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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary Appendix

Contents

Health Impact Model Methodology

The general approach of the health impact model is described in the main text. The first two sections below describe additional details about the broad model structure and demographic projections. Subsequent sections describe how input modelling parameters were obtained from literature or derived. These parameters generally fall into four categories: starting populations, transition probabilities, intervention effect sizes, and coverage estimates.

Code and Input Data Availability

The code used to conduct analysis is available in a public repository on GitHub: https://github.com/mccoates/rhd_invest_pub. Formatted input data are also found in this repository in the data directory. In some cases, files were pre-processed for their inclusion in the repository to reduce the size of the stored data.

Health Outcomes Model Overview Notes

Figure 1 in the main text outlines the structure of the health outcomes model. The model is shown here with additional detail as Appendix Figure 1 with numbers corresponding to transition probabilities described in a later section of the appendix. We used the first part of the model to estimate the number of cases of group A streptococcal (GAS) pharyngitis and acute rheumatic fever (ARF) from initial episodes and recurrences. We used the second part of the model to estimate RHD cases and subsequent health states, including RHD with heart failure (HF), stroke, RHD after valve surgery, and death. RHD presenting with HF was assumed to be severe disease until surgical intervention whether or not the individual was on treatment or exhibited evidence of ongoing clinical HF.

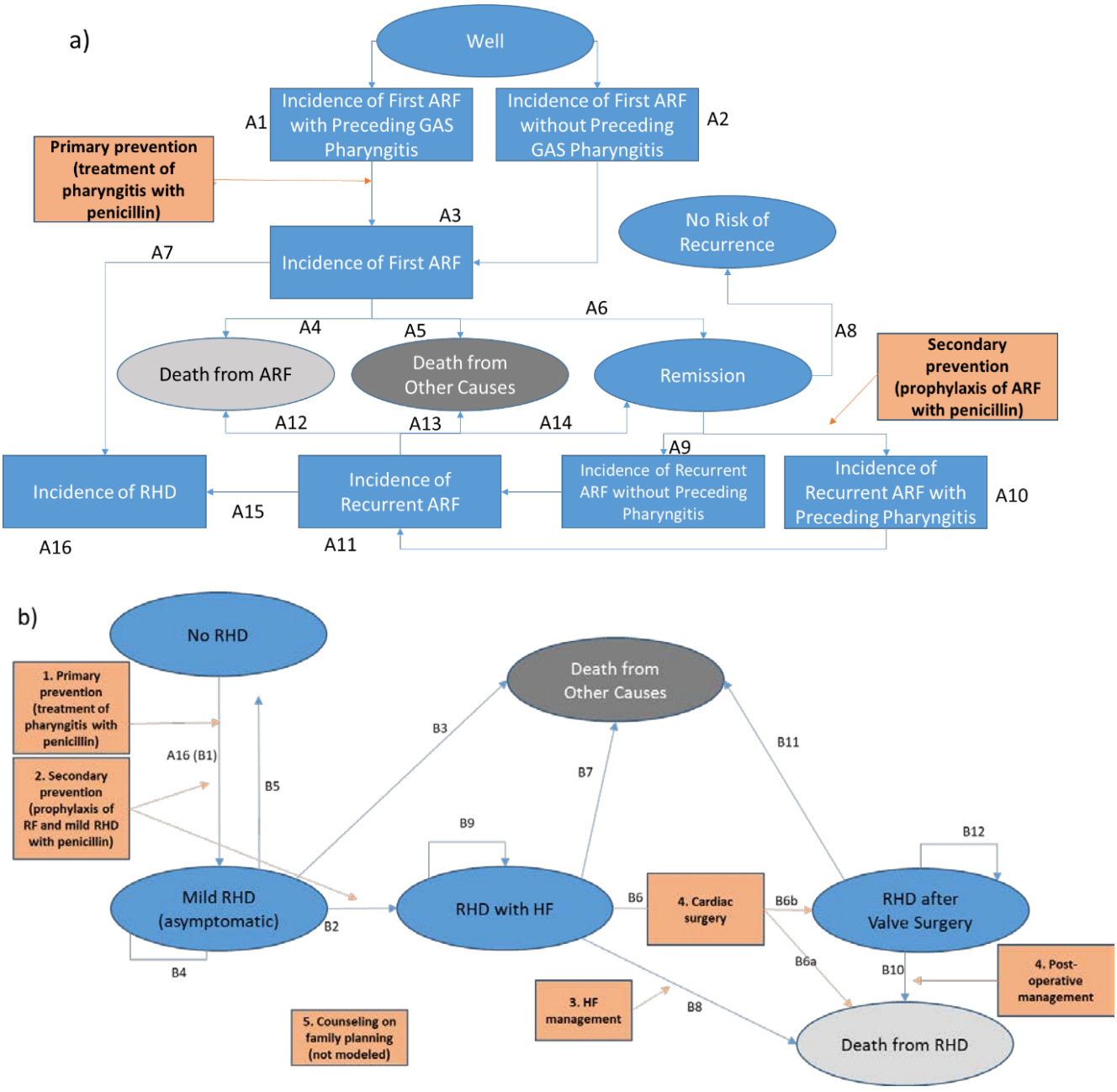
In the first part of the model, some of the events occur on a relatively short timeframe. Therefore, we did not have time steps of one year between GAS infection and ARF, for instance. Rather, we had parameters that were multiplicative in the course of a time step. So, for instance, the incidence of a first case of ARF after pharyngitis was the product of pharyngitis cases per person per year, the proportion of pharyngitis cases from GAS infection, and the probability of developing ARF after GAS pharyngitis. States in which people could end a year are shown as ovals in Appendix Figure 1, with the boxes representing calculations based on these rates of pharyngitis and other probabilities. These steps are described in more detail in the section on transition probabilities.

The first stage of the model produced estimates of RHD incidence. However, the estimates of some of the parameters in the first part of the model, such as GAS pharyngitis infections per year, the proportion of ARF cases with preceding symptomatic pharyngitis, and the risk of ARF after GAS infection are highly uncertain, originate from varied settings, and are not constrained to fit the prevalence data from screening studies. The estimates of RHD incidence from the GBD Study, by contrast, were modeled using RHD prevalence data from echocardiographic screening studies in Africa.[1] Therefore, we used the estimates of RHD incidence from the GBD. We then adjusted the parameters in the first part of the model to calibrate to the estimates of RHD incidence from the GBD so that the estimated number of ARF cases would be consistent with the number of incident RHD cases in 2017. These adjustments were a calibration, and the first part of the model was not designed to fit the RHD data precisely (see transition probability section in this appendix for the last parameter of the first part of the model). We used the first part of the model to estimate the net effects of expanded coverage of primary and secondary prevention by estimating RHD incidence in scenarios with and without scale-up of primary and secondary prevention and calculating the relative differences in RHD incidence. We then applied this effect size to the estimates of RHD incidence from the GBD study that we used in the second part of the model.

There is growing evidence that non-pharyngitis or asymptomatic GAS infections can also contribute to ARF and may particularly be relevant in more tropical climates.[2–4] However, the evidence is sparse, and it is not clear what proportion of ARF cases are not preceded by symptomatic pharyngitis. We included pharyngitis and non-pharyngitis pathways for the development of ARF to give the model flexibility in assumptions about this disease process, particularly as the effectiveness of primary prevention through the treatment of pharyngitis depends on the nature of this pathway.

The second part of the model, reflecting the progression of RHD was simpler, with mild RHD, severe RHD (with HF), and post-operative RHD as the only health states. The transition probabilities are described in the section below, and the effect sizes and how they operate are fully detailed in the section on effects.

The model was run for the five regions of the African Union (Appendix Table 1)—including the costing and health impact monetization, and results were aggregated for the African Union as a whole. Demographic inputs, such as populations and mortality rates from non-RHD causes, were aggregated from country-level estimates. Other parameters, such as the number of pharyngitis cases per year, lacked geographically specific evidence, and the same values were used across each region. The specificity of input parameters and the aggregation of any values from country-specific values are described in the sections on each parameter.



Blue rectangles in part (a) represent probability pathways broken into multiple parts, ovals represent health states with counts of population at the beginning and end of each year. Orange rectangles represent interventions. RHD=rheumatic heart disease, ARF=acute rheumatic fever, HF=heart failure. Treated heart failure that no longer meets criteria for heart failure remains in the "RHD with HF" category, and the proportion treated is based on the coverage of the HF management intervention.

Appendix Figure 1: Health impact model structure, (a) pharyngitis and acute rheumatic fever, (b) RHD progression (labels correspond to transitions described in Appendix Table 2)

Appendix Table 1: Countries in the African Union and geographic regions[5]

Country	Region
Republic of Burundi	Central Africa
Republic of Cameroon	Central Africa
Central African Republic	Central Africa
Republic of Chad	Central Africa
Republic of the Congo	Central Africa
Democratic Republic of Congo	Central Africa
Republic of Equatorial Guinea	Central Africa
Gabonese Republic	Central Africa
Democratic Republic of São Tomé and Príncipe	Central Africa
Union of the Comoros	Eastern Africa
Republic of Djibouti	Eastern Africa
State of Eritrea	Eastern Africa
Federal Democratic Republic of Ethiopia	Eastern Africa
Republic of Kenya	Eastern Africa
Republic of Madagascar	Eastern Africa
Republic of Mauritius	Eastern Africa
Republic of Rwanda	Eastern Africa
Republic of Seychelles	Eastern Africa
Federal Republic of Somalia	Eastern Africa
Republic of South Sudan	Eastern Africa
Republic of the Sudan	Eastern Africa
United Republic of Tanzania	Eastern Africa
Republic of Uganda	Eastern Africa
People's Democratic Republic of Algeria	Northern Africa
Arab Republic of Egypt	Northern Africa
Libya	Northern Africa
Islamic Republic of Mauritania	Northern Africa
Kingdom of Morocco	Northern Africa
Sahrawi Arab Democratic Republic*	Northern Africa
Republic of Tunisia	Northern Africa
Republic of Angola	Southern Africa
Republic of Botswana	Southern Africa
Kingdom of Eswatini	Southern Africa
Kingdom of Lesotho	Southern Africa
Republic of Malawi	Southern Africa
Republic of Mozambique	Southern Africa
Republic of Namibia	Southern Africa
Republic of South Africa	Southern Africa
Republic of Zambia	Southern Africa
Republic of Zimbabwe	Southern Africa
Republic of Benin	Western Africa
Burkina Faso	Western Africa
Republic of Cabo Verde	Western Africa
Republic of Côte d'Ivoire	Western Africa
Republic of the Gambia	Western Africa
Republic of Ghana	Western Africa
Republic of Guinea	Western Africa
Republic of Guinea-Bissau	Western Africa
Republic of Liberia	Western Africa
Republic of Mali	Western Africa
Republic of Niger	Western Africa
Federal Republic of Nigeria	Western Africa
Republic of Senegal	Western Africa

Republic of Sierra Leone	Western Africa
Togolese Republic	Western Africa

*Sahrawi Arab Democratic Republic not included separately in estimation because of lack of input estimates from the Global Burden of Disease and other sources.

Demographic Projection

In the background of the RHD model, we employed a simple demographic model to project total populations in the countries in the AU by age and sex. We used the medium fertility projections of all-cause mortality and fertility from the UN Population Division World Population Prospects (WPP) 2019 Revision.[6] Given that some of the starting parameters in the model were derived from the Global Burden of Disease (GBD) 2017 Study, and GBD mortality and fertility estimates are different than those from WPP, we chose to use the level of all-cause mortality and fertility estimates in 2017 from the GBD study and trends from the WPP estimates. We calculated age- and sex-specific ratios of the 2017 all-cause mortality rate estimates to the projected annual all-cause mortality rates in each year from 2018 to 2090 from WPP. We calculated these ratios by country, region, and for the AU as a whole by first creating estimates of age-, sex-, and year-specific mortality rates for the aggregate locations using population-weighted mortality rates with population projections from WPP. We then multiplied those ratios by the 2017 mortality rates from GBD to obtain projections consistent with the level of mortality estimates from GBD 2017 but trends from the WPP projections. Again, regional estimates were obtained through population-weighted aggregation of country-specific GBD estimates. We did the same for fertility projections.

Starting with the population estimates from 2017, we used the cohort component method of projection to project the population forward in time using these fertility and mortality estimates.[7] For simplicity, we did not account for migration. We adjusted all-cause mortality projections for the new RHD projections from our model by using the projected all-cause mortality described above, subtracting the fraction of all-cause mortality from RHD in the GBD estimates in 2017, and adding the RHD mortality from our RHD model. Given that we conducted this analysis in 2020 and the last year of estimates from GBD was from 2017, we projected the model forward starting in 2017 but we assumed scale-up of intervention coverage to begin in 2021.

Starting Populations

The model required starting populations in the baseline year for people with a history of ARF in the last 10 years (or under age 20), people with a history of ARF in the last 10 years (or under age 20) on secondary prophylaxis, mild RHD, severe RHD (with HF), and RHD with valve replacement. We describe here how each of the starting populations was estimated.

People with a history of ARF and people with a history of ARF on secondary prophylaxis

We simulated the population from the year 2000 to the year 2017 to obtain the number of people who had a history of ARF in the past ten years or who were under age 20. We used the transition parameters described later in the appendix and assumed similar levels of coverage from the year 2000 to 2017 as our baseline coverage assumption in estimating the number of people who ended up on secondary prophylaxis. This process was conducted at the regional level.

RHD with and without HF

The GBD estimates of prevalence of RHD and RHD with HF allowed us to separate those two categories.[1] The GBD estimates were for person-time or point prevalence. The risk of death among people with RHD with HF is relatively high, particularly in old ages, so the person-time does not represent the total number of people who might have RHD with HF in a particular age over the course of a year. We back-calculated the number of people with HF from RHD using our transition probability to death from RHD among people with severe disease (see transition probability section) and the number of deaths from RHD in 2017 by age and sex:

$$Cases\ HF\ from\ RHD_{a,s} = \frac{Deaths\ from\ RHD_{a,s}}{Risk\ of\ Death\ from\ RHD\ with\ HF_{a,s}}$$

Then, we subtracted the risk of death from all causes (RHD plus other causes) from one to obtain the probability of survival. We multiplied this probability of survival by the cases of RHD with HF above on an age- and sex-specific basis to obtain remaining cases surviving the year-long cycle, which we used as a starting value in the model. This process was conducted at the regional level.

RHD with Valve Surgery

The population with RHD assumed to have had valve surgery was relatively low. Zilla et al. (2018) found rates of open heart surgery per million population per year were low in several African countries, including Mozambique (7), Nigeria (0.5), Morocco (100), Tunisia (272), Namibia (127), Algeria (178), and South Africa (142).[8] We expected many countries in the African Union to have rates closer to Mozambique and Nigeria, based on health system development and wealth. The proportion of these surgeries for RHD were 25% in Mozambique, 7% in Nigeria, 31% in Algeria, and 7% in South Africa.[8] If the continent had a rate of heart surgeries of 20 per million and 10% of these were for people with RHD, there would be about 2,500 RHD surgeries per year on the continent. If there were roughly 2,000 to 4,000 surgeries per year for the past 20 years and annual survival ranged from 85% to 97%, the number of people living with RHD after valve surgery would be between 10,000 and 60,000.

Alternatively, if we assumed between 2% and 8% of people below age 45 annually with HF from RHD received surgery since the year 2000 (according to estimates of cases of RHD with HF from GBD) with between 85% and 97% annual survival, the number of people living to 2017 would be between 2,000 and 19,000. We used this as the range of estimates for the African Union. We then needed to divide this population having received surgery by age, sex, and location. We used the estimates of coverage by location (see section on intervention coverage) to create a cohort by multiplying the coverage by age-, sex-, and country-specific incident RHD cases between ages 10 and 45 from 2000 to 2017 using GBD incidence estimates. We multiplied the age-, sex-, and country-specific fractions of the population in this cohort by draws of people living after surgery, which were generated by taking draws from a distribution with a mean of log(7000) and a standard deviation of (log(20000)-log(2000))/(2*1.96). Counts were aggregated to the region level for running the model on regions.

Transition Probabilities

The transition probabilities defined the proportions of the populations in each health state moving to a different health state in each step of the model. We used a combination of transition probabilities derived from the GBD study and from primary literature sources. As described in the section of the appendix on demographic projection, age-specific all-cause mortality and fertility rates from GBD 2017 were projected for future years using trends from UN WPP projections, so probabilities based on those parameters varied over time.[6,9,10] We assumed the projected non-RHD mortality had the same trends as all-cause mortality by subtracting the fraction of all-cause mortality from RHD in 2017 from the GBD 2017 estimates. We added to this the RHD deaths from our estimates to obtain the all-cause mortality risk used to make the population projections in the model. The transition probabilities are summarized in Appendix Table 2 and described in greater detail below the table. Each of the parameters is labeled in Appendix Figure 1.

Appendix Table 2: Transition probabilities

Parameter	Label (Appendix Figure 1)	Parameter Value	Uncertainty	Source and Description
Incidence of pharyngitis	A1 (part)	2.3 per year in ages 5 to 15*	Sensitivity analysis	Ages 1-44 (ARF incidence assumed 0 after age 44), peaks in children and declines through adulthood [11,12,1]
Proportion of pharyngitis cases from GAS	A1 (part)	10% in ages 5 to 15*	Sensitivity analysis	Ages 1-44 (ARF incidence assumed 0 after age 44), lower in young children, peaks age 5-14, declines through age 24, constant after[11–13]
Risk of ARF after untreated GAS	A1 (part)	0.4%	0.1-0.9%	Ages 1-44 (ARF incidence assumed 0 after age 44), assumed constant across ages[14]
Incidence of first episode of ARF after pharyngitis	A1	0.06%*	0.01-0.14%	Ages 1-44, Incidence of pharyngitis x Proportion of pharyngitis cases from GAS x Risk of ARF after untreated GAS, adjusted for treatment (appendix)
Incidence of first ARF from non-pharyngitis infection	A2	0.01%*	0.003-0.034%	Varied percent of ARF without preceding pharyngitis in sensitivity analyses [2,4]
Incidence of first ARF	A3	0.07%*	0.02-0.17%	A1+A2
Risk of death from first ARF	A4	1%	0.5-2%	Assumed same across ages[14]
Risk of death from non-ARF causes	A5	0.69%*	0.66-0.71%	Mortality from non-RHD causes, varies by GBD age groups, converted to risk[10]
Probability of remission from first ARF	A6	-	-	100%-A4-A5-A7
Risk of RHD from first ARF	A7	32.4%*	19.6-48.6%	Scaled to be different in males/females (see full description in section below)[15,16]
Probability of no recurrence	A8	100%	-	Age 45+ assumed to have zero probability of ARF (first episode or recurrence)
Risk of recurrent ARF from non-pharyngitis infection	A9	1.7%*	0.8-2.6%	Among people with history of ARF, varied percent of ARF without preceding pharyngitis in sensitivity analyses (relative to A10)[2,4]
Incidence of pharyngitis	A10 (part)	See A1 (part)		
Proportion of pharyngitis cases from GAS	A10 (part)	See A1 (part)		
Risk of recurrent ARF after untreated GAS	A10 (part)	48%	24-76%	Ages 1-44 (ARF incidence assumed 0 after age 44), assumed constant across ages[16,17]
Risk of recurrent episode of ARF after pharyngitis	A10	6.9%*	3.3-10.4%	Ages 1-44, Incidence of pharyngitis x Proportion of pharyngitis cases from GAS x Risk of ARF recurrence after untreated GAS, adjusted for treatment (appendix)
Risk of recurrent episode of ARF	A11	8.6%*	4.2-13.0%	A9+A10

Risk of death from ARF recurrence	A12	2%	1-4%	Assumption higher than with first ARF[15]
Risk of death from non-ARF causes	A13	See A5		
Risk of remission from recurrence of ARF	A14	-	-	100%-A12-A13-A15
Risk of RHD from ARF recurrence	A15	64.3%	42.2-98.9%	Assumption of greater risk than from first ARF[15]
Incidence of RHD without HF	(A16) B1	0.035%*	0.034-0.037%	GBD 2017 RHD incidence used for B1, reductions from interventions calculated through relative reductions in A16[1]
Risk of HF in RHD Cases	B2	0.40%*	Sensitivity analysis	Sensitivity analyses conducted using information from multiple sources[1,15,18]
Risk of death in mild RHD	B3	See A5		
Probability of remaining in mild RHD	B4	-	-	100%-B2-B3
Probability of regression to normal status	B5	3.9%	1-15%	Regression only assumed under age 20[1,19]
Probability of surgery	B6	-	-	Incidence of surgery depends on scale-up of intervention, assumed 5% at baseline
Risk of death from valve surgery	B6a	3%	2-4%	Assumed risk of death from surgery
Probability of survival of surgery	B6b	-	-	1-B6a
Risk of death from non-RHD causes in RHD with HF	B7	See A5		
Risk of death from RHD in RHD with HF	B8	25%	16.2-37.7%	See full description
Probability of remaining in RHD with HF	B9	-	-	Calculated from B6 through B9
Risk of death from RHD after valve surgery	B10	1.7%*	1.5-1.8%	Risk from B8, reduced by roughly 85% (see effect size section)
Risk of death from non-RHD causes post valve replacement	B11	See A5		
Probability of survival post valve replacement	B12	-	-	1-B14-B15

*Note: Many parameters, including those derived from GBD estimates, are specific for age and sex, and some also vary by region—we present weighted averages across age and sex here for the base scenario at baseline levels of coverage in 2017 for the AU overall. How the parameters vary across age and sex, how some parameters are adjusted from the values extracted from literature, and how parameters vary across regions is discussed in full descriptions below.

A1: Incidence of first ARF from pharyngitis

The number of cases of ARF occurring after a case of GAS pharyngitis depends on the number of cases of pharyngitis, the proportion of these cases that are from GAS, and the risk of developing ARF after untreated GAS pharyngitis. A recent meta-analysis from Pearce and colleagues found a pooled estimate of 0.825 cases of pharyngitis per year.[11] However, this result was heavily influenced by a single clinic-based study reporting only cases of pharyngitis presenting to a clinic and using a population denominator corresponding to the clinic catchment area. We were not interested in the number of pharyngitis cases presenting at a facility but the overall number. We reproduced the meta-analysis from Pearce and colleagues excluding the study with this clinic-based estimate, using

only school-based or household-based studies. We additionally added an estimate from Jose et al. (2018) not included in the meta-analysis.[11,12] We calculated the value of 134.74 from the values in Table 3 of Jose et al. and an assumed 475 child-years as a denominator, given the 225-250 child roster that the authors write that they maintained throughout the study.[12] Estimates from the studies are shown in Appendix Table 3.

Appendix Table 3: Rates of pharyngitis per 100 person-years in children ages 5-15, adapted from Pearce et al. (2020)[11]

Study	Point Estimate	Lower Bound	Upper Bound
Engel 2012[20]	0.84	0.78	0.9
Kumar 2009[21]	232.34	216.55	249.27
Nandi 2001[22]	705.03	679.42	731.6
Steer 2009a[23]	150.23	136.19	165.71
Steer 2009b[23]	185.26	164.75	208.32
Jose 2018[12]	134.74		

Using the studies included in Appendix Table 3 without the Engel study, we obtained an estimate of 227.9 per 100 child-years or about 2.3 cases per child per year. GBD estimates of incidence of upper respiratory infection in the African Union in ages 5-14 were 2.1 per person and 2.6 per person under age 5 (estimates in India, for comparison, were 2.3 and 3.1 per person, respectively).[1] In our primary analysis, we assumed a rate of 2.3 cases of pharyngitis per year on average in the age range of 5 to 15. However, we explore other values in sensitivity analyses.

Pearce and colleagues also conducted a meta-analysis of GAS pharyngitis, finding 0.108 cases of GAS pharyngitis per year.[11] Appendix Table 4 shows the values from each of the studies. Again, we added an estimate from Jose et al. (2018) and excluded the estimate from Engel (2012), resulting in an estimate of 21.5 cases of GAS pharyngitis per 100 person-years in children ages 5-15 (roughly 10% of overall pharyngitis cases using the value from above). There was substantial variation across these studies, and none represent well the populations reflected across the African Union; however, these reflect the available evidence on pharyngitis infection. We took several approaches to validate the inputs on pharyngitis through multiple approaches described later in this section.

Appendix Table 4: Rates of GAS pharyngitis per 100 person-years in children ages 5-15, adapted from Pearce et al. (2020)[11]

Study	Point Estimate	Lower Bound	Upper Bound
Engel 2012[20]	0.18	0.15	0.21
Kumar 2009[21]	5.39	3.4	8.55
Kumar 2012[24]	16.60	12.27	22.46
Lennon 2000[25]	50.00	48.78	51.25
Nandi 2001[22]	94.97	85.87	105.05
Steer 2009a[23]	14.68	10.73	20.1
Steer 2009b[23]	14.61	9.62	22.19
Jose 2018[12]	23.16		

There was some evidence that the pattern of pharyngitis and the proportion of pharyngitis from GAS varies by age. Following other models, we assumed that the incidence of ARF below age 1 was 0, so we did not need to model pharyngitis incidence under age 1. We informed the age pattern of pharyngitis using incidence of upper respiratory infections in the African Union from the GBD 2017, which showed the highest incidence in ages 1-4, relatively consistent levels starting at approximately 85% of the peak incidence starting at age 5 that we assumed would decline to 75% of the peak by age 24, and then steadily declining rates down to approximately 50% of the peak levels through age 75. We assumed that cases of ARF among people without RHD did not occur at ages older than

44, consistent with previous cost-effectiveness analysis and the estimates of the incidence of RHD from the GBD, which near zero by age 50.[1,15] Therefore, we did not model pharyngitis cases after age 44.

Prevalence of GAS among incident pharyngitis appeared to be lower in very young children, peak in the 5-19 age range, and lower again in adults in non-OECD countries.[13] From age 1 to age 5, we assumed a linear increase from 50% of the peak proportion to the peak proportion at age 5. Then, we assumed the peak proportion from age 5 to 9, with a linear decrease to 80% of the peak by age 15, and a linear decrease to 20% of the peak at age 45. Once we defined these age patterns, we calibrated the levels of pharyngitis cases per person and the proportion from GAS by age such that the population weighted average pharyngitis cases per person in ages 5-15 was 2.3 and the proportion from GAS was 10%, using the population in the AU. There is considerable uncertainty about these age assumptions, but data were scarce. In sensitivity analyses varying assumptions about the number of pharyngitis cases per year, we used the same relative age patterns but shifted the overall level of cases per year.

To validate these inputs, we calibrated to the estimates of RHD incidence from the GBD in the AU overall. That is, we solved for a scalar by which to multiply the pharyngitis cases per year and the proportion from GAS such that the predicted RHD incidence from running our model was consistent with the GBD estimates, and we used this scalar to adjust these parameters. We separately scaled down the probability of ARF episodes transitioning to RHD for males to make the sex-specific RHD incidence rates consistent (see more detail under section on transition probability for A16). The inputs of 2.3 pharyngitis cases per person and 10% from GAS with the age patterns specified produced results very consistent with the GBD RHD estimates, and we only adjusted them up by 1.92% to ensure the incidence produced in 2017 was within 0.1% of the GBD incidence estimates. Scaling is described further in section A16. The adjusted parameters are shown in Appendix Figure 2. Additionally, we explore the implications of other values for these parameters in sensitivity analysis.

We obtained the risk of a first case of ARF after untreated GAS pharyngitis (0.3%) from Irlam et al. (2013).[14] Irlam et al. used a wide range of values for this parameter in sensitivity analysis (0.1% to 5%). We chose an uncertainty distribution that had wide spread but also had a high density around 0.3% and a mean close to 0.3%. We used a gamma distribution with a shape of 4 and a rate of 1000. This meant that the mode of the distribution was 0.3%, the mean was 0.4%, and the 2.5th and 97.5th percentiles of the distribution were roughly 0.11% and 0.85%.

Given the relatively low incidence of ARF in ages under 5 in the literature, we adjusted the chance of ARF after GAS pharyngitis under age 5 down so that the incidence of first GAS pharyngitis under age 5 was more consistent with observations in the literature.[26–28] One study suggests incidence of ARF among children from ages 1-4 may be roughly 33% of that in ages 5-9 or 20% of that in ages 10-14.[27] Another suggests incidence in ages 0-4 may be about 13% of the incidence in ages 5-14.[26] The estimates of RHD incidence in the GBD under the age of five are higher than might be expected from these other studies. Given our use of the GBD estimates, we adjusted the chance of ARF after untreated strep under age five using a scalar of 75% so that the estimates of RHD incidence produced by the model under age five were not substantially lower than those from the GBD (see section A16).

The incidence among the general population of a first case of ARF after a case of GAS pharyngitis was calculated by multiplying the annual pharyngitis cases by the percent from GAS by the chance of a first case of ARF after GAS pharyngitis infection. In addition to this incidence of first ARF, we also included incidence of first ARF not preceded by symptomatic pharyngitis infection (see A2).

We assumed a 15% decline in incidence of RHD over 2017 to 2030 (and an equivalent annualized rate of change for projections past 2030) in the second part of the model from improvements in primordial prevention (reduction in household crowding, greater sanitation and hygiene, better household conditions, etc.).[29] We did not have evidence about which probabilities primordial prevention would primarily affect, so we distributed the effect across pharyngitis cases per person, probability that the case was from GAS, and the probability it would become ARF such that the product of these three parameters experienced a 15% decline in the period.

The same age- and sex-specific probabilities were used across regions in the AU.

