-	

## Impetigo and Cellulitis

For GAS skin-related infections such as impetigo, and cellulitis, there was clearly a lack of existing studies which report economic burden. As shown in Supplementary Table 1.2, there were no studies identified for the skin infections in non-high-income settings except one for cellulitis in the upper-middle income group and the other for impetigo in the lower-middle income group. In particular, the economic burden of impetigo was rare even in the high-income settings showing only one study of each.

**Supplementary Table 1.2 Number of studies for impetigo and cellulitis**

Income group	Cost type	Disease type		Source
		Impetigo	Cellulitis	
High income	DMC	1	9	[2, 26-33]
	DNMC	-	-	
	DMC&DNMC	-	-	
	IC	-	2	[26, 28]
Upper-middle income	DMC	-	1	[34]
	DNMC	-	-	
	DMC&DNMC	-	-	
	IC	-	-	
Lower-middle income	DMC	1	-	[35]
	DNMC	-	-	
	DMC&DNMC	-	-	
	IC	-	-	
Low income	DMC	-	-	
	DNMC	-	-	
	DMC&DNMC	-	-	
	IC	-	-	

## Invasive and toxin-mediated diseases

GAS sometimes develops into invasive or toxin-mediated diseases Supplementary Table 1.3 demonstrates the number of studies which reports the economic burden of each infection. Similar to GAS skin

infections, while the occurrence of such infections has been reported in existing literature, the number of studies which reports the economic burden of them is very limited.

**Supplementary Table 1.3 Number of studies for invasive and toxin mediated diseases**

Income group	Cost type	Disease type	Source
		Invasive and toxin-mediated	
High income	DMC	5	[2, 36-39]
	DNMC	-	
	DMC&DNMC	-	
	IC	-	
Upper-middle income	DMC	-	
	DNMC	-	
	DMC&DNMC	-	
	IC	-	
Lower-middle income	DMC	-	
	DNMC	-	
	DMC&DNMC	-	
	IC	-	
Low income	DMC	-	
	DNMC	-	
	DMC&DNMC	-	
	IC	-	

### **Acute Rheumatic Fever (ARF), Rheumatic Heart Disease (RHD), and severe RHD**

There were 18 studies which reported the economic burden of either acute rheumatic fever (ARF), rheumatic heart disease (RHD), or severe RHD (or any combination of these). Severe RHD was defined if a patient went through any of the following processes: (congestive) heart failure, stroke, or any surgery-related procedures due to RHD. Overall, a smaller number of studies were identified compared to pharyngitis. As shown in Supplementary Table 1.4, The availability of the cost data for ARF, RHD, or severe RHD showed the similar patterns described for pharyngitis: most of the studies coming from the high-income countries, and DMC being the most commonly reported form of the economic burden. Again, no study was identified in low-income group settings, and there were only three and four studies identified in the upper-middle income and the lower-middle income settings, respectively. Among the studies which reported DMC in the lower-middle income group, one of them constructed a cost-effectiveness model targeting the African region [40], but their costs were mainly taken from a previous study conducted in Cuba [41] which belongs to the upper-middle income group. Given the previous study done in Cuba was already included in the upper-middle income group, the costs used in the other study [40] were not included to avoid any duplication. Soudarssanane et al. reported multiple cost items in three categories [25]: primary prevention, secondary prevention, and tertiary prevention. For the purpose of the current screening process, each cost of primary, secondary, and tertiary prevention was assumed to be that of ARF, RHD, and severe RHD respectively. In addition, the cost for ARF or mild RHD was grouped

into the cost for ARF, and the cost of moderate RHD was considered to be the cost of RHD for the study done by Cannon et al. [2].

**Supplementary Table 1.4 Number of studies for ARF, RHD, and severe RHD**

Income group	Cost type	Disease type			Source
		ARF	RHD	severe RHD	
High income	DMC	8	7	4	[3, 4, 10, 12, 14-16, 19, 22, 42-44]
	DNMC	-	3	2	[3, 4, 42]
	DMC&DNMC	2	2	2	[2] (general and indigenous populations separately)
	IC	2	3	1	[3, 15, 22, 42]
Upper-middle income	DMC	2	2	2	[41, 45]
	DNMC	-	-	-	
	DMC&DNMC	1	-	-	[46]
	IC	1	-	-	[46]
Lower-middle income	DMC	1	2	2	[25, 47]
	DNMC	1	1	-	[25]
	DMC&DNMC	-	-	-	
	IC	1	1	-	[25]
Low income	DMC	-	-	-	
	DNMC	-	-	-	
	DMC&DNMC	-	-	-	
	IC	-	-	-	



[illegible]

## **Summary**

The economic burden of GAS infections is scarce in existing literature. Among a few studies available, most of them reported the costs from the same high-income countries such as Australia, and United States. The number of available studies was disproportionately lower in upper-middle-, lower-middle-, and low-income countries. In particular, there was no study identified in the low-income settings for any of the GAS-associated manifestations. This is partly because a majority of the costs data identified in this search were taken from existing cost-effectiveness analyses which had been mainly conducted in the high-income country settings. This highlights the significant gap in health economic studies including cost of illness, particularly in non-high income settings.



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**Supplementary Table 2. Average number of outpatient visits and hospital bed days by disease over time**

Disease	Type	Year									
		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Pharyngitis	OP visits	1.9	1.8	1.9	1.8	1.8	1.8	1.8	1.7	1.7	1.7
	IP bed days	5.1	4.9	4.8	4.7	4.8	4.3	4.5	4.3	3.7	3.9
Impetigo	OP visits	1.5	1.6	1.6	1.8	1.6	1.7	1.7	1.6	1.6	1.6
	IP bed days	6.8	17.0	2.0	0.0	0.0	0.0	0.0	3.0	0.0	0.0
Cellulitis	OP visits	2.5	3.1	3.3	2.8	1.9	1.7	1.7	1.6	1.6	1.7
	IP bed days	12.3	10.4	8.9	9.0	8.8	6.0	12.0	4.2	6.0	0.0
Invasive infections	OP visits	2.8	2.5	2.4	2.4	2.4	2.4	2.4	2.3	2.4	2.6
	IP bed days	21.8	18.9	19.1	17.4	17.5	19.3	18.7	14.2	16.1	18.5
ARF	OP visits	2.2	2.4	3.6	3.9	4.6	4.9	4.2	4.2	3.6	3.0
	IP bed days	12.4	9.7	13.1	17.1	29.8	29.5	14.0	18.6	17.4	16.1
RHD	OP visits	4.4	2.8	3.0	2.7	2.8	2.5	2.2	2.3	2.0	2.3
	IP bed days	10.9	16.6	54.8	12.1	16.1	7.0	20.5	46.0	14.2	5.0
Severe RHD	OP visits	4.4	4.3	4.4	4.2	4.3	4.2	4.1	4.0	4.2	4.0
	IP bed days	17.8	17.1	17.0	16.5	16.4	16.9	16.6	17.0	18.1	17.5