A2: Incidence of first ARF from non-pharyngitis infection

The proportion of ARF arising from sore throat versus asymptomatic GAS throat infection versus other GAS infection (e.g. skin infection) may vary across settings and individuals.[3,21,30] Veasy et al. (1987), for instance, suggests that up to 66% of people may not recall sore throat in the three months prior to ARF.[2] There is considerable uncertainty about the proportion of ARF cases arising without a preceding symptomatic case of GAS pharyngitis, though it has traditionally been assumed that cases of ARF are preceded by pharyngitis. We assumed in our primary analysis that 20% of ARF cases were not preceded by GAS pharyngitis. To obtain the incidence of ARF occurring without preceding pharyngitis, we multiplied the estimate from A1 by .25 (20%/80%). We did not incorporate uncertainty in this parameter in our model—rather, we varied this parameter in sensitivity analyses. Note that the primary prevention intervention acted on A1, not A2. A more thorough description of the implications of the fraction of ARF cases without preceding symptomatic GAS pharyngitis can be found in the section on intervention effect sizes. As this parameter was calculated from other parameters that did not vary by region, this age- and sex-specific parameter did not vary across regions in the AU.

A3: Incidence of first ARF

This was the sum of A1 and A2. The age pattern is shown in Appendix Figure 2. Given the lack of reliable estimates of ARF incidence, particularly in Africa, estimates of RHD incidence have been suggested as a reasonable proxy for the trends in ARF incidence, as one would expect RHD incidence patterns to be similar to ARF incidence patterns.[31,32] As described in A1 and A16, we calibrated the parameters in this part of the model to be consistent with the RHD incidence estimates from the GBD, since estimates of ARF incidence in the AU were largely unavailable. As this parameter was calculated from other parameters that did not vary by region, this age- and sex-specific parameter did not vary across regions in the AU.

A4: Risk of death from first ARF

Irlam et al. (2013) used 1% (0.5-2%) as the probability of death during a first case of ARF. We used this probability.[14] This probability did not vary by region.

A5: Risk of death from non-ARF causes

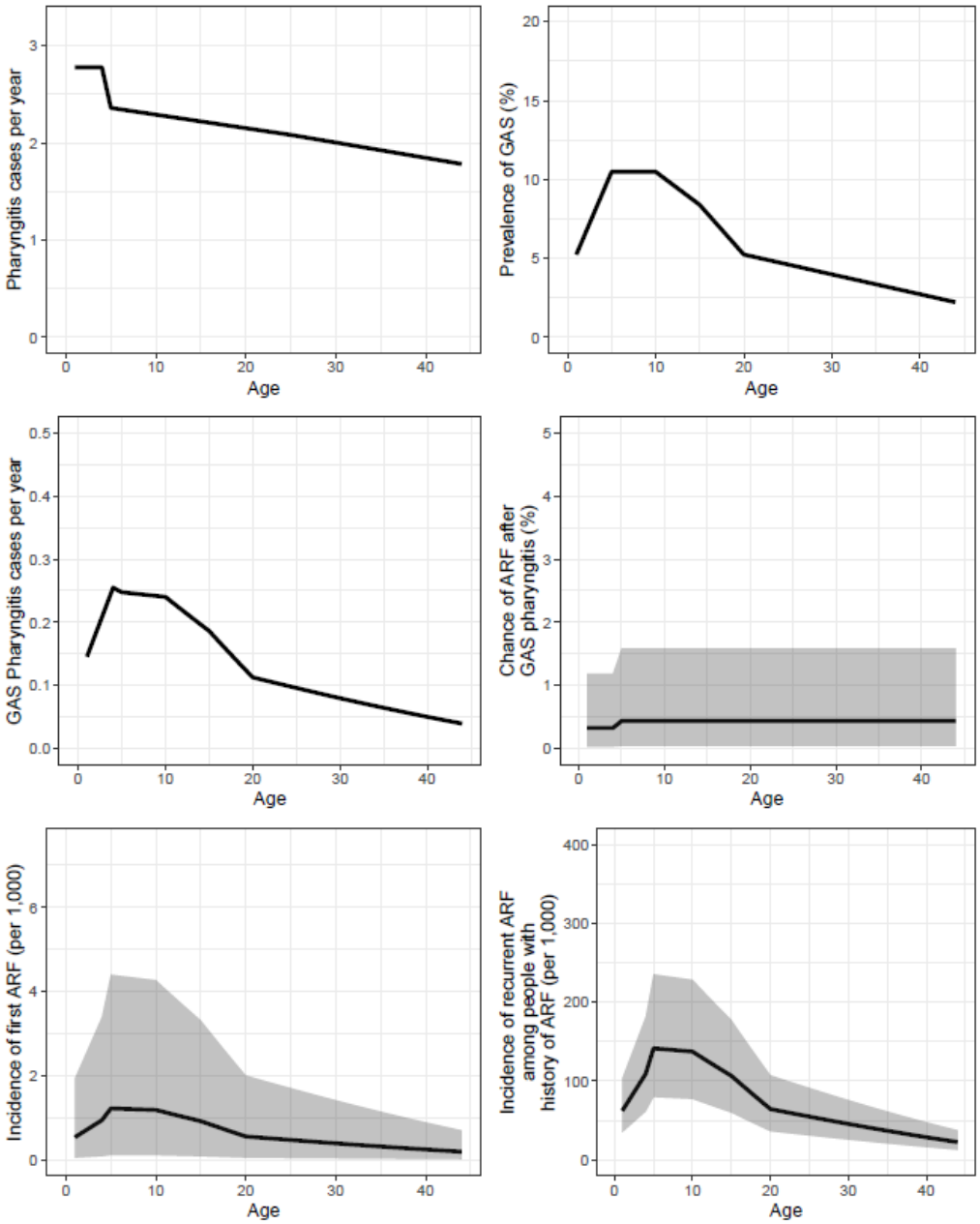
We used the risk of all-cause mortality from GBD (using the time trends projected from UN World Population Prospects as described earlier in the appendix).[6,10] We calculated age-, sex-, and location-specific mortality rates by multiplying the GBD estimates by the WPP-derived scalars. We created regional mortality rates by taking population-weighted averages using population projections from WPP. Given that the population facing this risk would not be dying from RHD in this stage, we needed to use a risk of death from non-RHD causes. We assumed that the mortality rates for 5-year age groups applied to each of the years within the age group to create single-year rates. We then transformed the rates (mx) to probabilities (qx) using a common demographic approximation.[7]

$$qx = 1 - e^{-n*mx}$$

Then, we found the fraction of all-cause mortality from RHD (using GBD 2017 estimates by age, sex, and location), and multiplied this fraction by the all-cause probability of death to obtain the probability of death from RHD. We subtracted this from the all-cause probability to obtain the risk of death from non-RHD causes.

A6: Probability of remission from first ARF

The probability of remission from first ARF was simply 1 minus the probability of death from ARF or non-ARF causes minus the probability of progression to RHD.



Appendix Figure 2: Age distribution of pharyngitis cases per year, prevalence of GAS among these cases, GAS pharyngitis cases per year, incidence of first ARF (pharyngitis and non-pharyngitis), and incidence of recurrent ARF (pharyngitis and non-pharyngitis) among people with history of ARF

A7: Risk of RHD from first ARF

Watkins et al. (2016) used a probability of 36% (24.1-47.9%) for the probability of progression to RHD from first untreated ARF.[15] This was calculated from Hewitson and Zilla (2010) based on the approximation that 40% of ARF cases involve carditis and 90% of those result in RHD.[16] We used this probability but scaled to make the incidence of RHD consistent with that from the GBD in 2017 (see A16). In particular, there is evidence that the risk of RHD after ARF may be higher among females than males, particularly in adolescence and adulthood, as the incidence of RHD is higher, but there is no evidence of substantially different rates of ARF.[33] Assuming rates of ARF were the same for males and females, we scaled down the risk of RHD after ARF among males by about 25%, resulting in a

probability of 26.8% (18.0-35.7%). We used the original probability for females. This parameter did not vary across locations.

A8: Probability of no recurrence

Starting at age 45, we assumed that no recurrent cases of ARF would occur. While studies do show incidence of ARF above age 44, it is quite small.[26] This probability (100%) was applied across regions.

A9: Risk of recurrent ARF from non-pharyngitis infection

As with the first case of ARF, we made an assumption about the proportion of recurrent ARF cases that occurred after asymptomatic or non-pharyngitis infection. As with A2 and A1, we multiplied A10 by 20%/80% to obtain A9. This assumption was applied across regions. This assumption was varied in sensitivity analysis.

A10: Risk of recurrent episode of ARF after pharyngitis

The probability of ARF recurrence used in Watkins et al. (2016) was 11.3% (7.5-15.0%), derived by multiplying a prevalence of 15% GAS by a 75% probability of ARF with reinfection from Hewitson and Zilla (2010).[15,16] Rather than using these estimates, we based the risk of a recurrent episode on our estimates of GAS pharyngitis incidence (described in A1). We multiplied the estimates of GAS pharyngitis incidence by a probability of ARF with re-infection of 25-75% based on the same source cited by Hewitson and Zilla (2010)—the T. Duckett Jones Memorial Lecture.[16,17] We assumed a mean of 50%. Like the components of A1, this was scaled such that the predicted incidence of RHD was consistent with that from the GBD (see A16), though the scalar for the default scenario was 1.019, resulting in little change. The resulting risk of recurrent ARF after an episode of pharyngitis was similar to that from Watkins et al. (2016) between ages 5 and 15 (see Appendix Figure 2, last panel). Averaged across ages 1 to 44, the risk was 6.9% (3.3%-10.4%). This did not vary by location except in relation to coverage of interventions.

A11: Risk of recurrent episode of ARF

This was the sum of A9 and A10. The age pattern of risk can be seen in Appendix Figure 2.

A12: Risk of death from ARF recurrence

We used the risk from Watkins et al. (2016) of 2% (1-4%).[15] This did not vary by region.

A13: Risk of death from non-ARF causes

See A5

A14: Risk of remission from recurrence of ARF

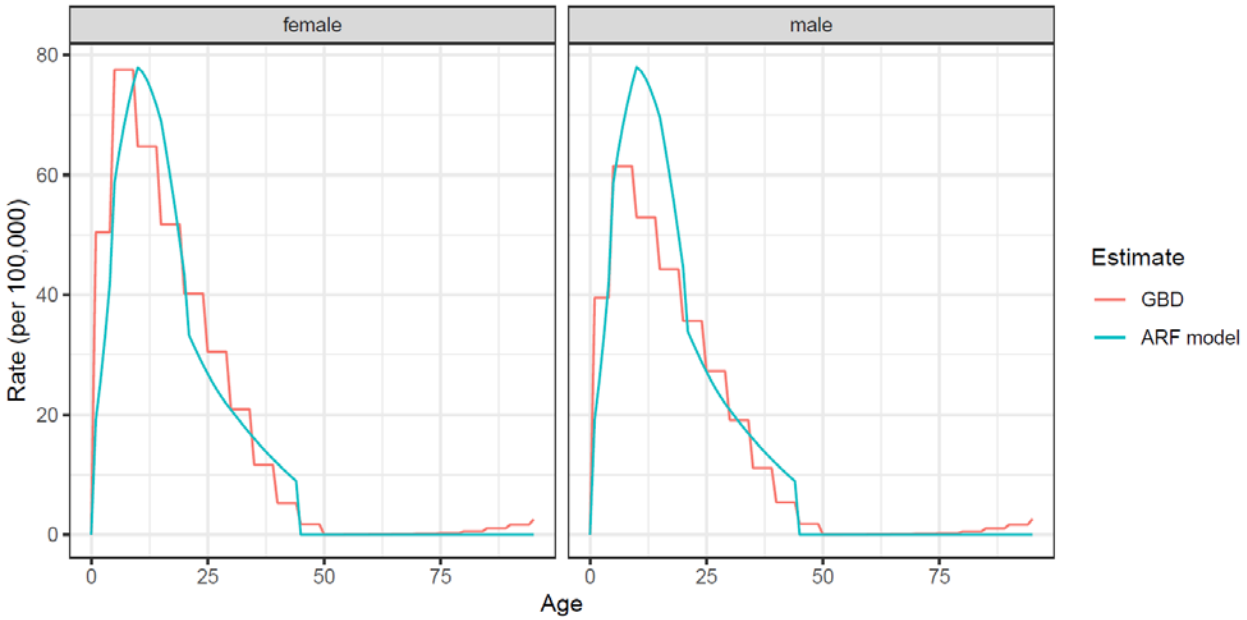
The risk of remission was 1 minus the probability of death from ARF recurrence, minus the risk of death from non-ARF causes, minus the progression to RHD from ARF recurrence.

A15: Risk of RHD from ARF recurrence

We used the chance of progression from Watkins et al. (2016) of 72% (48.2-95.8%).[15] Similar to A7, this was scaled down for men by about 25%, resulting in a probability of 52.2% (29.3-69.1%).

A16: Incidence of RHD without HF

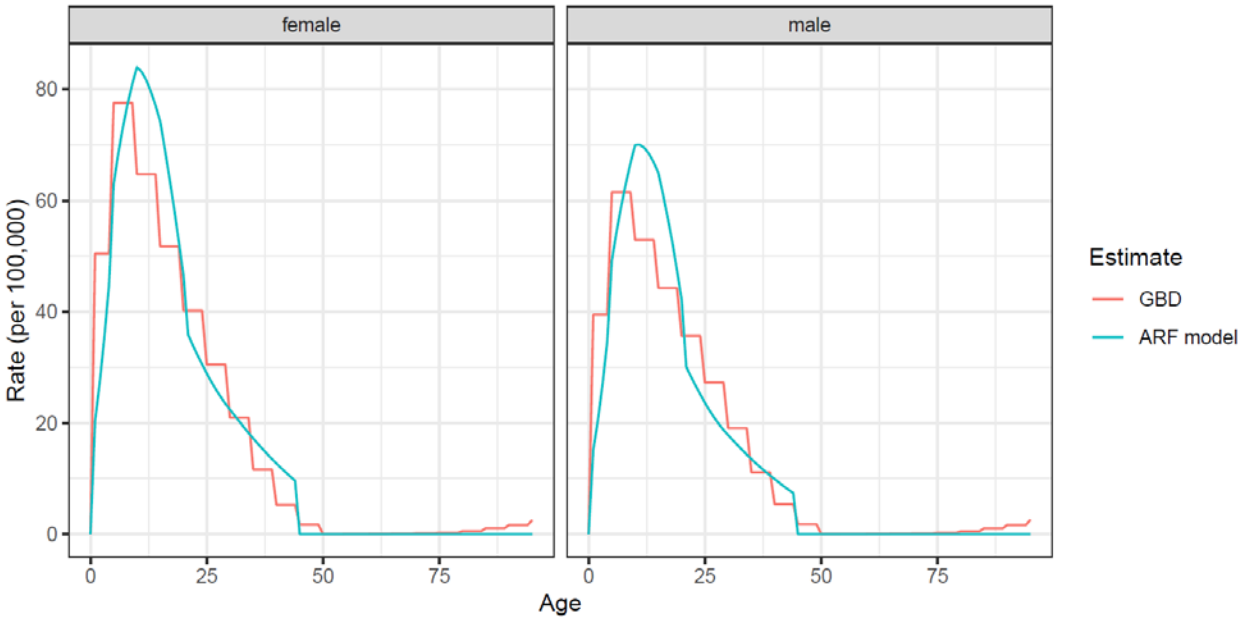
Calculated as a result of the prior steps (risk after ARF recurrence and risk after first ARF). The age pattern of the estimates with the initial parameters was similar to the age pattern from the GBD, and for females, the overall incidence estimate was very similar. However, for males, our ARF model implied higher RHD incidence than estimated from the GBD (Appendix Figure 3). We adjusted the parameters to calibrate the results to the GBD RHD incidence estimates.



Appendix Figure 3: Incidence rates of RHD by age and sex, estimates from our model of ARF using initial parameters versus estimates from the GBD

The parameters we could alter to have a meaningful effect on incidence were the number of pharyngitis cases per year, the proportion of pharyngitis cases that were from GAS infection, the chance of ARF from GAS pharyngitis infection, the risk of RHD from first ARF infection, the chance of recurrent ARF from GAS pharyngitis infection, and the risk of RHD from a recurrent ARF infection. We did not scale the proportion of ARF cases following pharyngitis; we explore the implications of assumptions about this parameter in parameter-specific sensitivity analyses. The risks of death from all causes were based on the GBD, and the risks of death from ARF would have very small consequences on the number of people progressing to RHD given their low probabilities relative to the other probabilities, so we did not adjust the probabilities of death.

We started with the discrepancy between males and females. In most populations, rates of ARF are similar in males and females, and the greater incidence of RHD in females may be tied to immune factors or gaps in prophylaxis, and differences are greater in adolescents and adults than children.[33] Our initial parameters did not account for any differences between males and females, so the difference in the amount we needed to scale the female versus male estimates was assumed to reflect the difference in the risk of RHD after ARF. Since the female RHD incidence from our model was very close to that from the GBD, we assumed that most of the extra reduction for males should occur in the risk of RHD after ARF. We ran the model from 2000 to 2017 for the AU as a whole to find the scalars that led to estimates of incident RHD cases in 2017 consistent with those from GBD, by sex. We calibrated the model such that the estimates were within 0.1% of the GBD estimates. The resulting scalars were 0.745 for the chance of RHD following ARF (first or recurrent) in males and 1.0192 for each of: the number of pharyngitis cases per year, the prevalence of GAS among these cases, and the chance of ARF (first or recurrent). The scaled results are in Appendix Figure 4. Our model estimated lower rates of RHD incidence under age 5 than the GBD, though higher than in other literature (see A1), but the overall age pattern was relatively consistent with that of the GBD estimates. For the second part of the model (below), we still used the GBD estimates of RHD incidence rather than these estimates, but the scaling process ensured that our estimates of ARF and pharyngitis in the first part of the model were more consistent with the GBD RHD estimates.



Appendix Figure 4: Incidence rates of RHD by age and sex, scaled estimates from our model of ARF using initial parameters versus estimates from the GBD

While we calculated the scalars using the AU as a whole, we used the same scalars for each region when running the model by region, as we did not have any data to estimate differences in patterns of GAS pharyngitis by regions within the AU. The incidence of RHD (A16) was region-specific based on the prior steps of the model.

Note that in the sensitivity analyses varying the proportion of ARF cases with preceding symptomatic pharyngitis and the number of pharyngitis cases per year, we also scaled to the GBD incidence estimates. In scenarios in which we varied the proportion of ARF cases with preceding pharyngitis (50% and 99%), we used the initial scalars, maintaining the number of pharyngitis cases and GAS prevalence, and added an additional scalar to the risk of ARF after pharyngitis to make the implied RHD incidence estimates consistent with those from the GBD. We ran a scenario with 4 cases of pharyngitis cases annually in the 5-15 age group on average, though to enforce consistency with the GBD RHD incidence estimates, we scaled down pharyngitis incidence, prevalence of GAS among those pharyngitis cases, and risk of ARF after a case of untreated GAS pharyngitis by multiplying those parameters by 0.8475 (resulting in 3.39 cases annually in the 5-15 age range). We ran a scenario assuming 1 case of pharyngitis annually among those in the 5-15 age group on average. To maintain the low number of pharyngitis cases in this scenario, we scaled up the chance of ARF after a case of untreated GAS pharyngitis by a factor of 2.8769 for first cases of ARF and 1.3 for recurrent cases in order to calibrate to the RHD incidence estimates from the GBD.

B1: Incidence of RHD without HF

We used the incidence of RHD from GBD 2017.[1] We created regional estimates from the country-level GBD estimates using the population-weighted incidence by age and sex. We assumed a linear 15% decline from 2017 to 2030 (extended at the same annualized rate of change past 2030 for projections past 2030) due to improvements in primordial prevention, along with other declines from the scale-up of interventions. However, to incorporate the effects of primary and secondary prevention, we needed to use the estimated impact from the first part of the model. We estimated B16 for the scale-up scenarios as well as without scaling up coverage to find the effect on RHD incidence of changes in primary and secondary prevention. We calculated age- and sex-specific scalars by which to adjust GBD RHD incidence using the ratio of the estimated rates from the first part of our model. These adjusted GBD incidence rates were used for B1.

B2: Incidence of HF in RHD cases

We estimated this parameter for the AU as a whole—the parameter did not vary by region, except as influenced by the coverage of interventions.

The GBD 2017 study did not report incidence of HF from RHD, but it did report prevalence. As discussed in the "Consistency of evidence on RHD epidemiology" section of the appendix (pp 61-67), the estimates from the GBD study did not appear consistent with other estimates. Given the conflicting estimates and data on the age distribution of HF, we took multiple approaches to estimate the probability of transitioning to severe RHD. For clarity, we will call them the primary analysis, the GBD approach, and the GBD plus Heart of Soweto approach. The GBD approach and GBD plus Heart of Soweto approaches were included for sensitivity analysis.

In the GBD approach, we derived the probability of transitioning from mild/asymptomatic RHD to RHD with HF using the estimates of HF prevalence from the GBD (see section of appendix on derivation of parameters from the GBD).

In the GBD plus Heart of Soweto approach, we used primary data to inform the age distribution of HF incidence. As noted earlier in the appendix, the age distribution of heart failure in people with RHD from the GBD study was at odds with that from hospital studies in Africa.[18,34,35] The Heart of Soweto Study reported the age pattern of de novo hospital presentations of RHD among adults starting at age 14, including incidence rates by age group.[18] Many of these cases were relatively advanced: 66% presented with dyspnea, 66% with palpitations or chest pain, and 27% with peripheral edema. We treated the incidence rates as incidence rates of HF from RHD. The median age was 43, and the age pattern of incidence is shown in Appendix Table 5. To obtain transition probabilities, we needed new cases of HF divided by prevalence of RHD without HF. We did not have an estimate of the prevalence of RHD without HF represented in the study population in Soweto to calculate such a probability. We multiplied age group presentation rates by the populations in the age groups in South Africa to obtain implied counts of HF incidence by age group. Since the Heart of Soweto study did not include children under age 14, we used the GBD implied transition probability under age 5 and interpolated between that probability and the probability we calculated for ages 14 to 19. To create more consistency in total estimates of HF and to account for possible discrepancies in rates of RHD between Soweto and the rest of South Africa, we scaled the aggregated age-specific RHD HF incidence counts to the RHD HF incidence from the GBD study.

Then, using the scaled age-specific incidence estimates, we solved for the transition probability (*trans prob*) from mild RHD to incident HF using the formula below, where the impact of secondary prophylaxis was calculated using the impact formula described in the main text and *cases mild* represented the cases of RHD without HF.

$$HF\ Incidence\ Scaled = trans\ prob * impact\ of\ secondary\ prophylaxis * cases\ mild$$

We assumed these transition probabilities would apply across all countries in the AU.

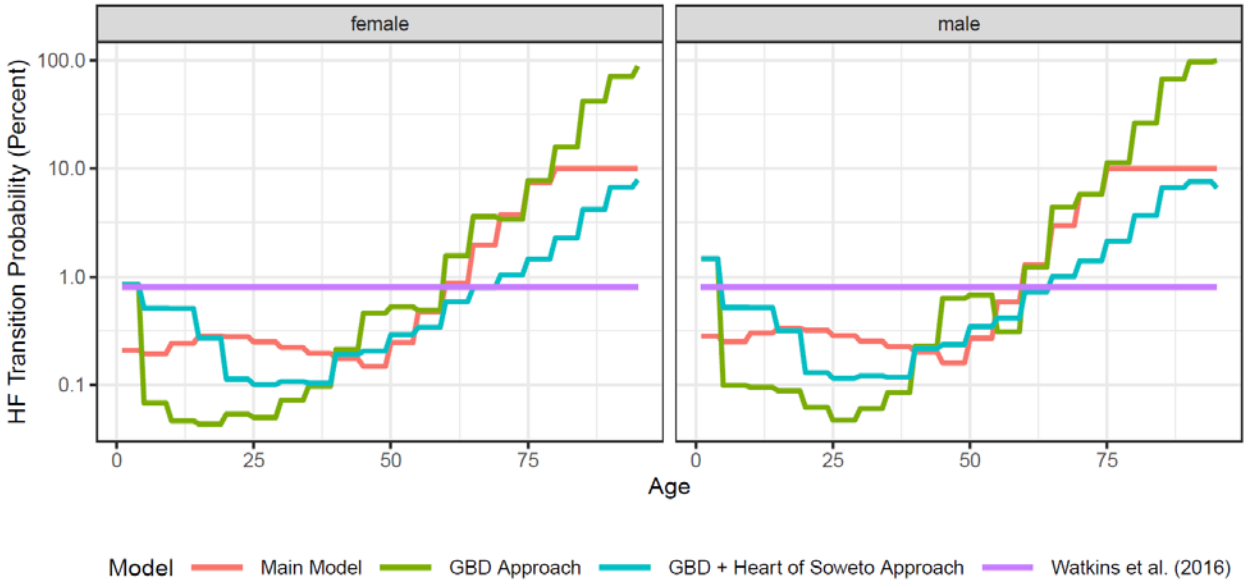
Appendix Table 5: Rate of de novo presentations of RHD to hospital from Heart of Soweto Study, by age group [18]

Age Group	Incidence (per 100,000)
14 to 19	30
20 to 29	15
30 to 39	17
40 to 49	31
50 to 59	39
60 plus	54

In the primary analysis, we had an age distribution of death rates and deaths as described early in the appendix, a probability of death of about 25% among people living with HF, and a prevalence of mild RHD. From these fixed parameters, we back-calculated the implied transition probability. As previously discussed, the small prevalence of RHD at old ages in the GBD and the relatively high death rate necessitated transition probabilities in old ages that seemed implausible. We set an upper limit of a 10% annual risk of developing heart failure. To check our implied transition probabilities for face validity, we compared to the 41% lifetime risk from Michaud et al. (1999) also used

in the Watkins et al. (2016) cost-effectiveness analysis.[15,36] For someone getting RHD at age 5, our transition probabilities give a 21% risk of developing HF by age 65 and 50% risk by age 75, provided the person lives to those ages.

Appendix Figure 5 shows a comparison of the transition probabilities implied in the several different approaches, with the annualized probability from Watkins et al. (2016) of 0.8% as a benchmark. Using the incidence estimates from the Heart of Soweto raised the risk of heart failure in young adults compared to the GBD estimates. The primary analysis, which used the death pattern from DisMod raised this risk higher in adults from around age 20 to around age 40. After age 55, the estimates from each approach were similar, though in the primary analysis we capped the annual probability of a transition to HF at 10%. Although this reduced death rates above age 75-80 in our model, it was more realistic than the extreme values implied by the other approaches. Additionally, the proportion of people in that age group in the African Union is low, so the effect on total deaths was low in the near term.



Note: y-axis log-transformed

Appendix Figure 5: Implied transition probability from RHD without HF to RHD with HF, multiple approaches

There is uncertainty about these age distributions. In the Heart of Soweto study from which we used incidence, not all of the patients had symptoms consistent with HF at presentation, so the age pattern of HF incidence in people with RHD may be somewhat older than that reflected by these rates of de novo hospital presentations.[18] On the other hand, some patients presenting with symptoms may have had HF for some time before presenting. The cumulative incidence of HF after 10 years of follow-up after RHD diagnosis in a study in the Northern Territory in Australia was about 18% (and higher in the first year after diagnosis, at about 8%, than in subsequent years).[37] This probability is higher than that assumed in the Watkins et al. (2016) analysis (cumulative probability of 7.7% over 10 years, using the 0.8% transition probability annually). However, it is possible that the study in Australia was more likely to capture serious cases, and the epidemiological patterns of the disease may vary across settings. Among the indigenous population making up 94% of the subjects in the study in the Northern Territory of Australia, the median age of diagnosis was 21, suggesting a relatively high annual probability of transition to HF at a relatively young age. Among the non-indigenous population making up the other 6% of subjects, the median age was 46.

Given that this parameter was intrinsically tied to other assumptions about prevalence and mortality, that there is considerable uncertainty about both the level and the age pattern, and that we conducted specific sensitivity analyses about this pattern, we did not include a distribution of uncertainty about this parameter.

B3: Risk of death in mild RHD

We used the risk of all-cause mortality from GBD (using the time trends projected from UN World Population Prospects as described earlier in the appendix).[6,10] We calculated age-, sex-, and location-specific mortality rates by multiplying the GBD estimates by the WPP-derived scalars. We created regional mortality rates by taking population-weighted averages using population projections from WPP. Given that the population facing this risk would not be dying from RHD in this stage (as we assumed RHD deaths to occur in those with severe disease), we needed to use a risk of death from non-RHD causes. We assumed that the mortality rates for 5-year age groups applied to each of the years within the age group to create single-year rates. We then transformed the rates (mx) to probabilities (qx) using a common demographic approximation.[7]

$$qx = 1 - e^{-n*mx}$$

Then, we found the fraction of all-cause mortality from RHD (using GBD 2017 estimates by age, sex, and location), and multiplied this fraction by the all-cause probability of death to obtain the probability of death from RHD. We subtracted this from the all-cause probability to obtain the risk of death from non-RHD causes.

B4: Probability of remaining in mild RHD

This probability was 1 minus the probability of transitioning to RHD with HF, minus the probability of death in mild RHD (non-RHD causes).

B5: Regression from mild RHD to normal

There has been increasing evidence of regression of definite RHD to borderline RHD and borderline RHD to normal based on echocardiographic findings.[19] There are notable weaknesses in existing evidence: length of follow-up is varied; certain regions are not well represented in the data; and there is varied coverage/adherence to prophylactic benzathine penicillin among the populations studied.[19] These limitations make probability of regression from mild RHD to normal status difficult to estimate accurately. The GBD study calculated regression rates from two studies (0.14 cases per person-year and 0.014 cases per person-year) and applied bounds of 0.01 and 0.15 for a prior in the estimation of remission rates.[1] The regression only applied to children under age 20 in the GBD, as the studies used were only in these ages.

Given the uncertainty about various factors, such as how coverage of and adherence to prophylactic penicillin, age, and duration of disease may affect rates of regression, we used these bounds to inform a distribution to create simulations of regression probabilities to propagate uncertainty. We log-transformed the bounds and found the average in log-space. We estimated a standard error by treating the bounds as upper and lower bounds of a 95% confidence interval: (log(0.15)-log(0.01))/(2*1.96). We then took draws in log-space using the mean and standard error, and we exponentiated these draws as our estimates of regression rates. We treated these as the probability of regression to a “normal” state from mild RHD.

B6: Probability of surgery

The incidence of surgery depended on the scale-up of the surgery coverage. We assumed 5% coverage at baseline in the AU (see section on coverage for more details and region-specific information). Surgery was restricted to ages 10 to 39, and the coverage was the probability of surgery. We applied this probability to the population with RHD with HF before other probabilities were applied—people who received surgery in a given year were transitioned either to the “RHD after Valve Surgery” state or the “Death from RHD” state because of the immediate risk of surgery from the operation.

B6a: Risk of death from valve procedure

We assumed a 3% risk of death from the operation itself, so 3% of those receiving surgery went straight to the “Death from RHD” state. This applied in any region.

B6b: Survival of valve procedure

We assumed that 97% of those receiving a valve procedure survived and went to the “RHD after Valve Surgery” state.

B7: Risk of death from non-RHD causes in RHD with HF

We used the same probability from B3 for consistency.

B8: Risk of death from RHD in RHD with HF

We used the risk of all-cause mortality from GBD (using the time trends projected from UN World Population Prospects as described earlier).[6,10] Before applying time trends, we created region-specific mortality rates using population-weighted averages of country-specific GBD estimates. We used single-year populations and assumed rates for broader 5-year age groups to apply to single-year ages within them. We calculated the overall mortality among people with RHD. To add the excess mortality from RHD, we took one of several approaches based on our strategy with parameter B2. For the full GBD sensitivity analysis approach (see B2), we derived this parameter from the GBD (WC="with-cause", s=sex, a=age, AC=all-cause, mx=mortality rate, prev=prevalence, RHD-HF=RHD with HF):

$$mx_{s,a}^{WC} = (mx_{s,a}^{AC} - mx_{s,a}^{RHD}) + \frac{mx_{s,a}^{RHD}}{prev_{s,a}^{RHD-HF}}$$

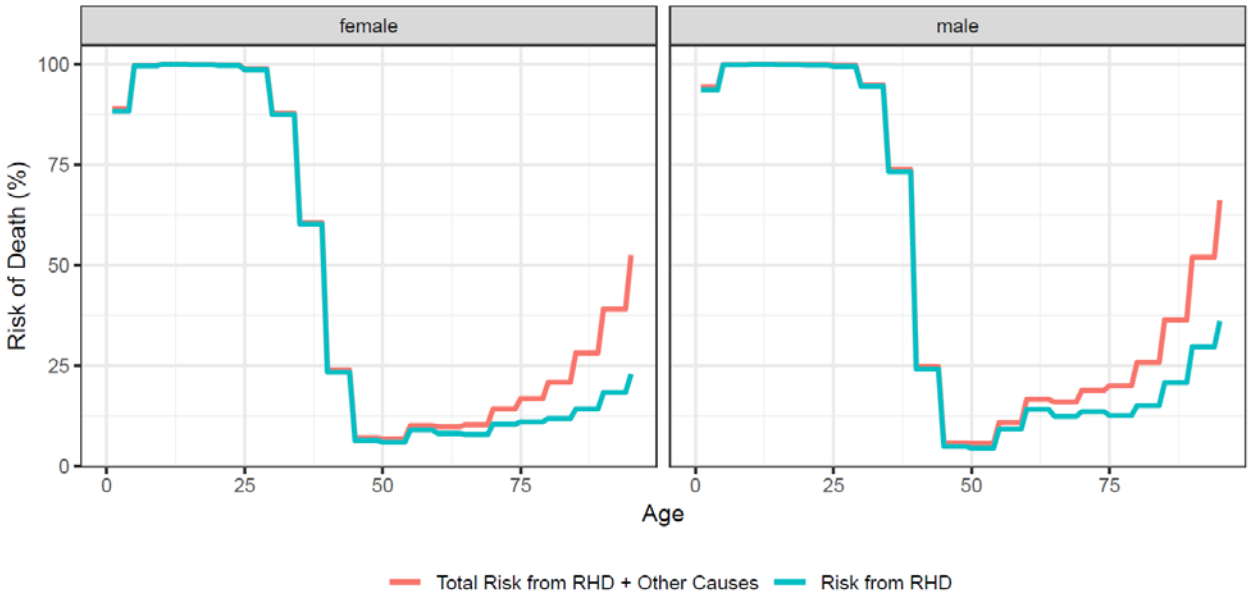
Then, we converted the overall mortality rate to a risk using a common demographic approximation (qx=mortality risk):[7]

$$qx_{s,a}^{WC} = 1 - e^{-mx_{s,a}^{WC}}$$

For consistency, we assumed the probability of death from non-RHD causes from B3 (see description of B3). We subtracted this from the total probability of death among people in the RHD with HF health state to obtain the probability of death from RHD:

$$qx_{s,a}^{RHD} = qx_{s,a}^{WC} - qx_{s,a}^{cause-subtracted}$$

The relatively old age pattern of severe RHD and inconsistencies between prevalence and death estimates in the African Union in the GBD create an implausible distribution of mortality risk from RHD across age groups (see Appendix Figure 6 and section on Consistency of evidence on RHD epidemiology, appendix pp 61-67). These estimates were internally consistent with the estimates of mortality and prevalence from GBD, and therefore generated death rates consistent with the GBD estimates, but lacked face validity.



Appendix Figure 6: Risk of death from RHD and from all causes including RHD among people with HF, derived from GBD 2017

Rather than using this pattern in the primary analysis, we assumed an RHD-specific mortality risk among people with severe RHD that did not have this extreme variation by age and was consistent with what has been observed in registry studies. In two years in the REMEDY study, 16.9% of patients died, translating to an annual risk of about 8.84%.[38] This was relatively consistent with the annualized mortality derived from 5-year survival probabilities observed in a cohort of patients managed for heart failure in Rwanda.[39] Given that some of the REMEDY cohort did not yet have severe disease (though most did) and the patients were receiving some level of care for their sequelae (e.g. anticoagulation or management of heart failure), this mortality risk is likely to be substantially lower than the risk among people with severe disease without intervention. In a Cox proportional hazards model of mortality in these patients, severe disease and heart failure were associated with a higher mortality hazard.[38]

Among people with severe RHD that are untreated, we assumed an annual mortality risk of 25%. This was consistent with the effect size we used for HF management (see section of appendix on intervention effect sizes) and the probabilities of death cited above. We incorporated uncertainty around this risk by taking draws from a log-normal distribution with a mean of 25%. We generated uncertainty assuming an uncertainty interval of roughly 15% to 40% using the following to obtain a standard deviation in log space:

$$sd = (\log(.4) - \log(.15))/(2 * 1.96)$$

We used this probability across regions.

B9: Probability of remaining in RHD with HF

This probability was calculated based on other probabilities. The model acted on the probability of surgery before the other probabilities, those probabilities applied to a smaller portion of the population.

$$B10 = 1 - B6 - \frac{1 - B6}{1} * (B7 + B8)$$

B10: Risk of death from RHD post valve replacement

We used the risk from B8 but applied to it the effect size of the mortality risk reduction from surgery (see intervention effect sizes), roughly an 85% reduction. This mortality assumed full coverage of post-operative management (the scale-up of this management was coordinated with scale-up of surgery).

B11: Risk of death from non-RHD causes post valve replacement

See B7.

B12: Probability of survival post valve replacement

The probability of remaining in the post valve replacement category was 1 minus the probability of death from RHD and non-RHD causes (1-B10-B11).

Intervention Effect Sizes

Appendix Table 6: Effect sizes of interventions

ID	Intervention	Target	Effect Size (% reduction)	95% Uncertainty Interval	Effect Source
1	Primary prevention (increasing treatment of GAS pharyngitis in ages 5-15, awareness raising, strengthening supply chains, provider training)	Reduction in transition post-GAS pharyngitis to ARF	68%*	52-79%	Robertson et al. (2005)[40]
2a	Secondary prevention (prophylactic penicillin after ARF—10 years or until age 20, whichever longer)	Reduction in transition from ARF to RHD	55%	8-78%	Padmavati et al. (1973)[41]
2b	Secondary prevention (prophylactic penicillin in asymptomatic RHD)	Reduction in transition from RHD without HF to RHD with HF	55%	8-78%	Assumption; Size of this reduction debated, may be lower than effect on ARF
3	Platforms for HF management, including management during pregnancy	Reduction in mortality risk from RHD	60%*	30-80%	Assumption (multiple studies examined below)
4	Cardiac surgery & post-operative care (ages 10-40)	Reduction in mortality risk from RHD; 3% operative mortality	85%; 3% operative mortality	70-92%	Assumption (multiple studies examined below)
5	Evaluation and counseling on family planning for women of reproductive age**	Percent of women of reproductive age with RHD desiring contraceptive method who have access	-	-	-

GAS=group A streptococcal, ARF=acute rheumatic fever, RHD=rheumatic heart disease, HF=heart failure
*Mortality risk reduction assumed to last 4 years, as HF management not curative. **Intervention included here because of the risk that RHD poses during pregnancy, but effects not modeled (see limitations)

Intervention 1: Primary prophylaxis

The effect of primary prevention in Robertson et al. (2005)[40] was a 68% reduction among people presenting with pharyngitis. The effect estimated from Robertson et al.[40] (RR=0.32 [95% CI: 0.21-0.48]) was converted to a percent reduction (68%). We applied this effect to the probability of ARF arising from GAS pharyngitis.

The effect on cases of ARF overall is less clear. Veasy et al. (1987)[2] suggests that up to 66% of people may not recall sore throat in the three months prior to ARF. That implies that only 33% of people would obtain the primary prevention intervention, as those without sore throat would not present for treatment. The proportion of ARF arising from sore throat versus asymptomatic GAS throat infection versus other GAS infection (e.g. skin infection) may vary across settings and individuals.[3,21,30] Multiplying the 68% effect size by 33% (from Veasy et al.) results in a 22% reduction estimate. This estimate is consistent with a 21% or 28% reduction (though statistically insignificant) in school-wide ARF rates from a school-based study in New Zealand, though some other community-based strategies have been more effective.[42,43] We use the 68% reduction effect size and constructed our model to be able to vary assumptions about the proportion of ARF cases occurring after symptomatic pharyngitis cases to understand the implications in sensitivity analyses.

Intervention 2a: Secondary prophylaxis (prophylactic penicillin for ARF before RHD)

The effect of secondary prophylaxis with penicillin in people with ARF who have not yet advanced to RHD is taken from Manyemba and Mayosi (2002).[44] Manyemba and Mayosi reviewed three studies that compared penicillin with control. Only Padmavati et al. (1973) showed a significant reduction in RF recurrence (RR=0.45, 95% CI 0.22-0.92) from administration of penicillin (benzathine), though the effect sizes of the others were similar.[41] Yet, no effect of prophylaxis was found on mortality from progression of acute carditis or HF or from all-cause mortality in that study.[41] Intramuscular penicillin was found to be more effective than oral penicillin in the review, and more frequent administrations were also found to be more effective compared to less frequent intramuscular administrations,

though the quality of evidence was poor.[44] We converted the relative risk to a percent reduction: 55% (95% CI 8-78%).

Intervention 2b: Secondary prophylaxis (prophylactic penicillin for ARF with RHD)

There has been some skepticism that secondary prophylaxis has clinically important benefits after the development of RHD. Padmavati et al. (1973) found a reduction in recurrence of ARF from prophylactic penicillin, but there was no reduction in mortality from progression of disease.[41] They suggest that the causes of death were mostly due to progression of initial heart disease that was severe in the beginning rather than recurrence of RF. In a recent book chapter, de Dassel and colleagues suggest that there is strong evidence that secondary prophylaxis also reduces severity of RHD by preventing progression.[45] It is unclear whether the effect size differs, as many older studies lacked echocardiography and several newer studies showing the possibility of regression in severity with prophylaxis have small sample sizes.[45] There is an ongoing study that should provide important new evidence on this effect and the effect of secondary prophylaxis on regression of latent RHD.[46] We used the same effect size as in 2a above.

Intervention 3: HF management

The degree of mortality reduction from medical management of HF is difficult to estimate, as randomized trials are limited. A meta-analysis of randomized trials on diuretic therapy in patients with congestive HF, found a 75% (16-93%) reduction in odds of death compared to placebo from three trials.[47] However, these studies were neither specific to valvular disease nor to low-resource settings.

Management of HF patients by mid-level providers in an outpatient model at district hospitals in Rwanda showed a 5-year survival of 73% in pediatric patients and 61% in adult patients using confirmed deaths.[39] Including loss to follow-up or transfer in deaths, 5-year survival would fall to 42% in pediatric patients and 43% in adult patients. These patients included those with HF from cardiomyopathy, RHD, hypertensive heart disease, congenital heart disease, and isolated right HF. The gap between the confirmed deaths and composite events (death, transfer, or loss to follow-up) for RHD was smaller than for other conditions, suggesting the survival may have been closer to the estimate using deaths alone. A 5-year survival probability of 60% corresponds to an annual mortality risk of 9.7%; a 5-year survival probability of 50% corresponds to an annual mortality risk of 12.9%. The estimated annual mortality risk among people with RHD with HF using the GBD-derived estimates of mortality, weighted using the age pattern of people with RHD with HF in our model was about 26%. While the age-specific mortality risks from GBD lacked face validity, this overall estimate of 26% was relatively consistent with other estimates (see transition probability section—B6). Achieving an annual mortality risk of 9.7% compared with 26% is a reduction of 63%. Of course, the estimates derive from very different sources—GBD estimates versus the younger population enrolled in care in a very specific geographic area in Rwanda. Deriving a realistic effect size from these two disparate sources of information may not be the best approach, but combining both may move estimates toward greater accuracy.

A pilot study on reductions in late maternal deaths due to cardiovascular disease found 94.1% survival in a group without the additional cardiovascular disease management interventions piloted in the study, compared to 99.1% survival among the interventions group.[48] This translates to a reduction in mortality from 5.9% to 0.9%, or an 85% reduction. It should be noted that this study was not RHD-specific, and the number of deaths was relatively small (10 total deaths out of 269 patients), though the difference between the groups was statistically significant.

These varied sources of evidence suggest that a relatively large effect size in reducing mortality risk with treatment of HF is possible, at least in the near-term. However, as RHD is a progressive disease, HF management primarily improves quality of life and helps those who have severe disease survive for the opportunity of valve surgery. We assumed a 60% reduction in annual mortality risk with considerable uncertainty (30-80%). If the annual mortality risk was approximately 15%, this would correspond to the 5-year survival probability changing from 44% to 73%. Given the progressive nature of the disease and than management of heart failure does not treat the cause of the heart failure (valve damage), we also assumed that the effect of the intervention only lasted 4 years. This made the 60% effect size and 25% mortality risk among people with severe disease/HF relatively consistent with the empirical evidence of annual mortality risk in Rwanda. We varied this assumption to assess sensitivity of the results to this parameter (see sensitivity analyses). We continued to add cost of HF management for longer than 4 years, but we assumed the reductions in mortality risk ceased after 4 years.

Intervention 4: Cardiac surgery and post-operative care

To our knowledge, there are no randomized controlled trials that compare outcomes of patients with HF from RHD, either with HF management or without, to those who receive valve surgeries to repair the valve causing HF. We assumed an 85% reduction in annual mortality risk post-surgery, with a 3% mortality risk associated with the surgery itself.

To validate this assumption, we compared documented survival in cohort studies to other estimates of mortality risk, including those from GBD. Rusingiza et al. (2018) documented a 3-year survival of 92.5% in a cohort of patients receiving valve surgery, implying an annualized survival of 97.47%, or a risk of death of about 2.5%.[49] We calculated age- and sex-specific implied mortality rates from the GBD for Rwanda in 2017 and converted to mortality risks. We took the weighted average of the age-specific risks, weighting by the number of individuals at each age from the cohort in Rusingiza et al. We found an implied mortality risk of 49%. Reducing mortality risk from 49% to 2.5% is almost a 95% reduction. However, we do not think these mortality risks are directly comparable. The GBD estimates in settings like Rwanda rely on very little data and are relatively crude for this comparison. However, they suggest that an 85% reduction in mortality risk post-surgery may be reasonable.

Zühlke et al. (2016) in the two-year follow-up of the Global Rheumatic Heart Disease Registry (REMEDY) study, found a hazard ratio of 0.78 (95% CI, 0.57-1.07) for prior valve intervention or surgery and 2.16 (1.70-2.72) for congestive HF at enrollment on mortality hazard.[38] If we treated these categories as mutually exclusive the hazard ratio between the two groups would be about 0.36 (.78/2.16), translating to a 64% reduction in hazard from surgery. In truth, these categories are not mutually exclusive, and variations in timing and severity complicate this comparison. But without a trial directly comparing mortality after valve surgery to mortality in patients with RHD complicated by HF who did not undergo surgery, estimates of the effect size will be approximate.

A study in Sudan compared outcomes in children with RHD who had and had not received operations.[50] Patients who underwent operation had a post-operative mortality of 10.5% over 8 years. Among children who did not receive operations, follow-up over a mean of 2 years found 14% mortality. Comparing these two survival probabilities is inherently flawed—selection bias and censoring make such a comparison imperfect. However, we compared the annualized risks of mortality implied in the two groups, finding that the group receiving surgery had an annualized risk of death that was 81% lower.

$$\frac{\left(1-(.86)^{\frac{1}{2}}\right)-\left(1-(.895)^{\frac{1}{8}}\right)}{1-(.86)^{\frac{1}{2}}}=81\%$$

A ten-year study in adults over age 15 found actuarial freedom from valve-related mortality of 96% at ten years for repair and 80% at ten years for replacement.[51]

Intervention 5: Counseling on family planning

RHD can cause risk to both mother and fetus during pregnancy. Severe RHD can cause high risk of peripartum morbidity and mortality, and pregnancy can increase risk of developing HF and other severe sequelae of RHD, even among women who are asymptomatic leading up to pregnancy.[52] Women with RHD of childbearing age should be evaluated for risk of developing complications during pregnancy in order to provide family planning advice.[53] Women of childbearing age with moderate to severe mitral stenosis should receive counselling before pregnancy and may require intervention prior to becoming pregnant.[54] Women with severe mitral or aortic regurgitation, impaired left ventricular function, or left ventricular dilation should be referred for surgery before pregnancy.[54] In all cases, careful management of RHD during pregnancy is necessary.

We did not assess the impact of this intervention for several reasons. First, it would require reliable estimates of the proportion of severe RHD and deaths from RHD that occur or are accelerated by pregnancy. Generating these estimates would be complex, requiring assumptions about several parameters, including the proportion of people with asymptomatic RHD with particular manifestations and severity levels of the disease, the risk of developing HF with these different types and stages of disease, the proportion of women at different stages who have been diagnosed and see a provider who would counsel them on family planning, and the proportion of these women who

have unmet need for family planning. To reach high coverage, echocardiographic screening programs could be necessary. Feasibility and cost-effectiveness studies on screening programs designed to identify and counsel women of reproductive age with the aim to reduce the impact of RHD on pregnancy and vice versa would be important before bringing such programs to scale.

It may be easier to reach women who already have severe disease to counsel them on the need for surgery or to avoid pregnancy. This is a relatively small population, and this type of service would be included in the integrated management of HF (Intervention 3). Among these women, particular interventions during pregnancy can substantially reduce risk of death during or after pregnancy.[48]

Intervention Coverage: Baseline and Expansion

We assumed relatively low coverage for the set of interventions at baseline. There is not strong evidence about the existing level of coverage for many of these interventions. The baseline coverage matters less than the change in coverage from baseline to target, as this is what primarily impacts the size of the effect of the intervention as well as the cost. We chose sizes of scale-up between baseline and target coverage that were operationally plausible over the period of scale-up, 2021-2030, given sufficient levels of funding. Appendix Table 7 contains the baseline coverage estimates, the assumed uncertainty, and the target coverage. The estimates are explained further in the text below.

We set the baseline and target coverage levels for the AU as a whole based on the available evidence and expert opinion. However, there is country-to-country variation in the levels of coverage at baseline. There were not data available to give country-specific or region-specific estimates needed to run the model at the regional level. We created country-specific coverage estimates using variation in the country-specific UHC index published as part of the GBD.[55] We downloaded the published estimates from the GHDx (http://ghdx.healthdata.org/record/ihme-data/gbd-2019-uhc-effective-coverage-index-1990-2019). We used the overall UHC effective coverage index. For each country, we calculated the position on the index, relative to the full set of countries in the AU. The calculation is shown below for a give country, *c*, where *Minimum* is the minimum observed index value across countries in the AU, and *Maximum* is the maximum observed value across these countries.

$$Relative\ Index\ Value_c = \frac{Index\ Value_c - Minimum}{Maximum - Minimum}$$

We used the relative index value to define the spread of country-specific coverage levels constrained such that the weighted average coverage for the AU equaled those in Appendix Table 7, and the minimum coverage across countries for a particular intervention equaled a value we determined. The weighted average was calculated using weights specific to each intervention (for instance, for the coverage of primary prevention, we used the population of children ages 5-15, given that there was no meaningful data on variation in pharyngitis rates across countries). The process for creating the coverage is described using equations below.

First, we found the weighted mean value on the UHC index across countries in the AU.

$$Weighted\ Mean\ Index\ Value = \frac{\sum_{c=1}^{n}(Index\ Value_c * Weight_c)}{\sum_{c=1}^{n} Weight_c}$$

Then, we found the relative index value that this weighted mean value for the AU would take in the range of values on the UHC index across the countries in the AU.

$$AU\ Relative\ Index\ Value = \frac{Weighted\ Mean\ Index\ Value - Minimum}{Maximum - Minimum}$$

Using this relative index value for the AU and a minimum value across countries that we defined, we then calculated coverage for each country.

$$Coverage_C = \frac{Relative\ Index\ Value_c * (AU\ Coverage - Min\ Coverage)}{AU\ Relative\ Index\ Value} + Min\ Coverage$$

This generated a coverage for each country such that the weighted average equaled the pre-specified AU average, and the country-specific estimates were bounded by the minimum we set across countries. For weighting, we used 5-15 population for primary prevention, incidence of RHD for prophylactic penicillin for people without a history of RHD (as RHD incidence is suggested as a proxy for ARF incidence without good ARF data), deaths from RHD for heart failure management, under-40 deaths from RHD for cardiac surgery, and RHD prevalence for prophylactic penicillin for people with RHD.

To create draws of country-specific coverage, we took draws from a normal distribution in logit-space using the logit-transformed country-specific coverage estimate we obtained for the mean and the standard deviation for the AU defined in Appendix Table 7, assuming each country had the same standard deviation for the uncertainty

distribution of coverage in logit-space. We took logit-transformed the means and calculated the logit-transformed standard deviation as follows, where BC is baseline coverage:

$$sd_{logit} = \frac{logit(AU\ BC + AU\ BC\ SD * 1.96) - logit(AU\ BC - AU\ BC\ SD * 1.96)}{2 * 1.96}$$

We took the weighted average coverage for each draw to obtain draws by region and for the AU as a whole using the weights described above (and regions defined in Appendix Table 1). We verified that the mean and standard deviation of the draws for the AU were approximately what was specified in the inputs. Appendix Table 8 shows the mean and 95% UI of the draws of coverage for the AU and by region.

For scale-up in coverage, rather than scaling each region to the same coverage, we took the difference between the AU starting coverage and the target coverage, and then added that difference to the location-specific starting coverage draw so that the percentage point increase in coverage was consistent. If the increase was to 100%, we increased each to 100%.

Primary prevention

Treatment of pharyngitis with antibiotics is not currently a typical task conducted by community health workers. Some proportion of sore throats are likely treated at health centers with antibiotics; however, there are two limiting factors: the proportion of children with sore throats that present to health centers and the availability of suitable antibiotics.

Tabulation of data from the Service Provision Assessments suggest moderate levels of availability of injectable benzathine penicillin in health centers and clinics in Malawi in 2013 (87%), Ethiopia in 2014 (79%), Tanzania in 2015 (70%), and Senegal in 2016-17 (67%) but lower levels in the Democratic Republic of the Congo (36%). These surveys suggest that a relatively high proportion of children are prescribed antibiotics during visits for sore throats in Kenya in 2010 (88%), Malawi in 2013-14 (89%), Namibia in 2009 (93%), Rwanda in 2017 (68%), Senegal in 2017 (50%), Uganda in 2005 (50%), and Tanzania in 2014-15 (84%), though samples were small in some of the surveys.[56] Specific data are lacking regarding the proportion of these cases that were likely GAS pharyngitis, and almost all of the visits assessed were among children under age 5, outside the targeted age group for primary prevention.[56] The cited numbers may overestimate the proportion of cases that seek care that are appropriately treated, as these numbers do not capture guidelines and provider training about the treatment of sore throat as a preventive intervention for ARF and RHD.

Even with treatment available, care seeking for pharyngitis is thought to be low, and in particular, the coverage of primary prevention may be limited by asymptomatic or low-grade cases that would be unlikely to be reached by the health system.

We assumed a coverage of 15% and a target coverage of 40%, which could be achieved through awareness and education campaigns to encourage parents to take their children to health centers for sore throat treatment, health center provider education and mentorship, and investments in supplying penicillin. One of the major barriers to reaching high coverage is seeking health care. Primary prevention is unlikely to achieve high levels of coverage without community awareness and education campaigns. It may be easier to achieve higher levels of coverage with community health workers, though delivery of primary prevention for RHD through community health workers has not been well studied.

Appendix Table 7: Baseline and target coverage

ID	Intervention	Coverage Definition	AU Baseline Coverage	AU Baseline Coverage SD	AU Target Coverage	Minimum Baseline Coverage (across countries)
1	Primary prevention (increasing treatment of GAS pharyngitis in ages 5-15, awareness raising, strengthening supply chains, provider training)	Percent of GAS+ pharyngitis cases treated	15%	3.75%	40%	5%
2a	Secondary prevention (prophylactic penicillin after ARF—10 years or until age 20, whichever longer)	Percent of people with ARF treated with prophylactic penicillin	5%	1.25%	40%	2%
2b	Secondary prevention (prophylactic penicillin in asymptomatic RHD)	Percent of people with asymptomatic RHD treated with prophylactic penicillin	5%	1.25%	40%	5%
3	Platforms for HF management, including management during pregnancy	Percent of people with HF from RHD having HF medically managed	8%	2%	55%	2%
4	Cardiac surgery & post-operative care (ages 10-40)	Percent of people with HF from RHD receiving cardiac surgery and post-operative care	5%	1.25%	25%	2%
5	Evaluation and counseling on family planning for women of reproductive age	Percent of women of reproductive age with RHD desiring contraceptive method who have access	45%	5%	75%	2%

Secondary prophylaxis

The Global Rheumatic Heart Disease Registry (REMEDY Study) found about 70% of patients in low-income countries and 60% of patients in lower-middle-income countries were on secondary prophylaxis upon enrollment in the study.[38] The people in this study were patients with symptomatic RHD enrolled in care. A large proportion of prevalent cases of RHD at any given time are asymptomatic or have mild symptoms—many of these patients may be unaware they have RHD and are unlikely to be on secondary prophylaxis. Further, there are many people who may have had an episode of ARF and were not given secondary prophylaxis or were lost to follow-up. Achieving high coverage of secondary prophylaxis can be done through a highly functioning health system that can diagnose ARF and enroll patients in prophylaxis with adherence support. Inevitably, such a strategy will be limited by cases of ARF that are not seen by the health system. Echocardiographic screening studies can also increase coverage of secondary prophylaxis by identifying people with RHD who should be receiving secondary prophylaxis (see below). There are no good estimates of coverage for the broader population of people with symptomatic disease, but they are expected to be low. Based on expert opinion from co-authors, we assumed a level of coverage of 5%.

We assumed that through mass media awareness and education campaigns and training of providers at first-referral level hospitals would make 40% coverage achievable. Without active surveillance using echocardiography, coverage is limited by patients presenting with ARF, but awareness campaigns can encourage people with symptoms of ARF to seek care. Provider training at health centers and first-referral hospitals can ensure that patients seeking care are diagnosed or referred to the appropriate level of care for diagnosis. Including patient transport costs for monthly BPG injections is critical to retaining patients in care to achieve the coverage increase. To achieve high coverage increases, active screening campaigns using echocardiography may be necessary, and there is an ongoing trial to assess the impact of BPG on latent RHD that will greatly improve evidence to make decisions about such strategies.[46]

Appendix Table 8: Baseline coverage mean and 95% UI, by region

Intervention	African Union	Central Africa	Eastern Africa	Northern Africa	Southern Africa	Western Africa
Primary prevention (increasing treatment of GAS pharyngitis in ages 5-15, awareness raising, strengthening supply chains, provider training)	15.4 (8.5-24.3)	13.9 (7.6-22.2)	16.3 (9-25.6)	20.3 (11.5-31.2)	17.1 (9.5-26.7)	12.8 (6.9-20.6)
Secondary prevention (prophylactic penicillin after ARF—10 years or until age 20, whichever longer)	5.3 (3-9.1)	4.8 (2.7-8.3)	5.5 (3.1-9.4)	6.7 (3.8-11.5)	5.8 (3.3-9.9)	4.5 (2.5-7.7)
Secondary prevention (prophylactic penicillin in asymptomatic RHD)	5.3 (3-9.1)	4.8 (2.7-8.3)	5.5 (3.1-9.4)	6.7 (3.8-11.5)	5.8 (3.3-9.9)	4.5 (2.5-7.7)
HF management, including management during pregnancy	8.2 (4.6- 13)	7.6 (4.3 to 12.1)	8.2 (4.6 to 13)	9.7 (5.5 to 15.2)	8.9 (5 to 14)	7.4 (4.2 to 11.8)
Cardiac surgery & post-operative care (ages 10-40)	5.2 (2.9-8.2)	4.6 (2.6 to 7.4)	5.3 (2.9 to 8.4)	6.8 (3.8 to 10.7)	6 (3.4 to 9.5)	4.4 (2.5 to 7.1)

HF management

At baseline, there is low coverage of services for HF. Estimates of treated HF from the GBD study are implausible, as there is no difference in the proportion of HF cases treated between high-income and low-income countries (all but one country between 37% and 40%) and the proportion did not vary meaningfully by age or sex.[1] We therefore disregarded these estimates. From Service Provision Assessment data, availability of a set of equipment and medications necessary to treat HF was low at facilities at the level of district hospitals in the Democratic Republic of the Congo (6%), Ethiopia (26%), Malawi (12%), Senegal (5%), and Tanzania (32%).[57] Effective coverage is likely lower, as these data do not account for provider training, guidelines, facility policies about providing these services, or quality. Despite low availability of services at levels of the health system easily accessible to patients, management of HF does not face some of the same barriers on the patient side that prevention might, as HF is severe enough to push people to seek care.

We made the assumption for this scale-up that at baseline, 10% of population catchment areas were covered by hospitals with these services that would reach 80% of the population in these catchment areas for a total of 8% coverage. These services are often restricted to higher level hospitals, and the populations covered at baseline may be those living near large referral hospitals or with resources to access these facilities.

There is some precedent for estimating what is achievable with scale-up. Estimated coverage of HF was between 63% and 90% compared to GBD estimates of HF in the catchment area of district hospitals in Rwanda implementing chronic care services for severe non-communicable diseases after approximately eight years.[58] Calculating what coverage might be achievable in a ten-year period required using information about the proportion of hospitals offering services and the proportion of the population accessing them (assumed to be 80% after about eight years). In order to estimate total population coverage, we increased the proportion of district hospitals offering services linearly from 10% to 100%, tracking the number of years that each percent had been offering services. Then, within these "cohorts" of hospitals, we scaled the coverage of HF patients from 0% to 80% over a period of eight years. So, for instance, hospitals that begin offering services in 2023 would reach 80% coverage in 2030, but hospitals that begin to offer services in 2028 would reach 30% coverage by 2030. To calculate the total coverage in a given year, we multiplied the percent of hospitals in each cohort by the percent of the population they were expected to cover in the given year. We estimated a coverage of 55% by 2030 (Appendix Table 9). Appendix Table 10 shows the overall coverage by year from 2020 to 2030.

Appendix Table 9: Illustration of HF target coverage estimation for 2030

Year Hospital Began Offering Services (Cohort)	Percent of Hospitals	Percent of Population Covered by Cohort in 2030	Percent of Total Population Covered in 2030
2020 or prior	10%	80%	8.0%
2021	9%	80%	7.2%
2022	9%	80%	7.2%
2023	9%	80%	7.2%
2024	9%	70%	6.3%
2025	9%	60%	5.4%
2026	9%	50%	4.5%
2027	9%	40%	3.6%
2028	9%	30%	2.7%
2029	9%	20%	1.8%
2030	9%	10%	0.9%
Combined	**100%**	**54.8%**	**54.8%**

For estimating health impact, we used the population covered. For costing, we broke costs into two parts. We used the population coverage to estimate the per patient components of the cost, but we used the proportion of hospitals with expanded coverage (higher proportion) to estimate the costs of equipment and training that would be necessary for a facility to begin offering any services (see costing section of appendix).

Appendix Table 10: Scale-up to target coverage for HF management

Year	Percent Coverage
2020	8.0%
2021	8.9%
2022	10.7%
2023	13.4%
2024	17.0%
2025	21.5%
2026	26.9%
2027	33.2%
2028	40.4%
2029	47.6%
2030	54.8%

Cardiac surgery

Zilla and colleagues have described the unmet need for cardiac surgery.[8] Zilla et al. (2018) found rates of open heart surgery per million population per year were low in several African countries, including Mozambique (7), Nigeria (0.5), Morocco (100), Tunisia (272), Namibia (127), Algeria (178), and South Africa (142).[8] We expected many countries in the African Union to have rates closer to Mozambique and Nigeria, based on health system development and wealth. The proportion of these surgeries for RHD were 25% in Mozambique, 7% in Nigeria, 31% in Algeria, and 7% in South Africa.[8] If the continent had a rate of heart surgeries of 20 per million and 10% of these were for people with RHD, there would be about 2,500 RHD surgeries per year on the continent. Meanwhile, estimates suggest that the number of people with HF from RHD between ages 10 and 40 was about 24,000 (133,000 in all ages). We assumed a coverage of about 5%.

The scale-up of surgery is limited by several factors. First, coverage of surgery cannot outpace coverage of the ability to provide long-term post-operative management. The resources for HF management and post-operative management are shared here (same human resources, overlap in equipment, etc.). Therefore, scaling surgery without scaling management of severe disease does not make sense. Second, the number of patients eligible for surgery is somewhat limited based on clinical presentation of disease. Third, there are multiple avenues of providing surgical

care. Countries without established programs must send patients internationally. Scale-up of programs takes time, as investment must be made in surgical training programs in addition to the facilities necessary. Cardiac surgery centers are growing in the AU, and the exact scenarios for implementation will be country-specific. We believe that a coverage of 25% for patients under 40 is achievable by 2030 with sufficient resources through a combination of investment in growing national and regional surgical capacity and sending additional patients for surgeries internationally.

Family planning

The Guttmacher Institute reports estimates of the proportion of women who want to avoid pregnancy who are able to access contraception. In most countries in the African region, estimates of this proportion fall between 30% and 60%.[59] The denominator for this proportion might also expand if women at very high risk are counseled about RHD and their health risks. We did not use this coverage in modelling for reasons discussed in the main text, but we note it for its relevance in showing the possibility for reducing adverse outcomes related to RHD during pregnancy for women who do not wish to become pregnant.

Estimating impact of interventions

The above sections describe the evidence for the parameters used for intervention effect sizes and coverage in the model. In general, the impact of the intervention in terms of a percent reduction in the transition probability was determined by the formula below, where *Cov* represents the estimated coverage of the intervention at the starting point (*t1*) and ending point (*t2*), and *Eff* represents the effect size of the reduction.[60]

$$Impact = \frac{Eff * (Cov_{t2} - Cov_{t1})}{1 - Eff * Cov_{t1}}$$

In certain cases, impact was incorporated differently. For instance, the scale-up in coverage of surgery was a direct parameter in the model, governing the transition between RHD with HF and RHD after valve surgery. The impact was captured through changes in that transition probability as well as a reduced risk of death after surgery compared to before.

Calculating key health model outcomes for reporting

We report several key outcomes from the health impact modeling in the main text. Deaths averted were calculated by first subtracting the age- and sex-specific mortality rates (in the overall populations) from ARF and RHD estimated in the reference scenario from those estimated in the intervention scale-up scenario, then multiplying by the corresponding population estimates from the reference scenario. We summed the averted deaths over the 2021 to 2030 time period for reporting.

For each scenario, we calculated crude rates of incidence, prevalence, and deaths from the models by dividing the counts produced from the models by the population estimates produced by the models. We calculated age-standardized rates using the age pattern of the population in the African Union overall in 2017. We reported the difference in age-standardized rates in 2030 to summarize the impact of the intervention compared to the reference at the end of the scale-up period.

Costing

We estimated the costs of scaling up the interventions using the numbers of people in different disease states in our health impact model. We assumed linear scale-up from the baseline coverage to the target coverage over the time period specified in the scenario. The costing strategy overall is described in the main text. Additional detail about the costing process is described below, unit costs are provided in Appendix Table 11, and the costing for each intervention is described in greater detail below, incorporating operational considerations about delivery strategies.

We started with all unit costs in US dollars from varied years, but converted these costs to 2019 US dollars with adjustment for inflation. There are several approaches to adjusting for inflation rates and currency exchange rates in global health costing studies.[61] We based our procedure on that recommended by the Global Health Cost Consortium, separating costs into tradeable (transacted on the international market, such as medications) and non-tradeable (such as human resources and labor) costs when possible.[61] We adjusted tradeable costs using US inflation rates to 2019 US dollars.[62] For non-tradeable costs, we converted back to the currency from the country in which the cost was originally obtained using the exchange rate in that year, adjusted using local inflation rates, and then converted back to US dollars using 2019 exchange rates.[62,63]

Some costs, such as those for a general outpatient visit from WHO-CHOICE, were estimated for a wide number of countries and weighted to create an estimate for the AU as a whole.[64] Other cost estimates were from particular countries. For the non-tradeable components of these costs, we adjusted for general price differences between countries. Following work from the Disease Control Priorities, Third Edition (DCP-3) study, we assumed that ratios between locations in per capita gross national income (GNI) roughly represented these cost differences.[65] We found the population-weighted GNI per capita for the AU as a whole and used the ratio between that value and the GNI per capita in the origin country of the cost in question to obtain an average unit cost for the AU. To run the model at a regional level, we used the same population-weighted GNI per capita strategy to adjust unit costs from those for the AU to those for particular regions within the AU. We did not make this adjustment for the cost of surgery, as the surgeries would take place in one of several centers in Africa conducting surgeries or outside the continent (e.g. in India) if capacity was insufficient, though investments in these interventions can build on the progress that has been made on increasing surgical capacity in Africa.

To estimate the costs of scale-up, we first summed the cost under the scale-up scenario, *int*, by multiplying the unit cost for each component (such as the cost of a benzathine penicillin injection), UC_i, by the corresponding number of units (such as the number of people receiving secondary prophylaxis), U_i, and the percent of the units being covered, Cov_i. Then, we calculated the cost under the scenario of no scale-up, *base*, and subtracted from the first scenario to find the cost difference associated with scaling up the interventions.

$$Scale-up\ Cost_i = \sum_{i=1}^{n} UC_i * U_i^{int} * Cov_i^{int} - \sum_{i=1}^{n} UC_i * U_i^{base} * Cov_i^{base}$$

In this formula, the coverage, *Cov*, corresponds to the coverage of the intervention. In some cases, this coverage term was used in the calculation. For others, the calculation for the number of "units" by which to multiply the cost was calculated directly within the modeling. For instance, the number of surgeries was directly calculated in the health impact model, so the coverage term was not needed. Notably, the number of pharyngitis cases seen by the health system and treated was higher than the number of GAS positive pharyngitis cases, as we assumed cases to be treated based on a clinical decision rule (see discussion of primary prevention below).[14,66] We conducted this procedure for the groups of costs associated with each intervention and shared cost components (Appendix Table 11) so that we could present costs for the scenarios that were specific to particular interventions.

Costs were calculated at the regional level and then aggregated for reporting for the AU.

Intervention 1: Primary prevention

The components of this intervention include awareness raising in the community about treatment of sore throat for prevention of ARF and RHD, strengthening supply chains for penicillin, provider training, cost of the medication and equipment for administration of penicillin treatment, and the cost of visits to health facilities or treatment by community health workers.

The preferred treatment for GAS pharyngitis in RHD endemic areas is a single administration of benzathine penicillin G (BPG) through intramuscular injection. A ten-day course of oral penicillin is also effective, though it may be less efficacious and there are concerns about adherence and creating antibiotic resistance.[30] A six-day course of amoxicillin is also a possibility. There is some risk of allergy to penicillin that can cause anaphylaxis (about 1 in 10,000 cases) or rash (assumed in about 1.5% of cases).[14,67] Administration of BPG at a health center with the presence of a more highly trained provider and access to epinephrine is therefore often preferred to treatment in the community with a community health worker.

We costed this intervention using two models: treatment of sore throats at health centers and treatment of sore throats by community health workers. For the health center model, we found the unit cost per population annually of provider education and mentorship and administration using 10% of the salaries of district hospital nurse mentors and 10% of health center nurse salaries from Partners In Health Rwanda. With monthly salaries of 328,217 Rwandan francs per month and 194,447 Rwandan francs per month for nurses at district hospitals and health centers respectively, we assumed 10% of the time of each would be dedicated to education and mentorship. With district hospital catchment areas of about one per 250,000 population and health center catchment of 1 per 25,000 population we assumed 1 district hospital nurse and 10 health center nurses per 250,000 population and multiplied by 12 months. Using the 2019 average exchange rate from January to July between the Rwandan franc and US dollar, we calculated a cost of $0.012 per population annually. This part of the intervention was a shared cost between primary prevention and secondary prevention, as it was necessary to strengthen referral pathways and decentralize monthly administration of BPG to health centers for secondary prevention as well. The other costs incurred by this intervention are on a per visit basis to a health center. For each case of pharyngitis that is seen at a health center, cost is incurred for the visit itself. Estimated outpatient visit costs from the World Health Organization Choosing Interventions that are Cost-Effective (WHO-CHOICE) project were averaged across countries in the African Union, weighting by the population in the 5-14 age range.[64] We took the average cost between health centers with and without beds for an estimated $2.02 per visit (2010 USD). We obtained the cost per vial of BPG ($0.18) from the International Medical Products Price Guide.[68] While the cost of a visit was multiplied by the total number of people with pharyngitis presenting at health centers (pharyngitis incidence times coverage), the cost of BPG was multiplied by the number of people treated based on a clinical decision rule assumed to have sensitivity of 92% and specificity of 38% and an assumed prevalence of 15% GAS.[14,66] Baseline coverage was assumed to be about 15% (Appendix Table 7).

In the community health worker model, we assumed that community health workers treated sore throat with a 6-day course of amoxicillin. The course of amoxicillin was approximately the same cost as injectable BPG.[68] We costed one visit for assessment, diagnosis, and medication administration and a second visit for adherence support. We assumed community health worker annual salaries of $960 (2012 USD), training per 50 community health workers costing $300 annually (2012 USD), community health worker equipment and phone airtime costing $400 annually (2019 USD), and managers with a salary of $9,600 (2012 USD) per 30 community health workers.[69] We scaled the costing based on assumptions about the number of working days in a year (260) and the number of clients per day that could be seen by the community health workers (6 or 12, varied in sensitivity analysis).

Further detail about estimates of pharyngitis cases seen and treated by the health system is given in the section of the appendix “Derivation of ARF incidence, pharyngitis cases seen and treated, and understanding effects of primary and secondary prophylaxis.”

To ensure coverage increases, we also costed a mass media advertising campaign for awareness and education. We based these costs on the costs of a mass media campaign for malaria bed net use in Cameroon.[70] We divided the total cost of the program by the population of the country to obtain a per capita cost. This program was quite extensive. We assumed a smaller-scale campaign, so we divided the costs by 3 to obtain a cost of $0.04 per capita. We then assumed that the campaign would run every 3 years over the scale-up period, so the annual cost would be about 33% of that per capita cost. We assumed full coverage for this intervention when implemented, so we did not multiply by coverage.

Appendix Table 11: Unit costs

Component	Cost (Low-High estimate)	Currency/Year	Country/Year Costed	Cost Unit	Source
Primary Prevention					
[1]Mass media advertising for awareness campaign	0.04 (0.03-0.05)	USD 2012	Cameroon 2012	per population per 3 years	Bowen (2013)[70], modified (see full description)
Health Center Delivery Model					
1 vial IM penicillin (1.5M IU)	0.18 (0.13-0.22)	USD 2015	Market	per treated pharyngitis case	International Medical Products Price Guide[68]
Health center outpatient visit	2.02 (1.33-2.69)	USD 2010	AU average	per pharyngitis case visiting facility	Stenberg et al. (2018)[64]/WHO-CHOICE, weighted average across countries
[1]Program costs (provider education, admin, evaluation)	0.01 (<0.01-0.02)	USD 2019	Rwanda 2019	per population annually	Assumption based on 10% district hospital nurse mentor salary and 10% health center nurse salary, Partners in Health Rwanda
Community Health Worker Delivery Model					
500 mg amoxicillin tablet (x6 day course)	0.18 (0.15-0.23)	USD 2015	Market	per treated pharyngitis case	International Medical Products Price Guide[68]
Community health worker salary	960 (300-1500)	USD 2012	AU average	per CHW annually	McCord et al. (2012)
Community health worker training time	300 (198-399)	USD 2012	AU average	per 50 CHWs annually	McCord et al. (2012)
Community health worker equipment (phone, phone airtime, backpack, etc.)	400 (264-532)	USD 2019	AU average	per CHW annually	Assumption, based on McCord et al. (2012)
Community health worker administrative costs (manager salary, etc.)	9,600 (6336-12,768)	USD 2012	AU average	per 30 CHWs annually	Assumption, based on McCord et al. (2012)
Secondary Prevention					
1 vial IM penicillin (1.5M IU)	0.18 (0.13-0.22)	USD 2015	Market	per month per case of ARF history until age 21	International Medical Products Price Guide[68]
Health center outpatient visit	2.02 (1.33-2.69)	USD 2010	AU average	per month per case of ARF history until age 21	Stenberg et al. (2018)[64]/WHO-CHOICE, weighted average across countries
Patient transport to HC (adherence support)	2.00 (1.32-2.66)	USD 2019	AU average	per month per case of ARF history until age 21	Assumption
Transport to district hospital for initial evaluation	10.0 (6.6-13.3)	USD 2019	AU average	per incident ARF in person without ARF history	Assumption
District hospital echo evaluation	28.55 (18.84-38.97)	USD 2014	Rwanda 2014	per incident ARF in person without ARF history	Assumption
[1]Program costs (provider education, admin, evaluation)	0.01 (<0.01-0.02)	USD 2019	Rwanda 2019	per population	10% district hospital nurse mentor salary and 10% health center nurse salary, Partners in Health Rwanda
[1]Mass media advertising for awareness campaign	0.04 (0.03-0.05)	USD 2012	Cameroon 2012	per population per 3 years	Bowen (2013)[70], modified (see full description)
[2]Handheld ultrasound equipment at district hospital	4,000 (3,960-7,980)	USD 2019	Market	per 300,000 people per 3 years	
[2]Baseline training	7,216 (4,763-9,597)	USD 2014	Rwanda 2009	per 300,000 people initial cost	Eberly et al. (2019)[58]

[2]Other clinic supplies	4,000 (2,640-5,320)	USD 2014	Rwanda 2009	per 300,000 people per 5 years	Eberly et al. (2019)[58]
HF management					
HF management: tradeable costs	20.22 (13.34-26.89)	USD 2014	Market	per patient-year	Eberly et al. (2019)[58]
HF management: non-tradeable costs	80.25 (52.97-106.73)	USD 2014	Rwanda 2014	per patient-year	Eberly et al. (2019)[58]
[2]Handheld ultrasound equipment at district hospital	4,000 (2,640-5,320)	USD 2019	Market	per 300,000 people per 3 years	
[2]INR machine	490 (323-652)	USD 2014	Market	per 300,000 people per 3 years	Eberly et al. (2019)[58]
[2]Baseline training	7,216 (4,763-9,597)	USD 2014	Rwanda 2009	per 300,000 people initial cost	Eberly et al. (2019)[58]
[2]Other clinic supplies	4,000 (2,640-5,320)	USD 2014	Rwanda 2009	per 300,000 people per 5 years	Eberly et al. (2019)[58]
Valve surgery and post-operative management					
Flight to international surgery	1,000 (700-1,500)	USD 2019	Market	per surgery	Assumption
Valve surgery	5,000, (4,000-6,000)	USD 2019	South Africa	per surgery	
Post-surgical management: tradeable costs	130 (85.80-172.90)	USD 2009	Market	per patient-year	PEN-Plus data in Rwanda (unpublished)
Post-surgical management: non-tradeable costs	214 (141.24-284.62)	USD 2009	Rwanda	per patient-year	PEN-Plus data in Rwanda (unpublished)
Advanced ultrasound equipment (national-level)	15,500 (10,230-20,615)	USD 2014	Market	per country per 5 years	
[2]INR machine	490 (323-652)	USD 2014	Market	per 300,000 people per 3 years	Eberly et al. (2019)[58]
[2]Baseline training	7,216 (4,763-9,597)	USD 2014	Rwanda 2009	per 300,000 people initial cost	Eberly et al. (2019)[58]
[2]Other clinic supplies	4,000 (2,640-5,320)	USD 2014	Rwanda 2009	per 300,000 people per 5 years	Eberly et al. (2019)[58]
[2]Handheld ultrasound equipment at district hospital	4,000 (3,960-7,980)	USD 2019	Market	per 300,000 people per 3 years	
Other costs (to calculate health care costs averted)					
ARF hospital admission	50	USD 2010	AU average	per 30% of ARF incident cases (varied in sensitivity analysis)	Based on cost of 3 bed days from WHO-CHOICE estimates, assuming very low coverage of more advanced care[64]

[1]Shared costs between primary and secondary prevention, [2]Shared costs between secondary prevention, HF management, and post-operative management (first referral hospital outpatient severe NCD clinic). Note: Risk evaluation and family planning counseling for women with severe RHD costed as part of provider training.

Intervention 2: Secondary prevention

The components of this intervention include awareness raising in the community about treatment of ARF for the prevention of RHD and prophylaxis with BPG for cases of mild RHD for prevention of severe RHD, strengthening supply chains for penicillin, provider training, cost of the medication and equipment for administration of penicillin treatment, and cost of visits to health facilities.

In this model of care, people presenting with ARF without prior diagnosis would be referred to the first referral hospital for evaluation. The program cost at the first level hospital includes several costs associated with the start of an advanced NCD clinic at the first referral hospital level to train providers, purchase administrative supplies for the clinic, and purchase a handheld ultrasound device. These start-up costs were based on analysis from the establishment of this type of program in Rwanda and assumed to reoccur with some frequency.[58] In addition to the start-up costs, costs of provider salaries and other items associated with that initial evaluation visit were based on the per-visit cost ($28.55, 2014 USD) for outpatients with HF enrolled in care in the program in Rwanda. Transport to and from the district hospital was also included for this initial assessment ($10, 2018 USD assumed).

The training and equipment start-up costs were multiplied by the percent of hospitals assumed to have scaled-up services (see section on coverage of HF management earlier in appendix). The per-visit costs were multiplied by the ARF incidence times the coverage of secondary prevention.

After the initial evaluation, regular costs were incurred from administration of regular monthly BPG injections for 10 years or to age 21 (whichever is later). We multiplied the costs of health center outpatient visits, the cost of transport to the health center for adherence support, and the cost of the BPG vial by the number of people per month on this treatment plan in our model.

The program costs associated with GAS pharyngitis and ARF awareness and education, administration, and evaluation were shared with the primary prevention intervention and were only costed once if both interventions were being implemented (see costing in Intervention 1 related to mass media campaign and provider training and mentorship). In the results, we showed these as shared costs between the two interventions. The costs associated with the clinic at the district hospital (ultrasound equipment, baseline training, clinic supplies) were shared with the HF management and post-surgical management intervention costs. We calculated these costs per capita based on rough averages of the catchment populations of district hospitals so that they could be multiplied by the population times the proportion of the population covered to calculate costs. In the results, we showed these as shared costs between the three interventions.

Intervention 3: HF management

The costs of HF management could be broken down into infrastructure/equipment costs, baseline training, and ongoing operational costs. In addition, we split operational costs into components that were "tradeable," such as medications and "non-tradeable," such as human resource costs so that we could adjust costs for cost differences between the source of costing and the AU as a whole, as described in the main text.

HF management costs were estimated per patient-year from Eberly et al. (2019) based on yearly cost of visits in a Rwanda district hospital.[58] These costs were multiplied by the patient coverage estimates to obtain total costs (see section on coverage estimates earlier in appendix). Other clinic costs were included as described for the secondary prevention intervention, with the addition of the INR machine. We reduced the cost of ultrasound equipment based on reductions in cost since the machines were purchased in the Eberly et al. study. The equipment and training start-up costs were multiplied by the percent of hospitals offering coverage rather than the proportion of the population assumed covered (see section on coverage estimates earlier in appendix). The costs of the equipment, training, and supplies for the first referral NCD clinic necessary for secondary prevention, HF management, and post-operative care were shown in results as shared costs between multiple interventions to avoid double counting.

We included costs of evaluation and counseling on family planning as part of training for providers at first referral hospitals and the outpatient visits that patients with severe RHD have on a regular basis.

Intervention 4: Cardiac surgery and post-operative care

The cost of cardiac surgery could be broken down into flight to and from the surgery, the surgery and hospital stay, the post-surgical outpatient management at first referral hospital, and the equipment, training, and supplies at the first referral hospital. We assumed a cost of $1,000 for the flight. We assumed cardiac surgery for valve replacement or repair. In some cases, balloon mitral valvuloplasty might be an effective intervention, though for the purposes of this analysis, we did not consider this procedure. The cost of valve surgery in South Africa from Irlam et al. (2013) was over $10,000.[14] Surgeries have subsequently become cheaper; we used a cost of $5,000. We used unpublished cost estimates of post-surgical management from the PEN-Plus model in Rwanda, which were more expensive per year than HF management. Like the HF costs, these were broken into tradeable ($130) and non-tradable components ($214) for conversion to costs in other countries. A more advanced ultrasound machine was costed per country per 5 years for a cardiologist use at a tertiary referral hospital.

The costs of the equipment, training, and supplies for the first referral NCD clinic necessary for secondary prevention, HF management, and post-operative care were shown in results as shared costs between multiple interventions to avoid double counting. These costs were multiplied by facility coverage rather than population coverage as described above. Given the relatively short length of our 2021-2030 time horizon, we did not include the possible need for additional valve surgeries after damage of the initial repair or replacement or damage to other valves from progression of disease.

Other costs

We also included the cost of ARF hospitalization in our model to estimate the cost averted through averting ARF hospitalizations. The cost in Irlam et al. (2013) assumed full diagnostic and management capacity, but in many cases, patients may not have echocardiography procedures, etc. if services are not available. Given the low coverage of many of these services, we assumed that the cost of hospitalization was similar to the cost of 3 inpatient bed days from WHO-CHOICE estimates.[64] We did not anticipate that all cases of ARF would rise to the level of hospitalization. We assumed 30% would seek hospitalization, but we also varied this parameter in sensitivity analyses with very little effect observed on the health impact monetization (see section below).

Health Impact Monetization and Return on Investment

We took a full income approach to monetizing the benefits of increasing coverage of these interventions, combining expected change in GDP based on population changes due to the increases in coverage of the interventions compared to the counterfactual scenario and the value of the welfare gained through averting deaths, captured by the value of a statistical life (VSL). This approach has been used in other places, such as the *Lancet* Commission on Investing in Health.[71]

We estimated the monetized health gains following the approach outlined by the Reference Case Guidelines for Benefit-Cost Analysis in Global Health and Development.[72] The approach uses the value of a statistical life (VSL) estimated in the United States, where more studies have been done to estimate this value. Then, it uses a relationship between the GNI per capita in the United States compared to a target location and the income elasticity of VSL:

$$VSL_{target} = VSL_{reference} * (\frac{Income_{target}}{Income_{reference}})^{elasticity}$$

The VSL estimated for the United States was $9.4 million. We used estimates of per capita GNI from the World Bank.[63] The 2015 per capita GNI was $56,740 (2015 USD). We needed to estimate the VSL for the AU in 2019, meaning we had to adjust for both the difference in location (US versus AU) and time (2015 versus 2019). First, we used the formula to estimate the VSL in the AU in 2015 USD using the recommended elasticity of 1.5 and a value of per capita GNI in the AU calculated using the population-weighted average of per capita GNI estimates downloaded from the World Bank (Atlas method, current USD).[63] The population-weighted average per capita GNI values for the AU were $2,080 in 2015 (2015 USD) and $1,843 (2019 USD). We used the same approach to calculate per capita GNI values for the AU and specific regions in the AU. Then, we used the same equation with an elasticity of 1 to estimate the VSL in the regions of the AU for 2019 using the 2015 values of per capita GNI and VSL as reference values, yielding an estimate of $58,466 for the VSL in the AU in 2019 USD. This exceeded 20 times the GNI per capita, which is recommended as a low bound. To calculate the total value of health gained, we multiplied the VSL by the deaths averted.

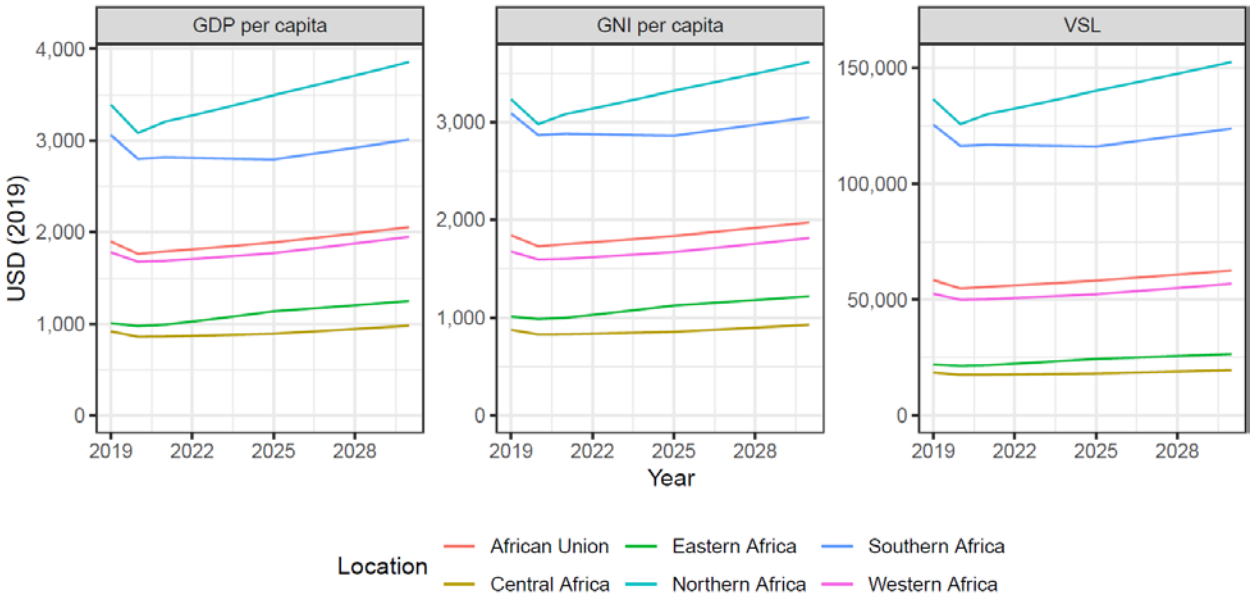
We incorporated projected growth in income over time. The International Monetary Fund (IMF) produces World Economic Outlook reports that project per capita GDP but not GNI.[62] We used the relationship between GDP per capita and GNI per capita to obtain projected per capita GNI from projected per capita GDP. We downloaded the time series of estimates of per capita GNI in constant international dollars and per capita GDP in constant international dollars from the World Bank.[63] We regressed the real annual percent change in per capita GNI values on the real annual percent change in per capita GDP values for countries, c, in the AU for years, *y*, with data before 2019.

$$\%\, Change\ GNI\ PC_{y,c} = \beta_0 + \beta_1 \%\, Change\ GDP\ PC_{y,c} + \varepsilon$$

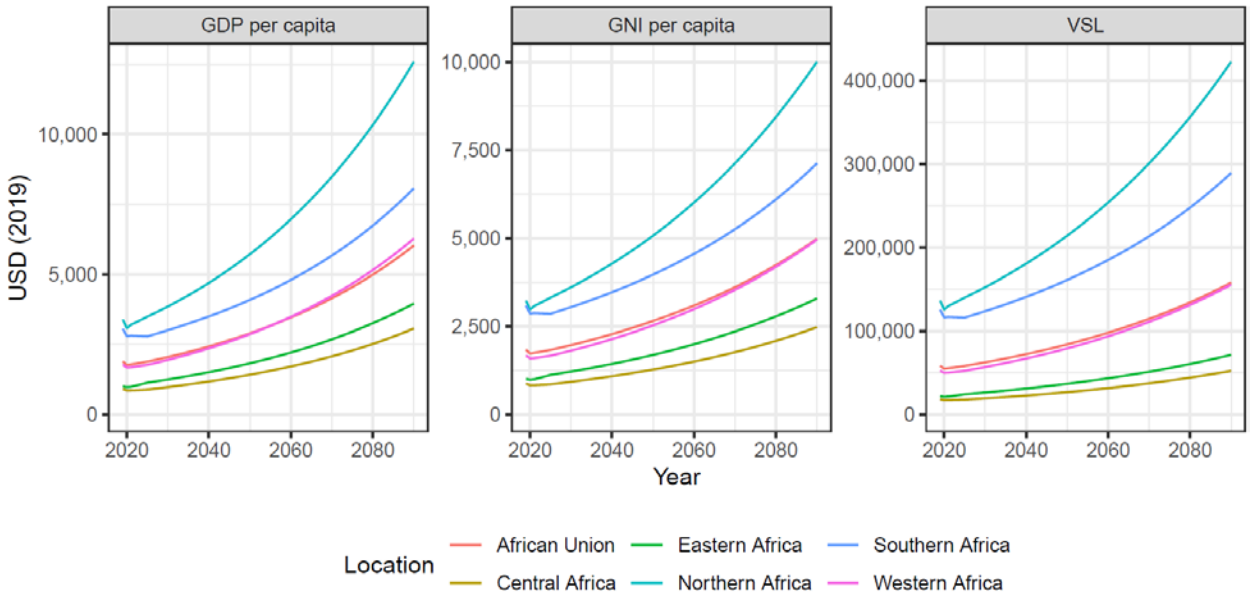
We tested multiple specifications, including a model with a random intercept by country, and model with a random slope and a random intercept by country. We also ran the model with the years restricted to 1991 to 2019. In each case, β_1 was between 0.85 and 0.87. We multiplied projected annual real percent changes in per capita GDP (described in the next paragraph) by 0.86 to obtain estimates of real percent changes in per capita GNI. From these projected changes in per capita GNI, we created estimates of GNI per capita from 2020 to 2090 by country (see below for how GDP per capita was projected through 2090). We then created average per capita GNI estimates for the AU and regions, weighting by population projections. We estimated VSL for 2020 to 2090 using the 2019 per capita GNI and VSL as the reference values and the projected per capita GNI values as the target values, assuming an elasticity of 1. We multiplied the deaths averted in each year by the VSL estimate for the given year to obtain the value of health gained. We did this with and without discounting 3% per year.

The other part of the full income was projected changes in GDP. We downloaded estimates of projected real changes in per capita GDP from the IMF by country.[62] The October 2019 projections predated COVID-19 and were much more optimistic than the April and June 2020 updates. The April update contained country-specific percent changes for 2020 and 2021. The June update was more pessimistic but only showed country estimates for certain countries. We used the difference in the regional estimates from the June update to the April update to adjust the

country-specific estimates from the April update. Then, we found the annualized projected rates of change from 2019 to 2024 from the October 2019 projections and used these values as the assumed annual rates of change from 2022 to 2025. From 2026 to 2090, we used a conservative 2% growth in real GDP per year across all regions. The resulting projected values are shown in Appendix Figure 7 through 2030 and Appendix Figure 8 through 2090. We multiplied projected per capita GDP by the difference in population between the scale-up scenario and the counterfactual to obtain a total change in GDP. We added this to the value of health quantified to obtain a full income estimate. The VSL was the main driver of full income, as it was much larger than GDP per capita.



Appendix Figure 7: Assumed projections of GDP per capita, GNI per capita, and VSL through 2030



Appendix Figure 8: Assumed projections of GDP per capita, GNI per capita, and VSL through 2090

We added averted healthcare costs from ARF hospitalizations in calculating the benefit-cost ratio and net benefits. Unit costs are listed in Appendix Table 11. We multiplied these costs by the number of estimated hospitalizations from these events. We assumed 30% of ARF cases would be hospitalized. This contributed marginally to the overall benefit, as the value from the VSL for all deaths averted was large.

We calculated net benefits by subtracting costs from these benefits and the benefit-cost ratio. We reported the benefits without discounting but the net benefits and benefit-cost ratio with 3% discounting of costs and benefits.

The long-term estimates of net benefits and benefit-cost ratios are very sensitive to discounting assumptions and projections of economic growth (see scenario sensitivity analyses).

Probabilistic Sensitivity Analysis

There were uncertainty distributions for many of the parameters we used. In general, we sought to incorporate draws from these distributions to propagate uncertainty throughout our analysis. We took 1000 draws from each distribution, ran the model on these 1000 different sets of draws, and calculated the mean, 2.5th, and 97.5th percentiles to summarize results.

Within the GBD study, from which many of our parameters are derived, uncertainty is propagated through the modeling processes using random draws from the uncertainty distributions of model parameters. The use of these draws allows certain correlations in uncertainty structure to be maintained. For instance, if draw number one from an epidemiological model had relatively high incidence, it would also have relatively high prevalence because the two parameters are related in the model. Draws of age-specific mortality rates are correlated across age groups because of the model life table process used to estimate them. These underlying draws that describe the uncertainty distributions require large amounts of data storage are not publicly available. The summary measures available (mean, 2.5th percentile, and 97.5th percentile of the draws) do not allow for two important pieces of information to be retained: specific shape of asymmetric distributions and correlation structure in uncertainty across different measures or demographics. We were therefore unable to properly include uncertainty from the GBD estimates. Rather, to generate uncertainty, we used a triangle distribution, with the lower and upper bounds of the GBD estimate representing the minimum and maximum of the triangular distribution.[73] We chose to assume the mean GBD estimate as the mode in the triangular distribution rather than making other assumptions about the skew of the uncertainty distribution in the GBD.

For parameters with reported uncertainty intervals, such as relative risks, we were often able to create draws from distributions similar to those from which they were derived (such as log-normal distributions). For other parameters, such as many of the costing estimates, uncertainty is unavailable and was assumed (in general using +/-33% of the point estimate to define the upper and lower bounds of a triangular distribution). Uncertainty is generally described in the above sections of the appendix on transition probabilities, intervention effect sizes, coverage, and costing. For some input parameters, such as the age distribution of risk of HF or the proportion of ARF with preceding symptomatic pharyngitis, the evidence was not sufficient to derive a sensible uncertainty range, and we only assessed uncertainty in the results from these parameters in the deterministic sensitivity analyses. Given all these limitations to the uncertainty estimation, we did not regard the uncertainty intervals as rigorous 95% confidence intervals, but rather as a range of plausible values.

To determine whether 1000 draws were sufficient to obtain stable uncertainty ranges, we ran an analysis for the African Union as a whole (not by region) with 4000 draws. We compared the uncertainty intervals for the major outcomes we reported for draws 1 to 1000, 1001 to 2000, 2001 to 3000, and 3001 to 4000. These results are in Appendix Table 12. There are small differences in some of the means and bounds, though these differences do not affect the interpretation of the results. We chose not to use more than 1000 draws given this relative stability, combined with computational constraints and the precedent of uncertainty being carried through the GBD study estimates using 1000 draws.

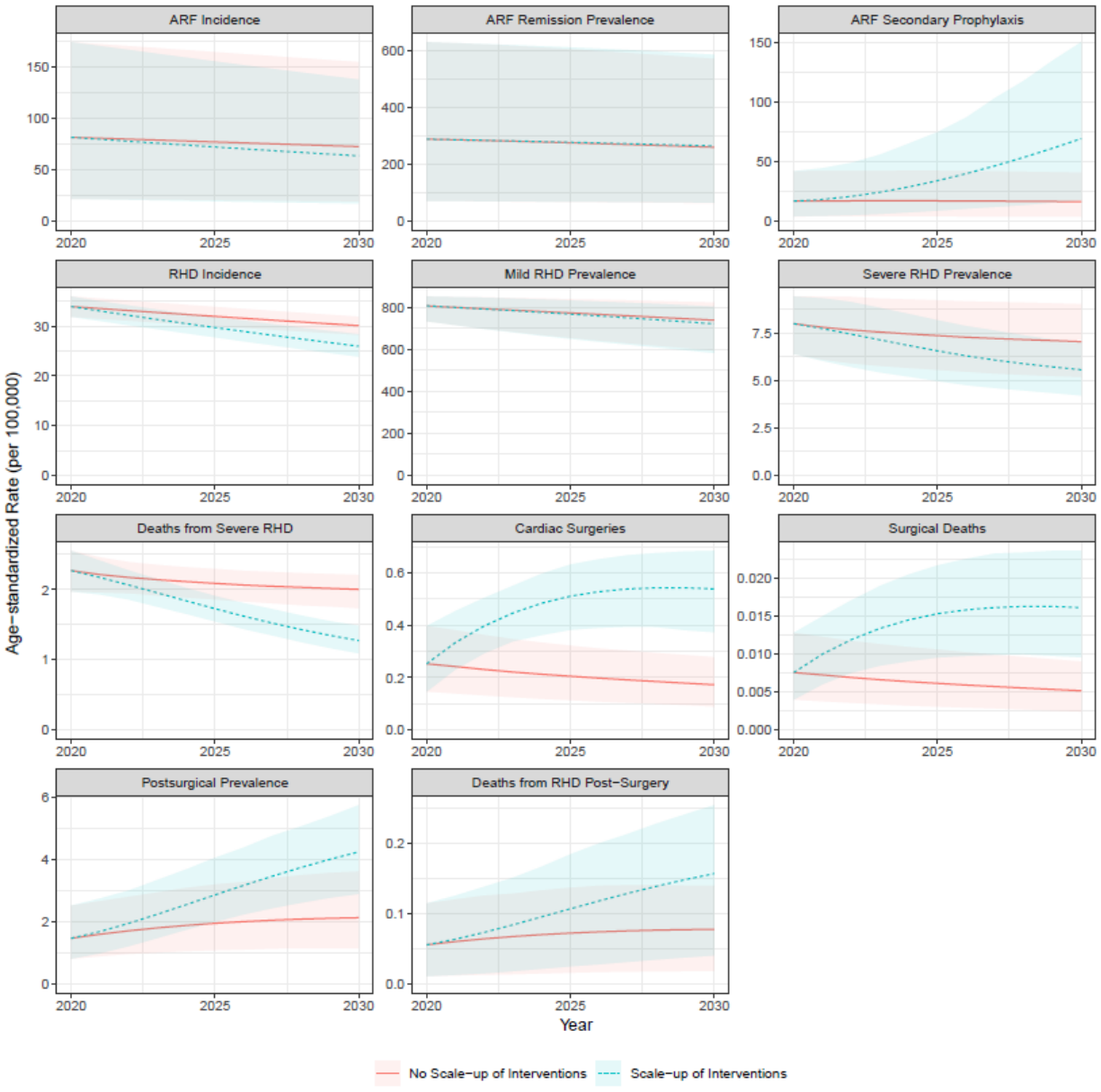
Appendix Table 12: Mean and uncertainty interval for key outcomes from different sets of 1000 draws

Outcome	Draws 1-1000	Draws 1001-2000	Draws 2001-3000	Draws 3001-4000
RHD Deaths Averted	58.53 (39.99-74.67)	58.91 (41.14-76.15)	58.84 (39.49-76.06)	58.66 (37.49-76.20)
Cost (Billions USD)	3.58 (2.42-4.82)	3.61 (2.47-4.95)	3.60 (2.44-4.86)	3.62 (2.52-4.95)
Health Benefits (Full Income Approach, Billions USD)	4.61 (3.00-7.78)	4.71 (3.07-7.73)	4.70 (3.09-7.97)	4.66 (2.93-8.02)
Net Benefits (Discounted, Billions USD)	0.80 (-0.62-2.81)	0.85 (-0.56-3.08)	0.86 (-0.73-3.00)	0.81 (-0.69-3.13)
Benefit-Cost Ratio (Discounted)	1.30 (0.81-2.05)	1.30 (0.83-2.09)	1.31 (0.77-2.08)	1.29 (0.78-2.06)

Results

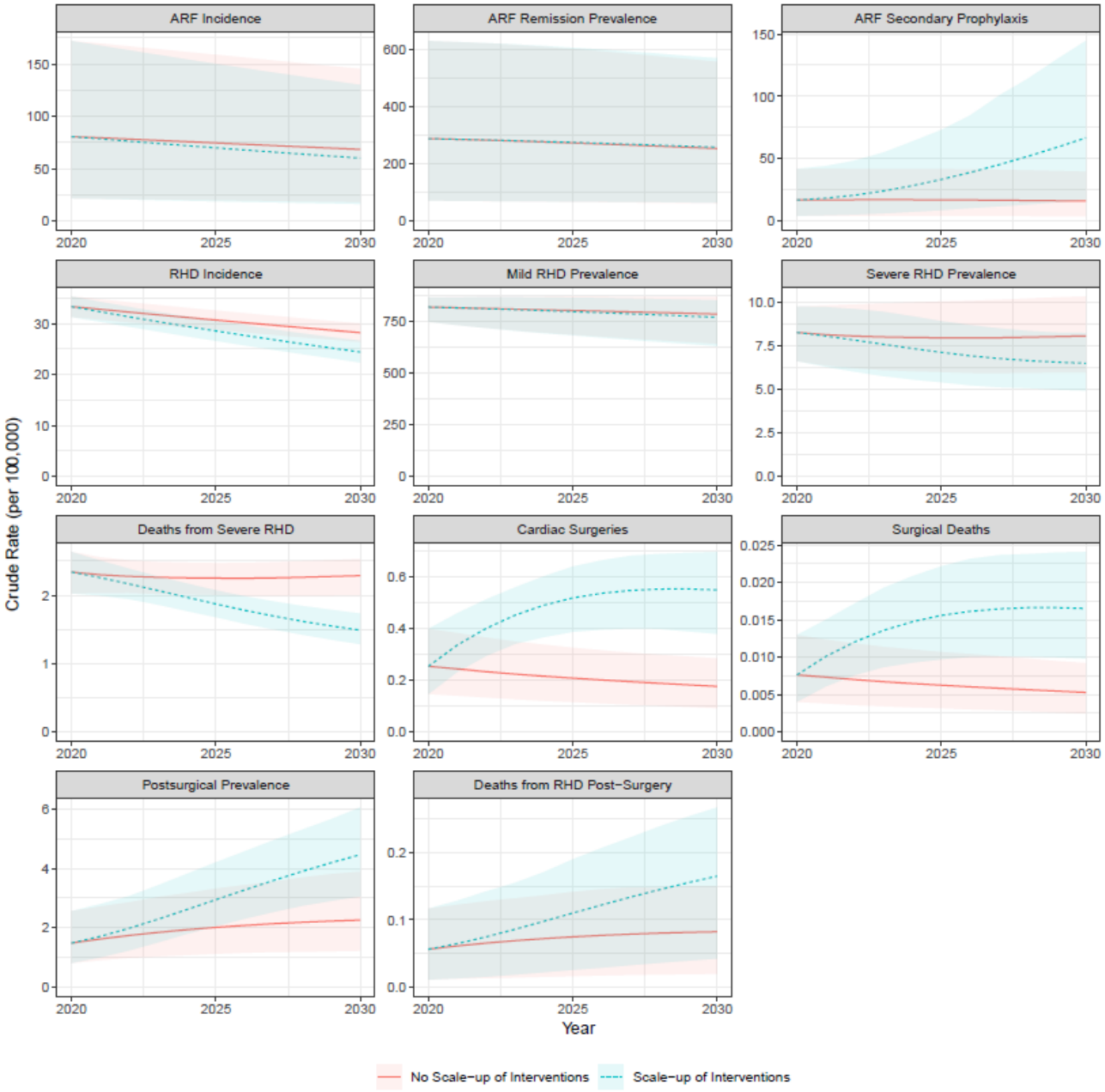
Disease state trends

Appendix Figure 9 shows trends from 2020 to 2030 of the several model outputs in age-standardized rates from scaling up all interventions to target levels through 2030 (main results). The same outputs are shown as crude rates in Appendix Figure 10.



Rates age-standardized using 2017 population in African Union

Appendix Figure 9: Age-standardized rates of disease states and transitions over time, primary model



Appendix Figure 10: Crude rates of disease states and transitions over time, primary model

Regional variation

We ran analysis at the regional level but reported results for the AU as a whole in the main text. The percent reductions in prevalence, incidence, and death rates in comparison to the reference scenario in 2030 were largely consistent across regions (Appendix Table 13). Differences arose in the magnitude of the reductions—lower rates of RHD deaths and prevalence in Northern Africa meant that the percent reductions led to lower absolute reductions in rates compared to those in the other regions. Costs per capita were higher in Northern Africa and Southern Africa because of countries with higher GDP per capita. Similarly, the full income value of health benefits accrued was higher in those regions because VSL was estimated using GNI; the assumption of elasticity above one in the calculation of VSL meant that countries with high GNI had even higher relative VSL estimates. This meant the benefit-cost ratios in Northern Africa and Southern Africa were higher than in other regions. Conversely, the cheaper costs of scaling up interventions in Central Africa, Eastern Africa, and Western Africa meant that the cost per death averted was lower in these regions, particularly in Central and Eastern Africa, where RHD rates were higher than in West Africa. While the benefit-cost ratio appeared higher in wealthier regions because of higher VSL; investments in regions with higher RHD burden and lower costs would maximize impact on burden.

Appendix Table 13: Regional variation in results

	African Union	Central Africa	Eastern Africa	Northern Africa	Southern Africa	Western Africa
Percent Reduction in 2030 RHD Death Rate	30.7 (21.6-39.0)	30.7 (21.6-38.9)	30.7 (21.6-39.1)	29.7 (20.2-38.1)	30.5 (21.4-39.0)	30.5 (21.5-38.6)
Reduction in 2030 RHD Death Rate (per 100,000)	0.6 (0.4-0.8)	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.4 (0.3-0.6)	0.7 (0.5-0.9)	0.6 (0.4-0.8)
RHD Deaths Averted, 2021-2030 (thousands)	60.0 (40.8-76.8)	7.2 (5.0-9.2)	19.1 (13.1-24.4)	7.4 (4.7-9.6)	9.2 (6.2-11.8)	17.2 (11.8-21.9)
Percent Reduction in 2030 ARF Death Rate	15.2 (9.0-20.5)	15.2 (8.9-20.4)	15.3 (9.0-20.6)	15.5 (9.3-20.8)	15.3 (9.1-20.6)	15.1 (8.8-20.3)
Reduction in 2030 ARF Death Rate (per 100,000)	0.2 (<0.1-0.4)	0.2 (<0.1-0.4)	0.2 (<0.1-0.4)	0.2 (<0.1-0.4)	0.2 (<0.1-0.4)	0.2 (<0.1-0.4)
ARF Deaths Averted, 2021-2030 (thousands)	13.9 (2.4-38.3)	1.7 (0.3-4.8)	4.2 (0.7-11.7)	1.5 (0.3-4.2)	1.7 (0.3-4.8)	4.7 (0.8-13.0)
Percent Reduction in 2030 RHD Prevalence	2.2 (1.1-3.2)	2.2 (1.1-3.1)	2.2 (1.1-3.1)	2.2 (1.1-3.2)	2.2 (1.1-3.2)	2.1 (1.0-3.1)
Reduction in 2030 RHD Prevalence (per 100,000)	16.7 (7.9-24.7)	17.1 (8.0-25.5)	18.9 (9.1-28.0)	11.4 (5.3-16.9)	19.2 (9.4-28.3)	15.1 (7.0-22.4)
Percent Reduction in 2030 RHD Incidence	13.7 (8.2-18.7)	13.7 (8.2-18.6)	13.9 (8.4-18.8)	13.7 (8.1-18.8)	13.9 (8.4-18.9)	13.5 (8.0-18.4)
Reduction in 2030 RHD Incidence Rate (per 100,000)	4.1 (2.4-5.6)	4.3 (2.5-5.8)	4.7 (2.8-6.4)	2.8 (1.6-3.8)	4.7 (2.8-6.4)	3.8 (2.2-5.1)
New RHD Cases Averted, 2021-2030 (thousands)	361.5 (207.2-497.3)	46.5 (26.5-63.9)	125.2 (72.1-171.9)	27.7 (15.2-38.5)	52.1 (29.9-71.4)	110.0 (62.2-151.8)
Total Cost, 2021-2030 (billions)	$3.9 ($2.7-5.1)	$0.3 ($0.2-0.3)	$0.7 ($0.5-0.9)	$0.8 ($0.5-1.0)	$0.9 ($0.6-1.1)	$1.3 ($0.9-1.7)
Full Income Value, 2021-2030 (billions)	$4.9 ($3.3-6.7)	$0.2 ($0.1-0.3)	$0.7 ($0.5-0.9)	$1.4 ($0.9-1.9)	$1.4 ($0.9-1.9)	$1.3 ($0.9-1.8)
Return on Investment (Discounted), 2021-2030	1.3 (0.8-1.9)	0.7 (0.5-1.1)	0.9 (0.6-1.4)	1.8 (1.1-2.8)	1.6 (1.0-2.5)	1.0 (0.6-1.6)
Cost per Death Averted (Discounted) (thousands)	$54.4 ($33.8-83.5)	$30.7 ($19.1-46.2)	$32.0 ($20.3-48.3)	$90.6 ($55.7-145.2)	$81.7 ($51.1-125.6)	$59.9 ($36.5-91.6)
Net Benefit (Discounted), 2021-2030 (billions)	$0.8 (-$0.8-2.3)	-$0.1 (-$0.1-<0.1)	-$0.1 (-$0.3-0.2)	$0.5 ($<0.1-0.9)	$0.4 ($<0.1-0.8)	$<0.1 (-$0.4-0.5)

Total cost and full income benefits not discounted, costs and full income value discounted at 3% per year in benefit-cost ratio. Rates age-standardized using 2017 AU population. Reductions and percent reductions in rates are relative to the reference scenario in 2030.

Scenario Sensitivity Analyses

As we noted, there was a high degree of uncertainty about several parameters that also had relatively large impacts on the outcomes in the model. The uncertainty in some of these parameters cannot be captured well in probabilistic sensitivity analysis because there is knowledge lacking about what an appropriate uncertainty distribution would be. In Appendix Table 14, we summarize the aspects of the model examined by particular sensitivity analyses.

Appendix Table 14: Parameters varied in sensitivity analyses

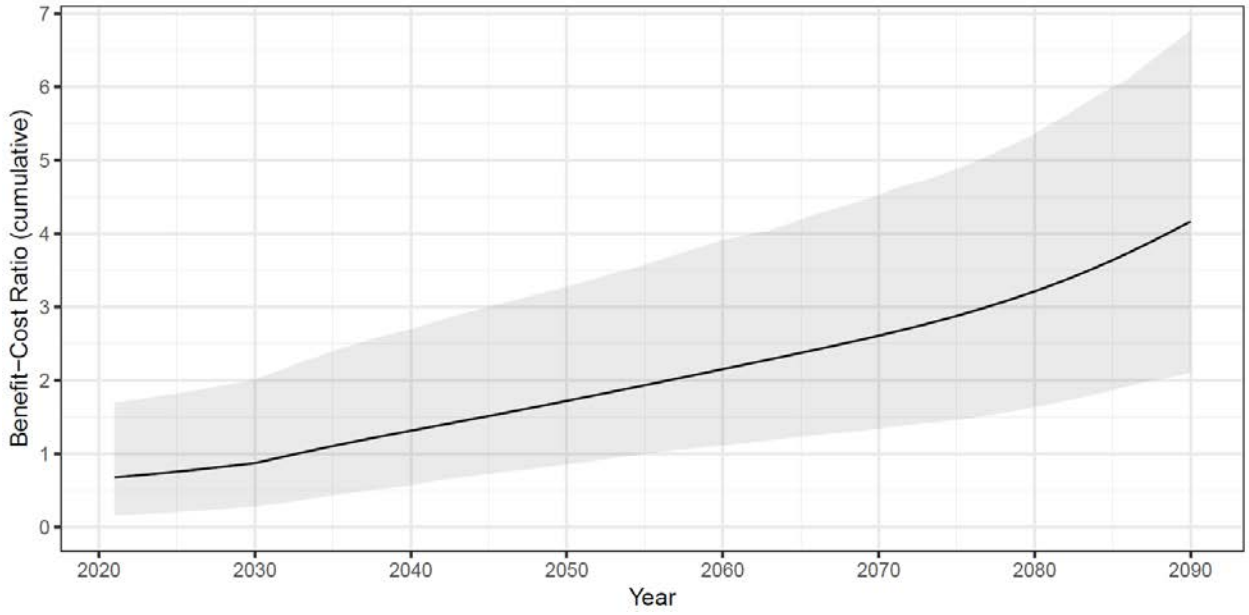
Parameter	Considerations	Inputs Varied
HF Risk Age Pattern and Death Numbers	Age distribution of HF from GBD does not match primary evidence, nor do death numbers	Age pattern of HF risk from (1) primary analysis, (2) GBD or (3) a combination of GBD and the Heart of Soweto Study (see transition probability section of appendix)
Percent of ARF with Preceding Pharyngitis	Evidence that ARF does not always occur with preceding pharyngitis	Proportion of ARF cases with preceding symptomatic pharyngitis cases: (1) 80%, (2) 50%, and (3) 99% (see also section on derivation of ARF incidence in appendix)*
Number of Pharyngitis Cases per Year	Mixed evidence on the number of pharyngitis cases per year	Number of cases on average in ages 5-15: (1) 1, (2) 2.3, (3) 4 (see also section on transition probability for ARF)**
Duration of HF Management Effect	High degree of uncertainty about annual mortality risk, effect size of HF management on mortality, and duration of effect, as HF management mostly a delaying measure	(1) Duration of effect in primary analysis was 4 years, (2) Sensitivity analysis included was 3 years
Delivery Model for Primary Prevention	Visits to health centers costly, but concerns about reaction to BPG often mean primary prevention facility-based	(1) Delivered at health centers, (2) Delivered by community health workers with 6 clients per day, (3) Delivered by community health workers with 12 clients per day (see costing section for discussion of costs)
Country	Demographics and epidemiological features of countries may lead to differences in the benefits and costs of prevention	We ran the model using regional inputs and primarily report results for the AU as a whole. Regional results are reported in the appendix (above). We additionally ran the model for (1) South Africa and (2) the Democratic Republic of the Congo for a country-specific direct comparison (below).
Time Horizon	The mortality-reducing effect of primary prevention is delayed, and the costs of expanded coverage to facilities precedes some of health effects, so benefit-cost ratios are impacted by time horizon	(1) The scale-up and period of projection was 2020 to 2030 in our primary analysis, (2) We examined benefits accrued through 2090 for several scenarios

*Note that we also rescaled the risk of ARF after pharyngitis accordingly so that the predicted RHD incidence would remain calibrated as described in the description of A16, **Note that 2.3 and 4 were the starting values before scaling to calibrate to RHD incidence (see description of parameter A16)

In the below section, we examine implications of varying these parameters. In these scenarios, the default parameters are as follows unless otherwise noted: primary prevention delivered through health centers, HF risk age pattern from our primary analysis (adjusted DisMod and CODEm approach), percent of ARF with preceding pharyngitis 80%, number of pharyngitis cases per year 2.3, time horizon through 2030, 4-year duration of effect of HF management, and all interventions scaled up.

Scenario: Low-cost delivery, long-run benefits to understand benefit-cost dynamics of prevention

To examine the benefit-cost ratio under a scenario designed to be more optimistic about primary prevention, we modelled the health effects and cost assuming 1 pharyngitis case per year in ages 5-15 on average, costing using a CHW delivery model in which workers see 12 clients per day, and 100% coverage for primary prevention from 2021 to 2030 and 0% thereafter, while benefits continued to accrue through 2090. In this scenario, we did not change the coverage of other interventions to understand the properties of primary prevention alone. The mean benefit-cost ratio remained below 1 through 2030 though grew consistently afterwards as the cohort affected by the prevention aged through 2090 with lower rates of RHD prevalence relative to the reference scenario. Individuals who were 10 in 2025 would be 65 in 2090. Much of the benefit also depends on competing risks and the cohort surviving to older ages to obtain the benefit. In this scenario using the UN World Population Prospects projected mortality, all-cause mortality falls substantially over this time period, causing a demographic shift that leads to more benefits accruing at old ages. There is considerable uncertainty in projections this far out, even beyond the uncertainty captured in the parameters in our model, but this suggests that with certain epidemiological assumptions and a lower-cost delivery model for primary prevention, the benefit-cost ratio may be substantially more favorable in the long run. The benefits this far out are also sensitive to both the discount rate and the assumptions about the growth in the VSL. Without discounting, the benefit-cost ratio for this scenario was 13.9 (6.3-22.9) through 2090, compared to 4.2 (2.1-6.8) with 3% discounting of costs and benefits. Additional studies on the epidemiology of GAS pharyngitis and ARF, as well as pilot studies providing low-cost primary prevention in the AU may help build the evidence needed to make stronger conclusions about the potential costs and population-level benefits of primary prevention.

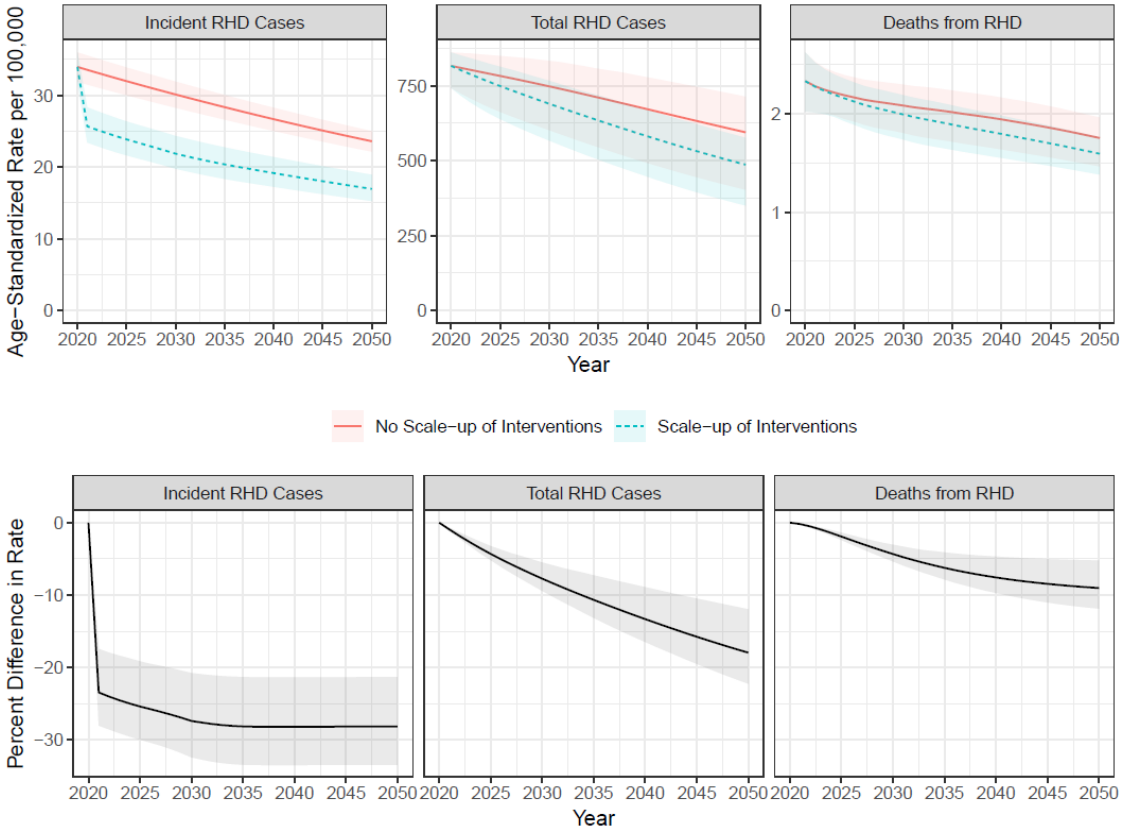


Scenario parameters: 1 pharyngitis case on average between age 5 and 15, CHW delivery model seeing 12 clients per day, 100% primary prevention coverage from 2021-2030, 0% primary prevention coverage 2031-2090 to let benefits accrue, no scale-up in non-primary prevention interventions

Appendix Figure 11: Benefit-cost ratio over time for lower-cost primary prevention scenario

Scenario: Limitations of primary prevention

We created a scenario to understand the limits of primary prevention, given that the population already living with RHD is quite large. To understand these limits, we scaled primary prevention up to 100% from 2021 to 2050. Of course, this immediate increase to full coverage is implausible, but this scenario was meant to illustrate the maximum impact that primary prevention could be expected to have in the medium term. There are two main reasons primary prevention has a limit in terms of impact on mortality. First, there are limitations of primary prevention in reaching children with GAS—the proportion of ARF occurring without previous pharyngitis (assumed 80% by default), imperfect clinical decision rules about treating pharyngitis (92% sensitivity), the targeting of the intervention to ages 5-15 (which reaches many but not all cases leading to ARF), and the 68% effect size of the treatment all cause reductions in impact. These limits are evident in the reduction shown in incidence of RHD relative to the baseline scenario (roughly 30% reduction) in Appendix Figure 12. Second, the number of people with existing RHD is relatively high, and while many of these people may not end up developing severe cases, there are many who will. Deaths from RHD among these people can only be prevented through secondary prophylaxis, management of disease, and surgery. This is evident in Appendix Figure 12, as the death rate is only reduced by about 10% compared to the baseline scenario by 2050. However, the impact of prevention continues to reduce deaths in the long term (see scenario on low-cost delivery and long-term benefits above).



Rates age-standardized using 2017 AU population

Appendix Figure 12: Incidence, prevalence, and death rates for scenario showing maximum scale-up of primary prevention

Scenarios: Pharyngitis cases per year

The number of pharyngitis cases per year is an influential factor in the costing of primary prevention. To examine the impact of this parameter, we ran the model with three scenarios to compare the results for scaling up primary prevention alone from 2021 to 2030. Appendix Table 15 compares results from models assuming 1, 2.3, and 4 cases of pharyngitis cases per year on average among children ages 5-15 (see transition probability section of appendix for more detail about age patterns and scaling of parameters). The costs were roughly proportional to the number of cases assumed, so the cost would be cut by about 50% if children only had 1 pharyngitis case per year (assuming the same proportion were from GAS infection).

Appendix Table 15: Comparison of model results with varying assumptions about pharyngitis cases per year

	1 Pharyngitis Case	2.3 Pharyngitis Cases	4 Pharyngitis Cases
Percent Reduction in 2030 RHD Death Rate	0.6 (0.4-0.8)	0.6 (0.4-0.8)	0.6 (0.4-0.8)
RHD Deaths Averted, 2021-2030 (thousands)	0.8 (0.5-1.1)	0.8 (0.5-1.1)	0.8 (0.5-1.1)
Percent Reduction in 2030 ARF Death Rate	8.3 (5.1-11.1)	8.5 (5.3-11.3)	8.5 (5.3-11.3)
ARF Deaths Averted, 2021-2030 (thousands)	6.8 (1.4-18.0)	7.2 (1.5-19.6)	7.2 (1.5-19.6)
Percent Reduction in 2030 RHD Prevalence	1.3 (0.8-1.8)	1.3 (0.8-1.8)	1.3 (0.8-1.8)
Percent Reduction in 2030 RHD Incidence	7.6 (4.6-10.0)	7.6 (4.7-10.1)	7.6 (4.7-10.1)
New RHD Cases Averted, 2021-2030 (thousands)	186.2 (114.0-246.8)	187.2 (113.3-247.2)	187.2 (113.3-247.2)
Total Cost, 2021-2030 (billions 2019 USD)	$1.4 ($0.9-1.9)	$3.1 ($1.9-4.3)	$4.4 ($2.6-6.1)
Full Income Benefit, 2021-2030 (billions 2019 USD)	$0.4 ($0.1-1.1)	$0.5 ($0.1-1.2)	$0.5 ($0.1-1.2)
Benefit-Cost Ratio (Discounted), 2021-2030	0.3 (0.1-0.8)	0.2 (<0.1-0.4)	0.1 (<0.1-0.3)
Cost per Death Averted (Discounted) (thousands 2019 USD)	$248.4 ($76.6-666.0)	$526.1 ($155.2-1389.4)	$750.4 ($220.8-1978.0)
Net Benefit (Discounted), 2021-2030 (billions 2019 USD)	-$0.8 (-$1.2--0.2)	-$2.1 (-$3.1--1.2)	-$3.2 (-$4.5--1.8)

Rates age-standardized using 2017 AU population. Reductions and percent reductions in rates are relative to the reference scenario in 2030.

Scenarios: Proportion of ARF occurring after symptomatic pharyngitis

The effect that primary prevention can have is heavily influenced by the proportion of ARF occurring after symptomatic pharyngitis (see transition probability section A2 for more detail). If children do not have symptomatic pharyngitis preceding ARF, the opportunity for primary prevention does not present itself. In our base case, we assumed 80% of ARF cases were preceded by symptomatic pharyngitis. We ran scenarios assuming 50% and 99% in addition to show the effect in the modelled outcomes. Appendix Table 16 shows results for scaling up primary prevention only from 2021 to 2030. There was a lower reduction in RHD and ARF deaths if only 50% of ARF cases were preceded by pharyngitis and a higher reduction in RHD and ARF deaths if 99% of cases were preceded by pharyngitis.

Appendix Table 16: Comparison of model results with varying assumptions about the proportion of ARF cases preceded by pharyngitis

	50% Preceded by Pharyngitis	80% Preceded by Pharyngitis	99% Preceded by Pharyngitis
Percent Reduction in 2030 RHD Death Rate	0.4 (0.2-0.5)	0.6 (0.4-0.8)	0.8 (0.5-1.0)
RHD Deaths Averted, 2021-2030 (thousands)	0.5 (0.3-0.7)	0.8 (0.5-1.1)	1.0 (0.6-1.3)
Percent Reduction in 2030 ARF Death Rate	5.4 (3.3-7.1)	8.5 (5.3-11.3)	10.5 (6.5-13.9)
ARF Deaths Averted, 2021-2030 (thousands)	4.5 (0.9-12.3)	7.2 (1.5-19.6)	8.9 (1.8-24.2)
Percent Reduction in 2030 RHD Prevalence	0.8 (0.5-1.1)	1.3 (0.8-1.8)	1.7 (1.0-2.2)
Percent Reduction in 2030 RHD Incidence	4.8 (3.0-6.4)	7.6 (4.7-10.1)	9.4 (5.8-12.4)
New RHD Cases Averted, 2021-2030 (thousands)	117.4 (71.0-155.1)	187.2 (113.3-247.2)	231.2 (140.1-305.3)
Total Cost, 2021-2030 (billions 2019 USD)	$3.1 ($1.9-4.3)	$3.1 ($1.9-4.3)	$3.1 ($1.9-4.3)
Full Income Benefit, 2021-2030 (billions 2019 USD)	$0.3 ($0.1-0.8)	$0.5 ($0.1-1.2)	$0.6 ($0.2-1.5)
Benefit-Cost Ratio (Discounted), 2021-2030	0.1 (<0.1-0.2)	0.2 (<0.1-0.4)	0.2 (0.1-0.5)
Cost per Death Averted (Discounted) (thousands 2019 USD)	$840.5 ($248.0-2221.1)	$526.1 ($155.2-1389.4)	$426.1 ($125.8-1124.3)
Net Benefit (Discounted), 2021-2030 (billions 2019 USD)	-$2.3 (-$3.2--1.3)	-$2.1 (-$3.1--1.2)	-$2.0 (-$3.0--1.0)

Rates age-standardized using 2017 AU population. Reductions and percent reductions in rates are relative to the reference scenario in 2030.

Scenarios: Calibrating to different HF and death estimates

The section of the appendix on the consistency of evidence on RHD epidemiology (appendix p 61) discusses in detail the three different sets of assumptions we used about the level and age pattern of heart failure prevalence and deaths from RHD. The main approach (here called DisMod+CODEm) combined death estimates from the epidemiological modeling (DisMod) and cause of death modeling (CODEm) from the GBD study to create a different level and age pattern of RHD mortality than the published GBD estimates. We took two other approaches—one derived the transition probability to severe disease from the published GBD estimates (here called GBD) and the other (here called HoS+GBD) combined the adult age pattern of disease from the Heart of Soweto study with an age pattern of severe disease among children informed by the GBD and constrained to fit within the total envelope of cases of heart failure from RHD estimated by the GBD (appendix pp 18-20). Appendix Table 17 shows results for the three approaches, scaling up all interventions from 2021-2030.

Appendix Table 17: Comparison of model results with varying approaches to deriving levels and age patterns of heart failure and death

	DisMod+ CODEm	GBD	HoS+GBD
Percent Reduction in 2030 RHD Death Rate	30.7 (21.6-39.0)	19.8 (11.0-25.9)	24.6 (14.2-32.1)
RHD Deaths Averted, 2021-2030 (thousands)	60.0 (40.8-76.8)	27.3 (14.6-37.5)	35.1 (19.5-47.3)
Percent Reduction in 2030 ARF Death Rate	15.2 (9.0-20.5)	15.2 (8.9-20.5)	15.2 (9.0-20.5)
ARF Deaths Averted, 2021-2030 (thousands)	13.9 (2.4-38.3)	13.9 (2.4-38.3)	13.9 (2.4-38.3)
Percent Reduction in 2030 RHD Prevalence	2.2 (1.1-3.2)	2.5 (1.3-3.4)	2.6 (1.4-3.6)
Percent Reduction in 2030 RHD Incidence	13.7 (8.2-18.7)	13.7 (8.2-18.7)	13.7 (8.2-18.7)
New RHD Cases Averted, 2021-2030 (thousands)	361.5 (207.2-497.3)	361.5 (207.3-497.4)	361.4 (207.2-497.3)
Total Cost, 2021-2030 (billions 2019 USD)	$3.9 ($2.7-5.1)	$3.6 ($2.4-4.8)	$3.6 ($2.4-4.9)
Full Income Benefit, 2021-2030 (billions 2019 USD)	$4.9 ($3.3-6.7)	$2.8 ($1.6-4.4)	$3.2 ($1.9-4.8)
Benefit-Cost Ratio (Discounted), 2021-2030	1.3 (0.8-1.9)	0.8 (0.4-1.3)	0.9 (0.5-1.5)
Cost per Death Averted (Discounted) (thousands 2019 USD)	$54.4 ($33.8-83.5)	$94.1 ($50.0-168.6)	$78.7 ($44.1-135.2)
Net Benefit (Discounted), 2021-2030 (billions 2019 USD)	$0.8 (-$0.8-2.3)	-$0.7 (-$2.0-0.8)	-$0.4 (-$1.8-1.0)

Rates age-standardized using 2017 AU population. Reductions and percent reductions in rates are relative to the reference scenario in 2030.

Scenarios: Duration of effect of HF management on mortality

Evidence on the effect size for heart failure management on mortality is limited. We ran a scenario to compare the difference in outcomes assuming a 4-year effect versus a 3-year effect (see appendix p 26-27 for more detail). Appendix Table 18 shows this comparison using results from scale-up of the non-primary prevention interventions from 2021 to 2030. The impact on the results of assuming a 3- versus 4-year effect is small. While heart failure management can prevent mortality in the short term and the services are an essential part of the continuum of care for RHD, surgery is necessary for long-term survival of patients with severe disease.

Appendix Table 18: Comparison of model results with varying assumptions about the duration of the effect of heart failure management on mortality

	3 years	4 years
Percent Reduction in 2030 RHD Death Rate	29.5 (20.4-37.6)	30.4 (21.4-38.7)
RHD Deaths Averted, 2021-2030 (thousands)	57.9 (38.7-74.4)	59.5 (40.3-76.3)
Percent Reduction in 2030 ARF Death Rate	7.4 (1.3-12.2)	7.4 (1.3-12.2)
ARF Deaths Averted, 2021-2030 (thousands)	7.1 (0.5-22.1)	7.1 (0.5-22.1)
Percent Reduction in 2030 RHD Prevalence	1.0 (-0.1-1.9)	1.0 (-0.1-1.9)
Percent Reduction in 2030 RHD Incidence	6.7 (1.2-11.3)	6.7 (1.2-11.3)
New RHD Cases Averted, 2021-2030 (thousands)	184.5 (31.0-310.6)	184.5 (31.0-310.6)
Total Cost, 2021-2030 (billions 2019 USD)	$1.0 ($0.7-1.2)	$1.0 ($0.7-1.2)
Full Income Benefit, 2021-2030 (billions 2019 USD)	$4.3 ($2.9-5.8)	$4.5 ($3.0-5.9)
Benefit-Cost Ratio (Discounted), 2021-2030	4.5 (2.8-6.2)	4.7 (2.9-6.3)
Cost per Death Averted (Discounted) (thousands 2019 USD)	$15.2 ($10.9-23.5)	$14.8 ($10.6-22.7)
Net Benefit (Discounted), 2021-2030 (billions 2019 USD)	$2.7 ($1.5-3.8)	$2.8 ($1.6-3.9)

Rates age-standardized using 2017 AU population. Reductions and percent reductions in rates are relative to the reference scenario in 2030.

Scenarios: Delivery model for primary prevention

A long-term scenario for parameters giving the most optimistic scenario for primary prevention is described earlier in this section. Here, we explore the impact of different delivery strategies and related parameters on the costs and benefits of primary prevention. Delivery of primary prevention with community health workers may be cheaper than delivery through health center visits (appendix p 37). Appendix Table 19 shows a comparison of model outputs comparing three scenarios: (1) primary prevention delivered through health centers, (2) primary prevention delivered through community health workers seeing 6 patients per day, and (3) primary prevention delivered through community health workers seeing 12 patients per day. The health effects are not assumed to be different here, though it is possible there would be a decrease in the fidelity of the interventions if delivered by community health workers if there is any difference in ability to use the clinical decision rule for treatment. Costs may be substantially lower with primary prevention delivered by community health workers, particularly depending on the volume of clients that they can see per day. Results are for scaling up primary prevention only from 2021-2030.

Appendix Table 19: Comparison of model results with varying approaches to deriving levels and age patterns of heart failure and death

	Health Center	CHW, 6 Patients	CHW, 12 Patients
Percent Reduction in 2030 RHD Death Rate	0.6 (0.4-0.8)	0.6 (0.4-0.8)	0.6 (0.4-0.8)
RHD Deaths Averted, 2021-2030 (thousands)	0.8 (0.5-1.1)	0.8 (0.5-1.1)	0.8 (0.5-1.1)
Percent Reduction in 2030 ARF Death Rate	8.5 (5.3-11.3)	8.5 (5.3-11.3)	8.5 (5.3-11.3)
ARF Deaths Averted, 2021-2030 (thousands)	7.2 (1.5-19.6)	7.2 (1.5-19.6)	7.2 (1.5-19.6)
Percent Reduction in 2030 RHD Prevalence	1.3 (0.8-1.8)	1.3 (0.8-1.8)	1.3 (0.8-1.8)
Percent Reduction in 2030 RHD Incidence	7.6 (4.7-10.1)	7.6 (4.7-10.1)	7.6 (4.7-10.1)
New RHD Cases Averted, 2021-2030 (thousands)	187.2 (113.3-247.2)	187.2 (113.3-247.2)	187.2 (113.3-247.2)
Total Cost, 2021-2030 (billions 2019 USD)	$3.1 ($1.9-4.3)	$2.4 ($1.4-3.5)	$1.3 ($0.8-1.9)
Full Income Benefit, 2021-2030 (billions 2019 USD)	$0.5 ($0.1-1.2)	$0.5 ($0.1-1.2)	$0.5 ($0.1-1.2)
Benefit-Cost Ratio (Discounted), 2021-2030	0.2 (<0.1-0.4)	0.2 (0.1-0.5)	0.4 (0.1-0.9)
Cost per Death Averted (Discounted) (thousands 2019 USD)	$526.1 ($155.2-1389.4)	$419.0 ($124.5-1089.9)	$229.7 ($68.7-591.8)
Net Benefit (Discounted), 2021-2030 (billions 2019 USD)	-$2.1 (-$3.1--1.2)	-$1.6 (-$2.5--0.8)	-$0.7 (-$1.2--0.1)

Rates age-standardized using 2017 AU population. Reductions and percent reductions in rates are relative to the reference scenario in 2030.

Scenarios: Time frame of investments and benefits accrued

The scenario on appendix page 53 shows the dynamics of the benefit-cost ratio in the long term for a scenario with parameters favorable for primary prevention. The scenarios presented here explore the dynamics of the main analyses presented in the paper with benefits accrued over a longer time horizon. We ran the model from 2021 to 2030, scaling up coverage to the target levels. Then, in 2031, we set coverage to the initial values such that costs would not continue to accrue, and benefits would only accrue from the changes in intervention coverage that took place between 2021 and 2030. For the scenarios with changes in surgical coverage, the costs of postsurgical care continued to accrue as long as patients remained alive. Additionally, some costs were saved through the reduction in cases of RHD that occurred from 2021-2030, and these costs savings were subtracted from the total costs. Appendix Table 20 shows the benefit-cost ratios and cost per deaths averted with and without 3% discounting of costs and benefits for the period 2021 to 2030 and with benefits accrued through 2090. Choice of discount rate has a large impact on the results in the long term. In addition, we note in other sections that the projections of VSL are highly influential in the benefit-cost ratios in the long term, and economic projections for that length of time are crude assumptions.

Appendix Table 20: Comparison of benefit-cost ratios (with and without 3% discounting) in short-term and long-term

	Benefit-Cost Ratio, No Discounting	Benefit-Cost Ratio, 3% Discount of Costs and Benefits	Cost per Death Averted (thousands 2019 USD), No Discounting	Cost per Death Averted (thousands 2019 USD), 3% Discount of Costs and Benefits
All Interventions, 2021-2030	1.3 (0.8-2.0)	1.3 (0.8-1.9)	$54.1 ($33.6-83.0)	$54.4 ($33.8-83.5)
All Interventions, Benefits Accrued to 2090	7.4 (4.4-10.7)	3.2 (1.9-4.7)	$45.7 ($29.7-74.9)	$53.8 ($33.8-86.0)
Non-Primary Prevention, 2021-2030	4.7 (2.9-6.4)	4.7 (2.9-6.3)	$14.7 ($10.5-22.5)	$14.8 ($10.6-22.7)
Non-Primary Prevention, Benefits Accrued to 2090	17.5 (10.0-26.3)	8.4 (4.8-12.1)	$22.5 ($13.2-39.0)	$21.3 ($14.1-36.4)
Primary Prevention, 2021-2030	0.2 (<0.1-0.4)	0.2 (<0.1-0.4)	$522.4 ($154.6-1376.1)	$526.1 ($155.2-1389.4)
Primary Prevention, Benefits Accrued to 2090	2.1 (1.0-3.3)	0.7 (0.4-1.1)	$107.2 ($59.6-203.8)	$208.9 ($97.9-388.1)

Rates age-standardized using 2017 AU population

Scenarios: Country-specific variation from demographic or epidemiological differences

Given the limitations in geographically specific input data for the model, we did not produce or report country-specific estimates. We note in the main text that countries should take factors like population age structure and local epidemiology into consideration, along with health systems factors, in designing specific implementation strategies. While better country-specific data may lead to different results than those from our model, we ran the model for the Democratic Republic of the Congo and South Africa to illustrate the differences that can be made by different population age structures, levels of RHD incidence, and per capita economic production (and costs). Results are shown in Appendix Table 21 for scaling up interventions from 2021-2030 (primary prevention only and all interventions). Reductions in 2030 rates are relative to the reference scenario.

There were not substantial differences in percent reductions in rates of RHD incidence, RHD prevalence, RHD death rate, or ARF prevalence in the two countries. The higher rates of RHD in the DRC meant that the absolute reductions in age-standardized rates of RHD deaths, prevalence, and incidence were slightly larger than in South Africa. The benefit-cost ratio was higher in South Africa, largely as a result of the higher value of a statistical life because of the greater GNI per capita (see appendix page 44, discussion of regional variation on appendix page 51). The cost per death averted was lower in the DRC compared to South Africa because of the lower non-tradeable costs in delivering medical care.

Appendix Table 21: Comparison of results for the Democratic Republic of the Congo and South Africa

	Primary Prevention Only DRC	Primary Prevention Only South Africa	All Interventions DRC	All Interventions South Africa
Percent Reduction in 2030 RHD Death Rate	0.6 (0.4-0.8)	0.6 (0.4-0.8)	30.6 (21.5-38.9)	29.9 (20.5-38.4)
Reduction in 2030 RHD Death Rate (per 100,000)	<0.1 (<0.1-<0.1)	<0.1 (<0.1-<0.1)	0.7 (0.5-0.9)	0.6 (0.4-0.8)
Percent Reduction in 2030 ARF Death Rate	8.5 (5.3-11.3)	8.8 (5.5-11.6)	15.2 (8.9-20.5)	15.5 (9.3-20.8)
Reduction in 2030 ARF Death Rate (per 100,000)	0.1 (<0.1-0.2)	0.1 (<0.1-0.2)	0.2 (<0.1-0.4)	0.2 (<0.1-0.4)
Percent Reduction in 2030 RHD Prevalence	1.3 (0.8-1.8)	1.4 (0.9-1.8)	2.2 (1.1-3.1)	2.3 (1.2-3.2)
Reduction in 2030 RHD Prevalence (per 100,000)	10.9 (6.4-14.9)	10.6 (6.3-14.4)	17.8 (8.5-26.4)	17.2 (8.5-25.3)
Percent Reduction in 2030 RHD Incidence	7.7 (4.8-10.2)	8.0 (5.0-10.4)	13.8 (8.3-18.7)	14.1 (8.6-19.1)
Reduction in 2030 RHD Incidence (per 100,000)	2.5 (1.5-3.3)	2.4 (1.5-3.1)	4.4 (2.6-6.0)	4.2 (2.5-5.7)
Benefit-Cost Ratio (Discounted), 2021-2030	0.1 (<0.1-0.2)	0.2 (0.1-0.6)	0.5 (0.3-0.7)	3.0 (1.8-4.6)
Cost per Death Averted (Discounted) (thousands 2019 USD)	$175.4 ($52.4-459.8)	$1812.4 ($538.1-4741.0)	$19.5 ($12.4-29.5)	$117.1 ($72.3-186.8)

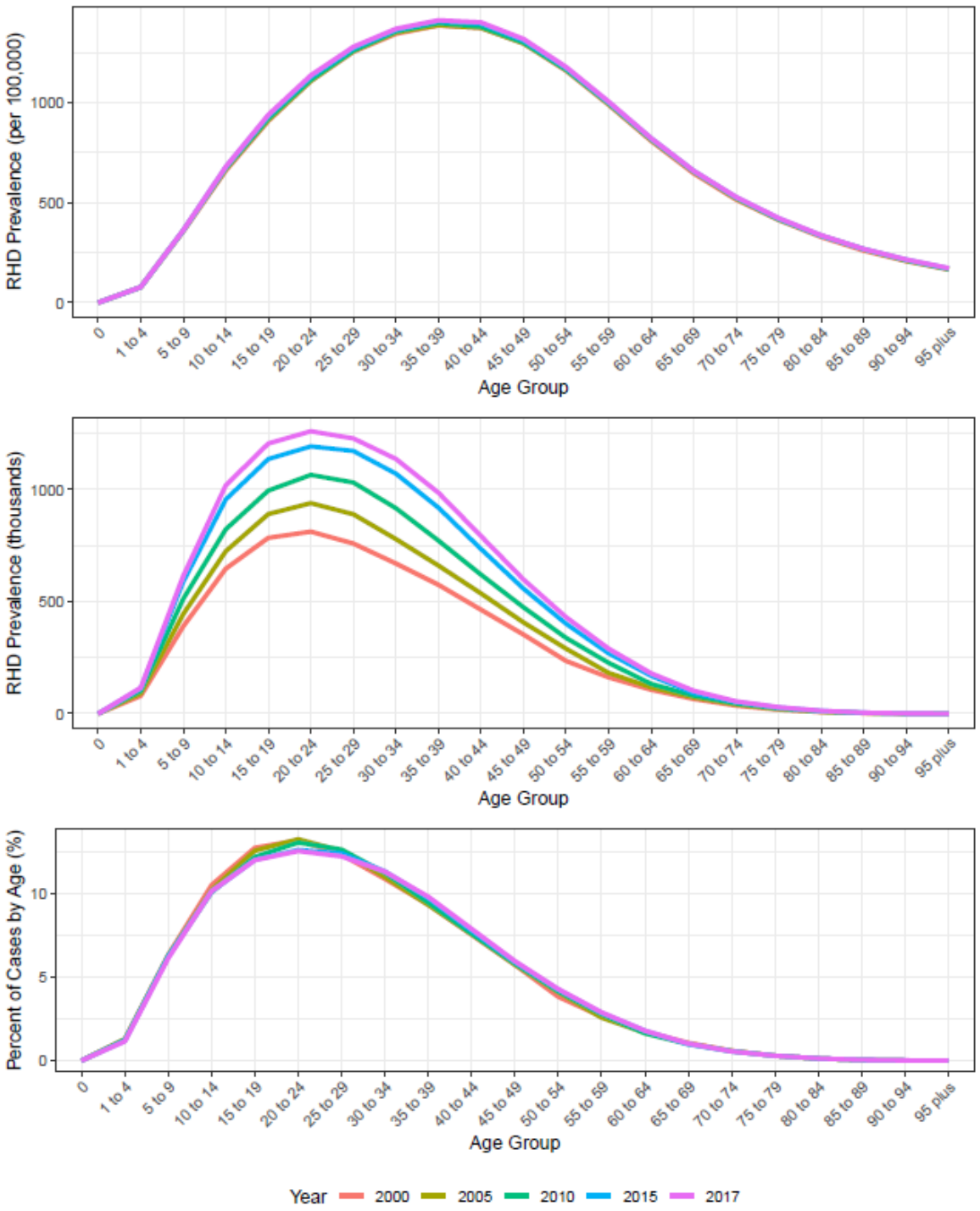
Rates age-standardized using 2017 AU population. Reductions and percent reductions in rates are relative to the reference scenario in 2030.

Additional Methodological Details

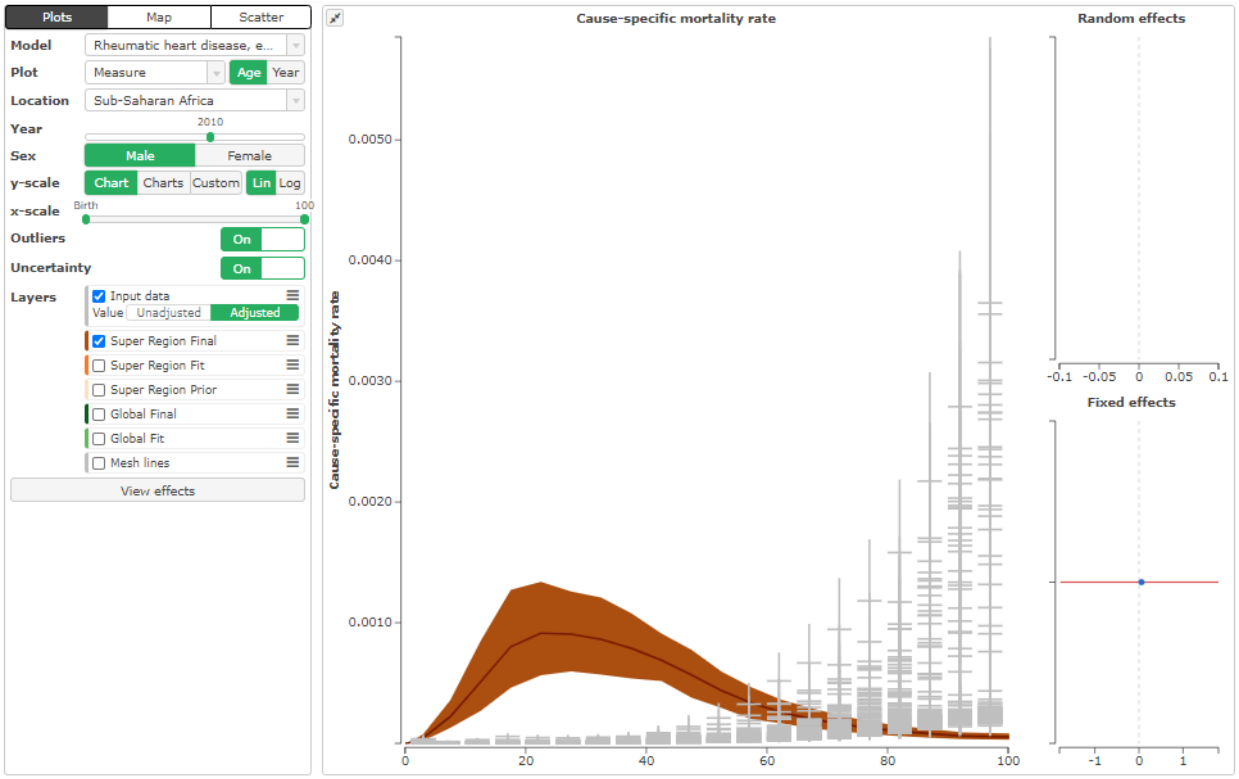
Consistency of evidence on RHD epidemiology

There was a range of strength of evidence across many of the parameters in the model. Echocardiographic screening studies made prevalence of RHD in young ages a parameter with fairly strong evidence, also providing reasonable confidence in the incidence of RHD in relatively young ages from the GBD.[1] The death estimates in GBD in most African countries were heavily reliant on modeling from data in other settings, as verbal autopsy data are typically not specific enough to include RHD and the number of countries with vital registration is limited (primarily South Africa).[10] The GBD estimates of deaths and prevalence were based on two separate modelling processes—one using a Bayesian meta-regression framework with epidemiological inputs (DisMod-MR) and the other using ensemble models of cause of death data (CODEm).[1,10] Although the results of the cause of death model were used to inform the epidemiological model, the prevalence estimates and death estimates for RHD reported in the GBD were largely inconsistent, which we explore here.

The prevalence of RHD according to the GBD dropped precipitously after age 20 or so and does so consistently over time (Appendix Figure 13). While there was a small amount of regression of asymptomatic disease assumed, it was not enough to account for a steady age distribution of prevalence that remains that young over time.[1] Similarly, the estimates of deaths from the GBD were much too small to account for the low prevalence of RHD at older ages. The modelled cause-specific mortality rates are compared to the RHD death rate inputs in the EpiViz tool online (Appendix Figure 14).[74] These estimates of these DisMod parameters were not directly downloadable, but we extracted data values from the plot using an online tool (www.graphreader.com).[75] The mortality rates implied in ages 20-30 by the DisMod model for Sub-Saharan Africa (estimates from this model are not run for the African Union) were roughly 150 times higher than those reported in the GBD cause of death estimates for the African Union (Appendix Figure 14). The higher rates across all age groups before age 75, combined with the age distribution of the population, generated death estimates from RHD of 652,911 in 2017, compared with the 18,297 published in the GBD results from the cause of death modelling process (Appendix Figure 15). Death estimates of 652,911 would have ranked RHD as the third largest cause of death in the AU in 2017, behind ischemic heart disease and lower respiratory infections and above diarrheal diseases, malaria, and HIV.[10] This number of deaths would be necessary to maintain the distribution of prevalence shown in Appendix Figure 13 (barring very high remission of disease or very high risk of deaths from other causes) but lacks face validity.

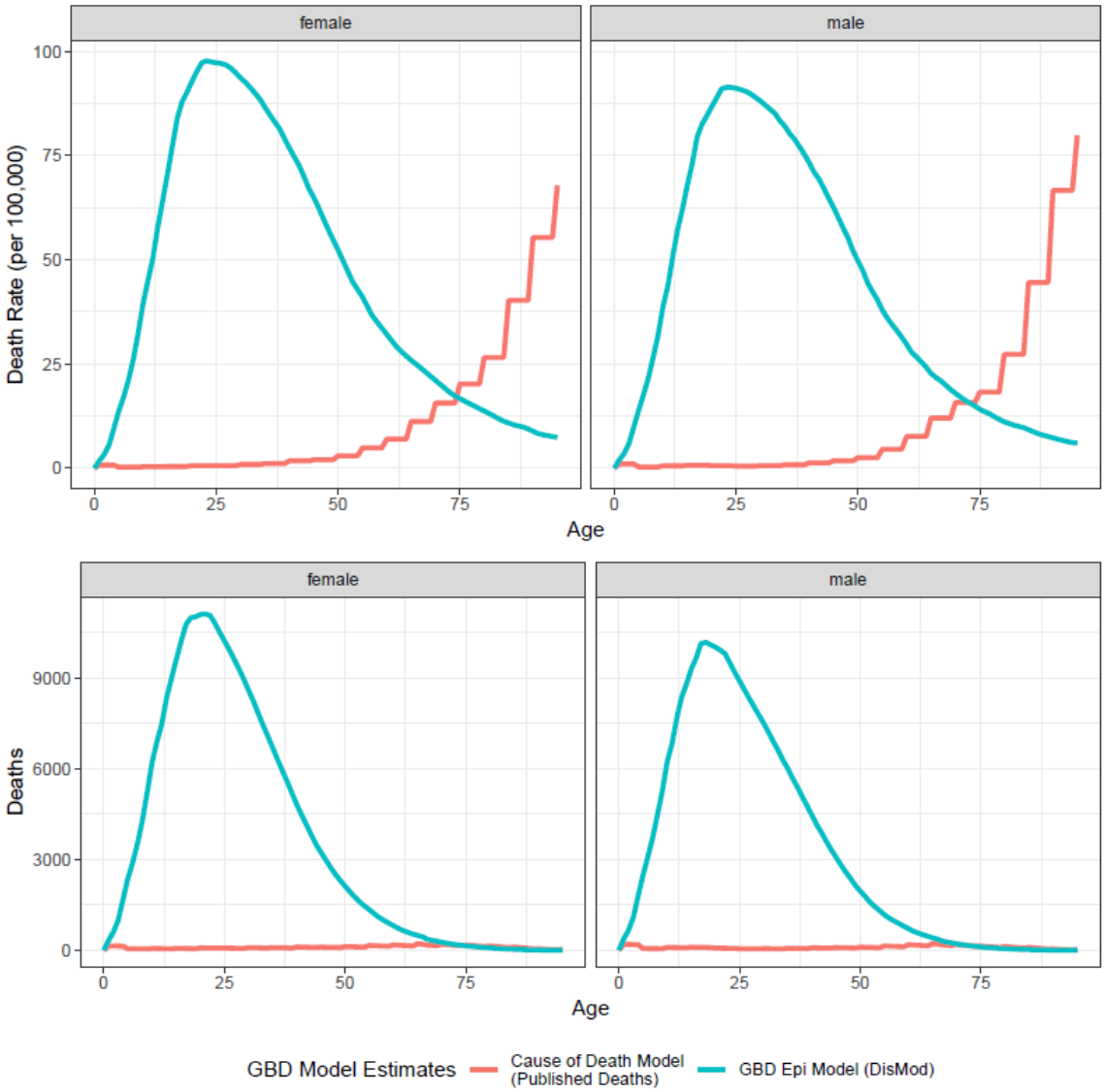


Appendix Figure 13: RHD prevalence estimates from GBD 2017 from 2000-2017 in rates, counts, and as a percent of all cases by age



Appendix Figure 14: Screenshot from the GBD EpiViz[74] tool comparing cause-specific mortality rates from RHD implied by the DisMod model (orange) and the rates from the cause of death modelling in the GBD (gray crosses)

We examined the case of Fiji to better understand the relative strengths and weaknesses of the GBD estimates because the cause of death estimates in Fiji have been previously examined for accuracy and there were echocardiographic studies informing the prevalence estimates.[76] The estimates of death rates in Fiji from the GBD were generally higher under age 10, lower from ages 10 to 50, and similar or slightly higher above age 50 compared to those from the more comprehensive examination of record-linked data in a population cohort study by Parks and colleagues (Appendix Table 22).[76] Yet, these adjusted death estimates were also inconsistent with the DisMod estimates in Fiji, which were higher and had an age pattern more similar to that from the DisMod estimates in Sub-Saharan Africa seen in Appendix Figure 14. In Fiji, given the stronger areas of empirical evidence—echocardiographic screening in young ages and estimates of deaths—it appears that the GBD estimates of deaths were somewhat low (and those assumed in DisMod very high) and the estimates of prevalence at older ages were substantially lower than would be true if the death rates from Parks and colleagues were accurate. There is very little evidence about the prevalence of echocardiographically diagnosed RHD in adults above age 25,[19] making it difficult to square the prevalence estimates at younger ages with the level and pattern of the mortality estimates.



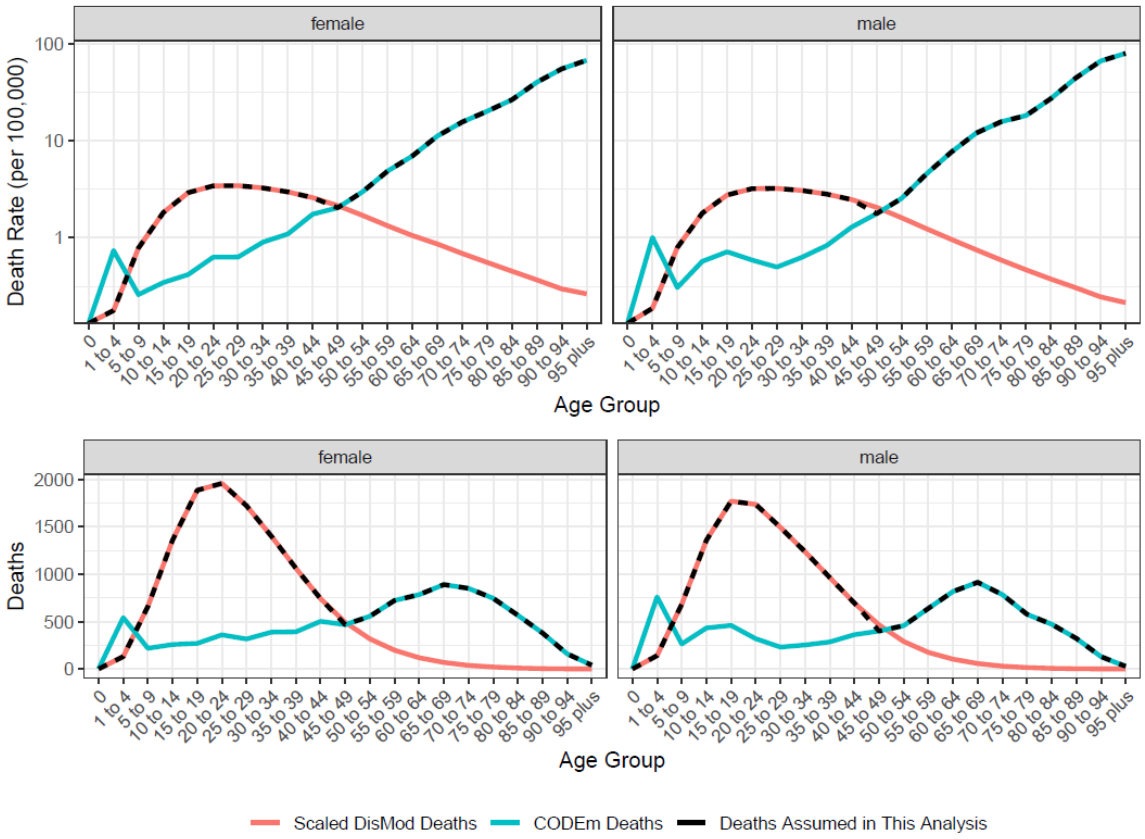
Appendix Figure 15: Comparison of RHD death rates and total deaths in 2017 from the published results in the African Union versus those implied by the GBD epidemiological model in Sub-Saharan Africa (DisMod)

Given the limited data on deaths from RHD within the AU informing the GBD estimates and the difference in age patterns between the GBD estimates and hospital-based cohorts of patients with symptomatic and mostly severe RHD within the AU,[34] we created a set of death rates informed by these different sources of evidence. We used a piecewise mortality function informed by a combination of GBD estimates, literature on primary data from within the AU, and clinical experience of causes of heart failure. Under age 45, we used the age pattern of DisMod deaths but constrained the deaths to fit under 75% of the envelope of cardiovascular disease deaths in ages 5-19 where the age pattern of DisMod is closest to reaching the total cardiovascular disease death envelope. This approach was informed by expert opinion on ischemic heart disease versus RHD death estimates, particularly the high estimates of IHD deaths at young ages in the GBD results in these settings. We anchored the estimates to the envelope of cardiovascular diseases to create a reasonable constraint. Over age 45 we used the RHD death rates published from the GBD as a result of the CODEm modelling process. The pattern is shown in Appendix Figure 16. This resulted in an estimate of about 35,000 total RHD deaths in the AU, compared to about 18,000 reported in the GBD 2017 from the cause of death modelling process. This number remains quite small in comparison to cardiovascular disease deaths overall (1.3 million).

Appendix Table 22: Comparison of death rates in Fiji from Parks et al. (2015) for 2008-2012 versus GBD 2017 for 2010

Age Group	GBD Death Rate[10]	Parks et al.[76]	Ratio
1 to 4	2.9	0	0
5 to 9	1.8	0.3	0.17
10 to 14	3.8	6.5	1.73
15 to 19	4.1	7	1.70
20 to 24	4.2	6.5	1.54
25 to 29	3.5	6.6	1.89
30 to 34	7.4	10.4	1.41
35 to 39	5.8	12.2	2.11
40 to 44	10.1	12.2	1.21
45 to 49	10.6	18.6	1.76
50 to 54	16.1	14	0.87
55 to 59	20.6	19.7	0.95
60 to 64	30.5	22.1	0.73
65 to 69	35.2	34.9	0.99
70 plus		Not included	Assumed 0.99

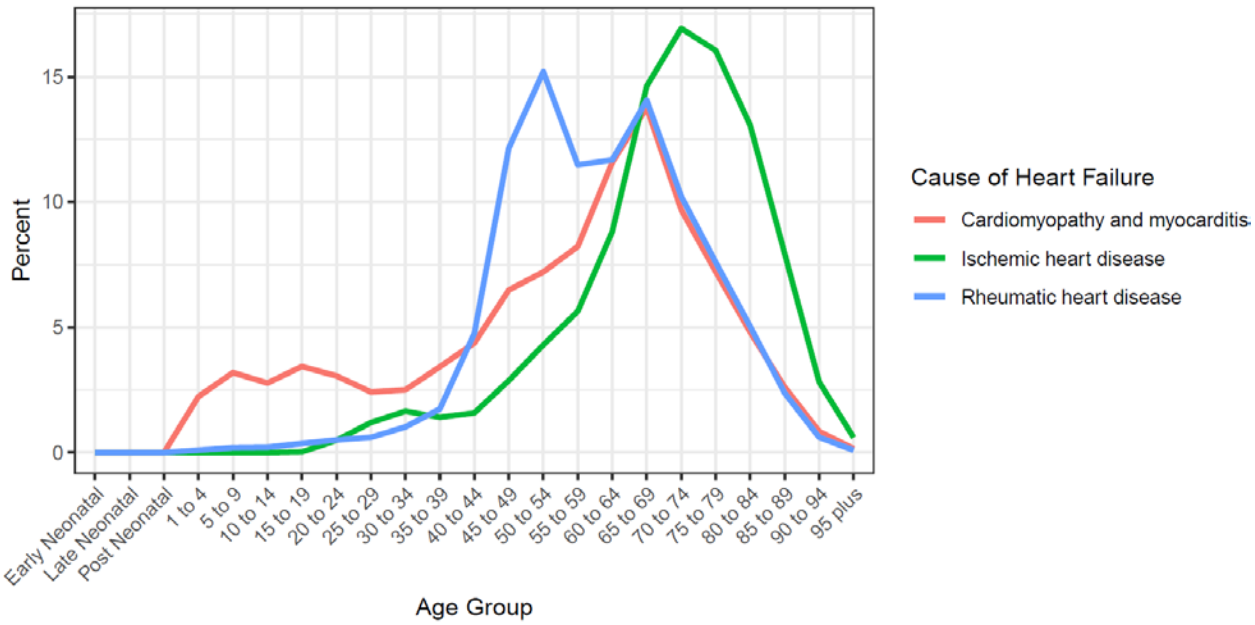
Once we established a plausible pattern of death rates and deaths, we sought to find a plausible risk of transition to severe RHD/RHD with HF. The GBD estimates of the prevalence of HF and the implied incidence of HF from RHD lacked face validity. The age distribution of HF by cause of HF in the AU in 2017 from the GBD study is shown in Appendix Figure 17.[1] The age distribution of HF from RHD was younger than from ischemic heart disease, which is expected. However, 90% of HF cases from RHD were estimated to be among people age 45 and older, with the median over age 60. In light of data on the age distribution of HF patients and patients with RHD in several studies in the AU and the estimates of deaths from RHD from the GBD itself, the GBD estimates for heart failure from RHD seemed unlikely to be accurate.[18,34,35,38,39,77] The Global Rheumatic Heat Disease Registry (REMEDY) Study found a young age distribution of patients enrolled with RHD across 12 African countries plus Yemen and India.[34] Patients were enrolled regardless of age, and patients with asymptomatic diseases diagnosed through community screening were not included. Many of these patients would be considered to have severe disease. The median age was 24 (IQR: 15-34) in low-income countries, 28 (18-38) in lower-middle-income countries, and 39 (22-52) in upper-middle-income countries, with 37% under age 19 in LICs, compared to 26% in LMICs and 19% in UMICs. However, the balance of types of facilities (i.e. some pediatric, some general/adult) did to some extent determine the age distribution.[34] At outpatient clinics at three hospitals in Rwanda, 42.4% of HF patients were children under 18 years old at enrollment compared to <1% of the prevalence of HF in the GBD estimates.[77] The average age of enrollment was 21 years old. Even excluding children, the average age among adults was approximately 31 years (making a crude assumption of an average age of 8 among the 89 children to calculate the average age among the remaining 121 adults).[77] In stark contrast, only 10% of HF cases from RHD in the AU were estimated to be among people under age 45 in the GBD estimates.[1] The mean age of admitted patients with "endemic causes" (idiopathic cardiomyopathy, RHD, peripartum cardiomyopathy, pericardial effusion tamponade, HIV cardiomyopathy, and endomyocardial fibrosis) of HF in the THESUS-HF study in a cohort of HF patients admitted to university hospitals in nine sub-Saharan African countries from 2007-2010 was 47 in men and 41 in women (median ages 46 and 36).[35] The mean age of valvular HF in one analysis from the Heart of Soweto study was older (53); however, that study also found no cases of ARF, perhaps suggesting that development of RHD through ARF is no longer common in that population, contributing few cases among children and young adults.[78] Additionally, the GBD estimates indicate that HF from non-rheumatic valvular disease is about as prevalent as HF from RHD in the African Union, and the age pattern of the non-rheumatic disease is older. Among adults over age 14, the median age of newly diagnosed RHD patients in another publication from the Heart of Soweto study was 43.[18] Not all were diagnosed with HF, but many had severe symptoms.



Appendix Figure 16: Pattern of death rates and death counts in 2017 by age, comparison of approaches

Given the lack of face validity in the implied incidence of HF from the GBD data (derived as described in the section "Derivation of Parameters from GBD" in this appendix), we treated the transition to severe disease/heart failure as a parameter in the model that could be derived based on other parameters. We used the prevalence of mild RHD, an assumption about the risk of mortality in people with severe disease/HF, and the mortality rates described above to back-calculate a risk of transitioning to severe disease/HF (see transition probability section for more detail).

In general, we sought to use parameters in our model that were epidemiologically consistent with one another; however, the gaps in empirical evidence and the inconsistencies in the available estimates were limiting in this regard. The estimates of RHD prevalence in older ages appear inconsistent with the mortality rates in the GBD. This has two effects on the projections—an age distribution of prevalence rates that shift towards higher ages as the model projects forward in time (because we do not use the implausibly high numbers of deaths as in DisMod that maintain the age distribution of prevalence seen in Appendix Figure 13) and an age distribution of death rates that shifts somewhat to older ages as a result.



Each line shows the percent of HF cases by age from the given cause; the area under each curve (the percent across ages within a cause) is 100%.

Appendix Figure 17: Estimated percent of cause-specific HF cases by age in the African Union, GBD 2017

Derivation of Parameters from GBD

In instances where the average duration of a case is short (because of high mortality or probability of transition to another state), the prevalence estimates from GBD, which represent person-years in a state, can be substantially different than the number of total people exposed to that state in a given year. Our model uses counts of people moving between different states, so we sought to obtain counts.

To obtain the starting case numbers for each health state for the scenario fully based on the published GBD estimates (i.e. not using death patterns from DisMod), we used GBD estimates of mortality, prevalence, and incidence to back-calculate several parameters. We assumed that deaths from RHD in the GBD happen exclusively among cases of RHD that reach the stage of HF. This assumption allowed us to estimate the overall mortality rate ("with-cause" mortality rate, or rate from RHD and from other causes) among people with HF from RHD (mx^{WC}) using the all-cause mortality rate in the general population (mx^{AC}), mortality rate from RHD in the general population (mx^{RHD}), and the prevalence of HF from RHD ($prev^{RHD\text{-}HF}$), for a given sex (s) and age (a).

$$mx_{s,a}^{WC} = (mx_{s,a}^{AC} - mx_{s,a}^{RHD}) + \frac{mx_{s,a}^{RHD}}{prev_{s,a}^{RHD-HF}}$$

The first term represents a "baseline" mortality from non-RHD causes, and the second term represents "excess" mortality from RHD. We used estimates of population for single-year age groups from the GBD study, but single-year age group estimates are not produced for every type of parameter. To obtain these, we replicated estimates of rates of mortality and prevalence from corresponding GBD age groups (typically 5-year age groups). To start the projection, we needed counts of individuals in each category rather than the person-year values that the GBD prevalence estimates represented. To obtain these, we broke the total case counts into two parts: people with HF from RHD who survived the previous year and people with newly incident HF from RHD.

$$Cases_{s,a}^{RHD-HF\ eff} = Persistent\ Cases_{s,a-1,y-1}^{RHD-HF} + New\ Cases_{s,a,y}^{RHD-HF}$$

First, we converted the mortality rate to a probability of death (qx) using a common demographic approximation.[7]

$$qx_{s,a}^{WC} = 1 - e^{-mx_{s,a}^{WC}}$$

We treated this probability as the percent of cases of HF from RHD in a given year that would go on to die of any cause (D^{WC}).

$$qx_{s,a}^{WC} = \frac{D_{s,a}^{WC}}{Cases_{s,a}^{RHD-HF\ eff}}$$

We calculated the total deaths (D^{WC}) using the mortality rate in the HF population, the total population (pop), and the prevalence of HF from RHD:

$$D_{s,a}^{WC} = mx_{s,a}^{WC} * prev_{s,a}^{RHD-HF} * pop_{s,a}$$

Note that $prev^{RHD\text{-}HF} * pop$ is different from $Cases^{RHD\text{-}HF\ eff}$ in that the prevalence represents a point prevalence or person-years of prevalence, while $Cases^{RHD\text{-}HF\ eff}$ approximates a count of cases in the year, as described above. We used qx^{WC} and D^{WC} to calculate $Cases^{RHD\text{-}HF\ eff}$. Then, we subtracted D^{WC} and to estimate the number of cases that would continue to exist in the next year.

$$Persistent\ Cases_{s,a,y}^{RHD-HF} = Cases_{s,a}^{RHD-HF\ eff} - D_{s,a}^{WC}$$

The GBD study gives a time series of estimates from 1990 to 2017, so we could make these calculations for every year. From this, we calculated new incident cases ($New\ Cases^{RHD\text{-}HF}$) using the estimate of cases held over from the previous year.

$$New\ Cases_{s,a,y}^{RHD-HF} = Cases_{s,a,y}^{RHD-HF} - Persistent\ Cases_{s,a-1,y-1}^{RHD-HF}$$

For more stable estimates, we combined these incident cases into the GBD aggregate age groups rather than using single-year age groups. We divided by the corresponding cases of RHD without HF to estimate the annual probability of transitioning to RHD with HF from RHD without HF ($P^{HF\ trans}$).

$$P_{s,a}^{HF\ trans} = \frac{New\ Cases_{s,a}^{RHD-HF}}{Cases_{s,a}^{RHD-no\ HF}}$$

To estimate the total cases of RHD without HF, as opposed to prevalence in person-time, and to estimate the number of cases continuing into the initial year of the projection, we took a similar approach. We used the prevalence, incidence of RHD overall, and death rates from GBD, as well as the incident cases transitioning from RHD without HF to RHD with HF derived above. We also used a probability of regression of disease based on the approach used in the GBD study. The large number of subclinical RHD cases means the difference between total people and person-time is small, but at old ages, there are larger differences because of high overall mortality—though these differences are in a relatively small number of people because of the age structure of the population. First, we subtracted the prevalence of RHD with HF from the overall prevalence of RHD estimated in the GBD, by age and sex, to obtain the prevalence of RHD without HF. Then, we calculated the number of cases of RHD without HF leaving that category through advancing to RHD with HF, death, or regression of disease to normal. Following the GBD study, we only included regression rate under age 20.[1] Given the modeling assumption that all RHD deaths occur through more advanced stages of the disease, we used cause-subtracted mortality rates for estimating the deaths transitioning out of the category.

$$Num\ Trans_{s,a}^{RHD-no\ HF} = \left(mx_{s,a}^{AC} - mx_{s,a}^{RHD}\right) * prev_{s,a}^{RHD-no\ HF} + New\ Cases_{s,a}^{RHD-HF} + Remission\ Rate_{s,a}^{RHD-no\ HF} * prev_{s,a}^{RHD-no\ HF}$$

We calculated the rate leaving this category:

$$Rate\ Trans_{s,a}^{RHD-no\ HF} = \frac{Num\ Trans_{s,a}^{RHD-no\ HF}}{prev_{s,a}^{RHD-no\ HF}}$$

We converted this rate into a probability using the same demographic approximation used for death rates in estimating the number of incident HF cases.

$$Prob\ Trans_{s,a}^{RHD-no\ HF} = 1 - e^{-Rate\ Trans_{s,a}^{RHD-no\ HF}}$$

Then, we solved for the count of RHD without HF using this probability and the number transferring out of the group.

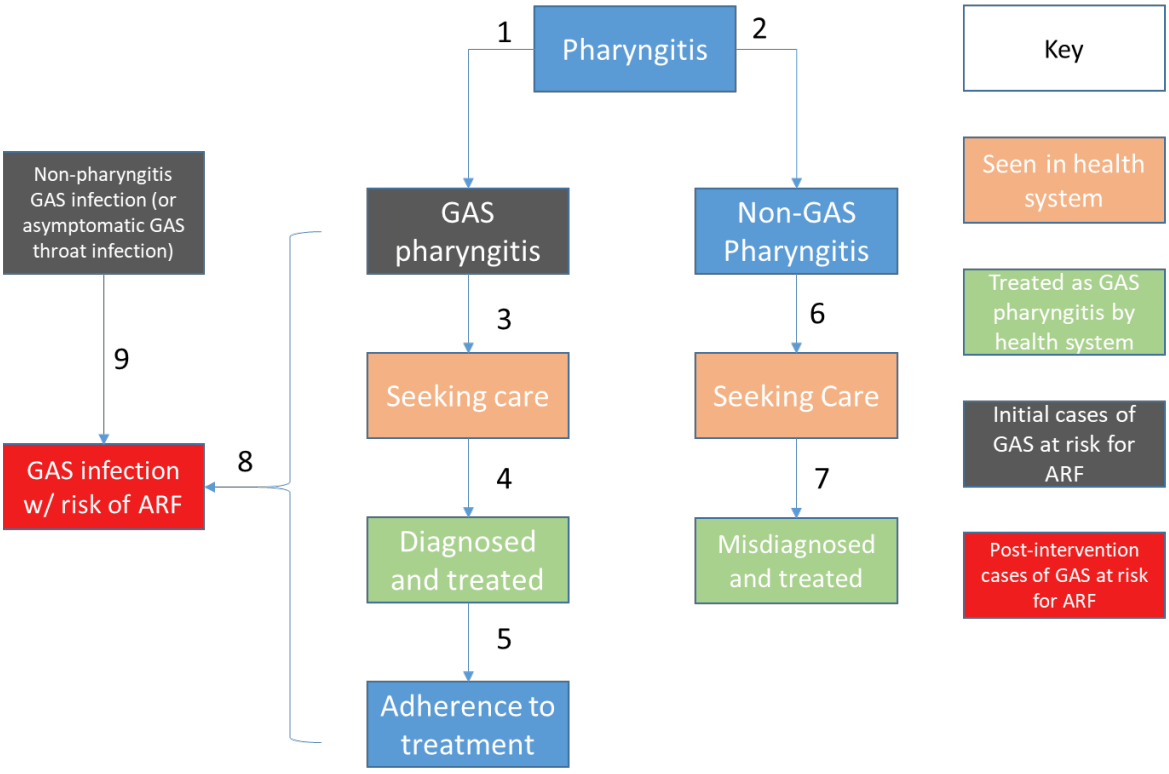
$$Cases_{s,a}^{RHD-no\ HF} = \frac{Num\ Trans_{s,a}^{RHD-no\ HF}}{Prob\ Trans_{s,a}^{RHD-no\ HF}}$$

To get the number of cases surviving and not transitioning to HF from the previous year, we subtracted the newly incident cases from the total cases. This would be the number of cases to start running the model, before adding newly incident cases.

Derivation of ARF incidence, pharyngitis cases seen and treated, and understanding effects of primary and secondary prophylaxis

Appendix Figure 18 shows several keys to how primary prevention works conceptually. There are several complications. The total number of pharyngitis cases seen by the health system is the number of pharyngitis cases times the proportion from GAS (1, see number in figure) times the proportion of these seeking care (3) plus the number of total pharyngitis cases times the proportion not from GAS (2) times the proportion seeking care (6). This number is used for costing, as this is the number that are either seen at a health center for assessment or seen by a community health worker, depending on the delivery model.

$$Pharyngitis\ Seen = Total\ Pharyngitis * \%\ GAS * \%\ GAS\ Seeking\ Care + Total\ Pharyngitis * (100 - \%GAS) * \%\ Non - GAS\ Seeking\ Care$$



Appendix Figure 18: Pathways determining effectiveness and cost-effectiveness of primary prevention

The total number of pharyngitis cases treated by the health system is the number of GAS pharyngitis cases that reach the health system times the sensitivity of a decision rule for treatment (4) plus the number of non-GAS cases that reach the health system times 100% minus the specificity (7). This number is used for costing, as it is the number of cases receiving benzathine penicillin injection or a course of oral amoxicillin/penicillin depending on the delivery model.

$$Pharyngitis\ Treated = Total\ Pharyngitis * \%\ GAS * \%\ GAS\ Seeking\ Care * Sensitivity\ of\ Treatment\ Rule + Total\ Pharyngitis * (100 - \%GAS) * \%\ Non - GAS\ Seeking\ Care * (1 - Specificity\ of\ Treatment\ Rule)$$

The total number of cases that end up at risk for ARF, on the other hand, is the number of asymptomatic or non-pharyngitis GAS infections (some portion of which may cause risk), the number of GAS pharyngitis infections not seen by the health system, the number of GAS pharyngitis infections not treated by the health system once seen, and the number of GAS pharyngitis infections for which treatment was ineffective (either because of lack of adherence or simply the incomplete effectiveness). This is depicted in red in Appendix Figure 18.

One challenge is understanding what proportion of ARF cases result from non-pharyngitis GAS infection or asymptomatic GAS throat infection versus GAS pharyngitis. This is critical for estimating the effectiveness of primary prevention. Given that we do not have an estimate of the number of non-pharyngitis GAS infections that convey risk for ARF, we cannot use pathways (8) and (9) as probabilities by which to multiply the counts from previous steps. Instead, we assume that some proportion of ARF cases come from pharyngitis versus non-pharyngitis GAS infections or asymptomatic GAS throat infections.

We calculated the incidence of ARF at baseline, using information about the coverage and the transition probabilities. First, we calculated the implied incidence of a first ARF case from GAS pharyngitis ($Inc_{1ARF\ phar}$) at baseline using the input parameters about the incidence of GAS pharyngitis ($Inc_{GAS\ phar}$), the chance of ARF given GAS pharyngitis (*ARF risk*) at baseline levels of coverage (Cov_{t1}) with the given effect size of treatment of GAS pharyngitis on ARF risk (*Eff*), where 1-*Eff* is a relative risk, and the sensitivity of the decision rule used to treat (*Dec*). We treated coverage as the percent of cases seen in the health system (percent seeking care) times the proportion of the time that the health system has the capacity to diagnose and treat (health center or community health workers, depending on the delivery strategy), so we also adjusted for the sensitivity of the clinical decision method used to treat, *Dec*, to calculate the impact:

$$Inc_{1ARF\ phar} = Inc_{GAS\ phar} * \big(1 - Cov_{t1} + Cov_{t1} * (1 - Dec)\big) * ARF\ risk + Inc_{GAS\ phar} * Cov_{t1} * Dec * (1 - Eff) * ARF\ risk$$

Then, we calculated the total implied incidence of a first ARF case at baseline using the percent of ARF from GAS pharyngitis (Pct_{Phar}) and percent from non-pharyngitis GAS infection that are varied as sensitivity analysis:

$$Inc_{1ARF} = Inc_{1ARF\ phar} * \frac{100\%}{\text{Pct}_{Phar}}$$

Next, we calculated the impact on ARF incidence from the intervention on GAS pharyngitis infections given some increased coverage (time *t2*) compared to the number at a baseline coverage.

$$Impact\ Scalar = 1 - \frac{Eff * (Cov_{t2} - Cov_{t1}) * Dec}{1 - Eff * Cov_{t1} * Dec}$$

Then, we used this impact on the portion of the ARF incidence assumed to come from GAS pharyngitis to estimate the overall ARF incidence at the later time points with increased coverage.

$$Inc_{1ARF,t2} = Inc_{1ARF,t1} * \text{Pct}_{Phar} * Impact\ Scalar + Inc_{1ARF,t1} * (100\% - \text{Pct}_{Phar})$$

So, the proportion of incident ARF not happening through the symptomatic GAS pharyngitis pathway changed as a result of the treatment, and the input assumption about the proportion occurring through the pharyngitis pathway varied in the sensitivity analysis applied to proportion at the baseline level of primary prevention coverage.

The probability of recurrent ARF was done with a similar calculation. Assuming the same probabilities of GAS pharyngitis infection and that the recurrent ARF cases happen through the same mechanisms as the initial ARF cases, we used a similar equation but also accounted for the coverage of secondary prevention. For clarity, we have separated the equation into two parts here—incidence among people being covered with secondary prophylaxis and those without, where the *Cov* and *Eff* terms still apply to primary prophylaxis, but $ARF\ risk_{recur}$ reflects the higher risk of ARF recurrence with GAS pharyngitis infection after an initial ARF case has already occurred. The first equation estimates the incidence risk among those without secondary prophylaxis:

$$Inc_{ARF\ phar\ recur}^{No\ 2prophylaxis} = Inc_{GAS\ phar} * \left(1 - Cov_{t1} + Cov_{t1} * (1 - Dec)\right) * ARF\ risk_{recur} + Inc_{GAS\ phar} * Cov_{t1} * Dec * (1 - Eff) * ARF\ risk_{recur}$$

The second equation estimates the incidence risk among those with secondary prophylaxis. We assumed that secondary prophylaxis acted through reducing the incidence of GAS pharyngitis here and that in cases where secondary prophylaxis failed to prevent a case, the same process of GAS pharyngitis treatment applied as in the earlier equations. Here, Eff_2 refers to the effectiveness of secondary prophylaxis:

$$Inc_{ARF\ phar\ recur}^{2prophylaxis} = (1 - Eff_2) * (Inc_{GAS\ phar} * \left(1 - Cov_{t1} + Cov_{t1} * (1 - Dec)\right) * ARF\ risk_{recur} + Inc_{GAS\ phar} * Cov_{t1} * Dec * (1 - Eff) * ARF\ risk_{recur})$$

We combined these two components of incidence risk, weighting by the coverage to find total incidence risk among the population of people with a history of ARF, where Cov in this equation refers to the coverage of secondary prophylaxis:

$$Inc_{recur\ ARF\ phar} = Inc_{ARF\ phar\ recur}^{2prophylaxis} * Cov_{t1} + Inc_{ARF\ phar\ recur}^{No\ 2prophylaxis} * (1 - Cov_{t1})$$

Secondary prophylaxis would likely contribute to a reduction in both the contribution of pharyngitis and the contribution of non-pharyngitis or asymptomatic GAS throat infection (if ARF is assumed to be caused solely by GAS), so we assumed the same proportion applied by which to scale-up the pharyngitis-caused ARF to the total ARF.

$$Inc_{recur\ ARF} = Inc_{recur\ ARF\ phar} * \frac{100\%}{\mathrm{Pct}_{Phar}}$$

Recurrence may be impacted by both primary and secondary prevention. The secondary prevention impact scalar was calculated in the same way as the primary but without the adjustment for sensitivity of a clinical decision rule, as the coverage for secondary prevention represented the proportion of people with a history of ARF covered by secondary prophylaxis.

$$Impact\ Scalar_{secondary} = 1 - \frac{Eff_2 * (Cov_{t2} - Cov_{t1})}{1 - Eff_2 * Cov_{t1}}$$

The primary prevention impact scalar was calculated the same way as for the effect on the first episode of ARF and applied in the same way as well, but to the probability of recurrence:

$$Inc_{recur\ ARF,t2,primary} = Inc_{recur\ ARF,t1} * \mathrm{Pct}_{Phar} * Impact\ Scalar_{primary} + Inc_{recur\ ARF,t1} * (100\% - \mathrm{Pct}_{Phar})$$

The secondary prevention would apply to the whole term, as we assumed that it would also prevent recurrence in the non-pharyngitis pathway:

$$Inc_{recur\ ARF,t2} = Inc_{recur\ ARF,t2,primary} * Impact\ Scalar_{secondary}$$

We used this process to derive the incidence of first and recurrent ARF at baseline. Then, as we scaled-up coverage from interventions, we recalculated these incidence rates based on the changing coverage.

References

1 James SL, Abate D, Abate KH, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2018; **392**: 1789–858.

2 Veasy LG, Wiedmeier SE, Orsmond GS, *et al*. Resurgence of acute rheumatic fever in the intermountain area of the United States. *N Engl J Med* 1987; **316**: 421–7.

3 McDonald M, Currie BJ, Carapetis JR. Acute rheumatic fever: a chink in the chain that links the heart to the throat? *Lancet Infect Dis* 2004; **4**: 240–5.

4 Parks T, Smeesters PR, Steer AC. Streptococcal skin infection and rheumatic heart disease. *Curr Opin Infect Dis* 2012; **25**: 145–53.

5 Member States | African Union. https://au.int/en/member_states/countryprofiles2 (accessed Jan 14, 2021).

6 United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2019 Revision. United Nations, 2019 https://population.un.org/wpp/ (accessed April 10, 2020).

7 Preston S, Heuveline P, Guillot M. Demography: Measuring and Modeling Population Processes. Wiley, 2000.

8 Zilla P, Yacoub M, Zühlke L, *et al*. Global Unmet Needs in Cardiac Surgery. *Global Heart* 2018; **13**: 293–303.

9 Murray CJL, Callender CSKH, Kulikoff XR, *et al*. Population and fertility by age and sex for 195 countries and territories, 1950–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2018; **392**: 1995–2051.

10 Roth GA, Abate D, Abate KH, *et al*. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2018; **392**: 1736–88.

11 Pearce S, Bowen AC, Engel ME, Lande M de la, Barth DD. The incidence of sore throat and group A streptococcal pharyngitis in children at high risk of developing acute rheumatic fever: A systematic review and meta-analysis. *PLOS ONE* 2020; **15**: e0242107.

12 Jose JJM, Brahmadathan KN, Abraham VJ, *et al*. Streptococcal Group A, C, and G Pharyngitis in School Children: A Prospective Cohort Study in Southern India. *Epidemiol Infect* 2018; **146**: 848–53.

13 Oliver J, Wadu EM, Pierse N, Moreland NJ, Williamson DA, Baker MG. Group A Streptococcus pharyngitis and pharyngeal carriage: A meta-analysis. *PLOS Neglected Tropical Diseases* 2018; **12**: e0006335.

14 Irlam J, Mayosi BM, Engel M, Gaziano TA. Primary Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease With Penicillin in South African Children With Pharyngitis. *Circulation: Cardiovascular Quality and Outcomes* 2013; **6**: 343–51.

15 Watkins D, Lubinga SJ, Mayosi B, Babigumira JB. A Cost-Effectiveness Tool to Guide the Prioritization of Interventions for Rheumatic Fever and Rheumatic Heart Disease Control in African Nations. *PLOS Neglected Tropical Diseases* 2016; **10**: e0004860.

16 Hewitson J, Zilla PPT. Children's heart disease in sub-Saharan Africa: Challenging the burden of disease. *SA Heart Journal* 2010; **7**: 18–29.

17 Denny F W. T. Duckett Jones and rheumatic fever in 1986. T. Duckett Jones Memorial Lecture. *Circulation* 1987; **76**: 963–70.

18 Sliwa K, Carrington M, Mayosi BM, Zigiriadis E, Mvungi R, Stewart S. Incidence and characteristics of newly diagnosed rheumatic heart disease in Urban African adults: insights from the Heart of Soweto Study. *Eur Heart J* 2010; **31**: 719–27.

19 Noubiap JJ, Agbor VN, Bigna JJ, Kaze AD, Nyaga UF, Mayosi BM. Prevalence and progression of rheumatic heart disease: a global systematic review and meta-analysis of population-based echocardiographic studies. *Scientific Reports* 2019; **9**: 1–14.

20 Engel ME. A Study of Determinants and Prevalence of Rheumatic Heart Disease in Cape Town. 2012. https://open.uct.ac.za/bitstream/item/3165/thesis_hsf_2012_engel_m.pdf?sequence=1.

21 Kumar R, Vohra H, Chakraborty A, *et al.* Epidemiology of group A streptococcal pharyngitis & impetigo: a cross-sectional & follow up study in a rural community of northern India. *Indian J Med Res* 2009; **130**: 765–71.

22 Nandi S, Kumar R, Ray P, Vohra H, Ganguly NK. Group A streptococcal sore throat in a periurban population of northern India: a one-year prospective study. *Bull World Health Organ* 2001; **79**: 528–33.

23 Steer AC, Jenney AWJ, Kado J, *et al.* Prospective surveillance of streptococcal sore throat in a tropical country. *Pediatr Infect Dis J* 2009; **28**: 477–82.

24 Kumar R, Chakraborti A, Aggarwal AK, *et al.* Streptococcus pyogenes pharyngitis & impetigo in a rural area of Panchkula district in Haryana, India. *Indian J Med Res* 2012; **135**: 133–6.

25 Lennon D. Rheumatic fever, a preventable disease? The New Zealand Experience. In: Streptococci and streptococcal disease: entering the new milennium. Proceedings of the XIV Lancefield International Symposium on Streptococci and Streptococcal Disease. Aukland, New Zealand, 2000.

26 Australian Institute of Health and Welfare. Acute rheumatic fever and rheumatic heart disease in Australia. Canberra, Australia: Australian Institute of Health and Welfare, 2019 https://www.aihw.gov.au/reports/indigenous-australians/acute-rheumatic-fever-rheumatic-heart-disease/contents/acute-rheumatic-fever/arf-among-indigenous-australians (accessed Aug 20, 2020).

27 Beaudoin A, Edison L, Introcaso CE, *et al.* Acute rheumatic fever and rheumatic heart disease among children--American Samoa, 2011-2012. *MMWR Morb Mortal Wkly Rep* 2015; **64**: 555–8.

28 Carapetis JR, Currie BJ. Rheumatic fever in a high incidence population: the importance of monoarthritis and low grade fever. *Archives of Disease in Childhood* 2001; **85**: 223–7.

29 Baker MG, Gurney J, Oliver J, *et al.* Risk Factors for Acute Rheumatic Fever: Literature Review and Protocol for a Case-Control Study in New Zealand. *Int J Environ Res Public Health* 2019; **16**. DOI:10.3390/ijerph16224515.

30 Ali SKM, Engel ME, Zühlke L, Jack SJ. Chapter 10 - Primary Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease. In: Dougherty S, Carapetis J, Zühlke L, Wilson N, eds. Acute Rheumatic Fever and Rheumatic Heart Disease. San Diego (CA): Elsevier, 2020: 195–206.

31 Karthikeyan G, Guilherme L. Acute rheumatic fever. *The Lancet* 2018; **392**: 161–74.

32 Tibazarwa KB, Volmink JA, Mayosi BM. Incidence of acute rheumatic fever in the world: a systematic review of population-based studies. *Heart* 2008; **94**: 1534–40.

33 Carapetis JR, Beaton A, Cunningham MW, *et al.* Acute rheumatic fever and rheumatic heart disease. *Nature Reviews Disease Primers* 2016; **2**: 1–24.

34 Zühlke L, Engel ME, Karthikeyan G, *et al.* Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J* 2015; **36**: 1115–22.

35 Damasceno A, Mayosi BM, Sani M, *et al.* The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. *Arch Intern Med* 2012; **172**: 1386–94.

36 Michaud C, Rammohan R, Narula J. Cost-effectiveness analysis of intervention strategies for reduction of the burden of rheumatic heart disease. In: Narula J, Virmani R, Reddy K, Tandon R, eds. Rheumatic Fever. Washington, USA: American Registry of Pathology, 1999: 485–97.

37 He VYF, Condon JR, Ralph AP, *et al.* Long-Term Outcomes From Acute Rheumatic Fever and Rheumatic Heart Disease. *Circulation* 2016; **134**: 222–32.

38 Zühlke L, Karthikeyan G, Engel ME, *et al.* Clinical Outcomes in 3343 Children and Adults With Rheumatic Heart Disease From 14 Low- and Middle-Income Countries: Two-Year Follow-Up of the Global Rheumatic Heart Disease Registry (the REMEDY Study). *Circulation* 2016; **134**: 1456–66.

39 Eberly LA, Rusingiza E, Park PH, *et al.* 10-Year Heart Failure Outcomes From Nurse-Driven Clinics in Rural Sub-Saharan Africa. *Journal of the American College of Cardiology* 2019; **73**: 977–80.

40 Robertson KA, Volmink JA, Mayosi BM. Antibiotics for the primary prevention of acute rheumatic fever: a meta-analysis. *BMC Cardiovascular Disorders* 2005; **5**. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1164408/ (accessed Nov 17, 2019).

41 Padmavati S, Sharma KB, Jayaram O. Epidemiology and prophylaxis of rheumatic fever in Delhi--a five year follow-up. *Singapore Med J* 1973; **14**: 457–61.

42 Lennon D, Stewart J, Farrell E, Palmer A, Mason H. School-Based Prevention of Acute Rheumatic Fever: A Group Randomized Trial in New Zealand. *The Pediatric Infectious Disease Journal* 2009; **28**: 787–94.

43 Lennon D, Kerdemelidis M, Arroll B. Meta-analysis of trials of streptococcal throat treatment programs to prevent rheumatic fever. *Pediatr Infect Dis J* 2009; **28**: e259-264.

44 Manyemba J, Mayosi BM. Penicillin for secondary prevention of rheumatic fever. *Cochrane Database of Systematic Reviews* 2002; **3**. https://www.ncbi.nlm.nih.gov/pubmed/12137650 (accessed Nov 17, 2019).

45 de Dassel JL, Lennon D, Dougherty S, Ralph AP. Chapter 11 - Secondary Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease. In: Dougherty S, Carapetis J, Zühlke L, Wilson N, eds. Acute Rheumatic Fever and Rheumatic Heart Disease. San Diego (CA): Elsevier, 2020: 207–34.

46 Beaton A, Okello E, Engelman D, *et al.* Determining the impact of Benzathine penicillin G prophylaxis in children with latent rheumatic heart disease (GOAL trial): Study protocol for a randomized controlled trial. *American Heart Journal* 2019; **215**: 95–105.

47 Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *International Journal of Cardiology* 2002; **82**: 149–58.

48 Sliwa K, Azibani F, Baard J, *et al.* Reducing late maternal death due to cardiovascular disease - A pragmatic pilot study. *International Journal of Cardiology* 2018; **272**: 70–6.

49 Rusingiza EK, El-Khatib Z, Hedt-Gauthier B, *et al.* Outcomes for patients with rheumatic heart disease after cardiac surgery followed at rural district hospitals in Rwanda. *Heart* 2018; **104**: 1707–13.

50 Ali S, Karadawi N, Elhassan NB, *et al.* Patterns, outcomes and trends in hospital visits of un-operated and operated children with rheumatic heart disease in Sudan. *Cardiovasc Diagn Ther* 2019; **9**: 165–72.

51 Geldenhuys A, Koshy JJ, Human PA, Mtwale JF, Brink JG, Zilla P. Rheumatic mitral repair versus replacement in a threshold country: the impact of commissural fusion. *J Heart Valve Dis* 2012; **21**: 424–32.

52 Mocumbi A, Beaton A, Soma-Pillay P, Dougherty S, Sliwa K. Chapter 9 - Rheumatic Heart Disease in Pregnancy. In: Dougherty S, Carapetis J, Zühlke L, Wilson N, eds. Acute Rheumatic Fever and Rheumatic Heart Disease. San Diego (CA): Elsevier, 2021: 171–93.

53 Zühlke L, Acquah L. Pre-conception counselling for key cardiovascular conditions in Africa: optimising pregnancy outcomes. *Cardiovasc J Afr* 2016; **27**: 79–83.

54 Sliwa K, Johnson MR, Zilla P, Roos-Hesselink JW. Management of valvular disease in pregnancy: a global perspective. *Eur Heart J* 2015; **36**: 1078–89.

55 Lozano R, Fullman N, Mumford JE, *et al.* Measuring universal health coverage based on an index of effective coverage of health services in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020; **396**: 1250–84.

56 Knowles R, Sharland M, Hsia Y, *et al.* Measuring antibiotic availability and use in 20 low- and middle-income countries. *Bull World Health Organ* 2020; **98**: 177-187C.

57 Gupta N, Coates MM, Bekele A, *et al.* Availability of equipment and medications for non-communicable diseases and injuries at public first-referral level hospitals: a cross-sectional analysis of service provision assessments in eight low-income countries. *BMJ Open* 2020; **10**: e038842.

58 Eberly LA, Rusangwa C, Ng'ang'a L, *et al.* Cost of integrated chronic care for severe non-communicable diseases at district hospitals in rural Rwanda. *BMJ Global Health* 2019; **4**. DOI:10.1136/bmjgh-2019-001449.

59 Singh S, Darroch JE, Ashford LS. Adding it up: the costs and benefits of investing in sexual and reproductive health 2014. Guttmacher Institute, 2014 https://www.guttmacher.org/report/adding-it-costs-and-benefits-investing-sexual-and-reproductive-health-2014 (accessed Oct 1, 2020).

60 Bhutta ZA, Ali S, Cousens S, *et al.* Interventions to address maternal, newborn, and child survival: what difference can integrated primary health care strategies make? *The Lancet* 2008; **372**: 972–89.

61 Turner HC, Lauer JA, Tran BX, Teerawattananon Y, Jit M. Adjusting for Inflation and Currency Changes Within Health Economic Studies. *Value in Health* 2019; **22**: 1026–32.

62 International Monetary Fund. World Economic Outlook Database. 2020; published online April. https://www.imf.org/external/pubs/ft/weo/2020/01/weodata/index.aspx (accessed July 19, 2020).

63 The World Bank. World Development Indicators. 2020; published online July. https://data.worldbank.org/ (accessed July 19, 2020).

64 Stenberg K, Lauer JA, Gkountouras G, Fitzpatrick C, Stanciole A. Econometric estimation of WHO-CHOICE country-specific costs for inpatient and outpatient health service delivery. *Cost Effectiveness and Resource Allocation* 2018; **16**: 11.

65 Watkins DA, Qi J, Kawakatsu Y, Pickersgill SJ, Horton SE, Jamison DT. Resource requirements for essential universal health coverage: a modelling study based on findings from Disease Control Priorities, 3rd edition. *The Lancet Global Health* 2020; **8**: e829–39.

66 Steinhoff MC, Walker CF, Rimoin AW, Hamza HS. A clinical decision rule for management of streptococcal pharyngitis in low-resource settings. *Acta Paediatr* 2005; **94**: 1038–42.

67 International Rheumatic Fever StudyGroup. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. *The Lancet* 1991; **337**: 1308–10.

68 Management Sciences for Health, World Health Organization. International medical products price guide. Medford, Masachusetts: Management Sciences for Health, 2015 https://www.msh.org/sites/default/files/msh-2015-international-medical-products-price-guide.pdf.

69 McCord GC, Liu A, Singh P. Deployment of community health workers across rural sub-Saharan Africa: financial considerations and operational assumptions. *Bull World Health Organ* 2013; **91**: 244–253b.

70 Bowen HL. Impact of a mass media campaign on bed net use in Cameroon. *Malar J* 2013; **12**: 36.

71 Jamison DT, Summers LH, Alleyne G, *et al.* Global health 2035: a world converging within a generation. *The Lancet* 2013; **382**: 1898–955.

72 Robinson LA, Hammit JK, Cecchini M, *et al.* Reference case guildelines for benefit-cost analysis in global health and development. 2019 https://cdn1.sph.harvard.edu/wp-content/uploads/sites/2447/2019/05/BCA-Guidelines-May-2019.pdf (accessed Sept 23, 2020).

73 Vecino-Ortiz AI, Jafri A, Hyder AA. Effective interventions for unintentional injuries: a systematic review and mortality impact assessment among the poorest billion. *The Lancet Global Health* 2018; **6**: e523–34.

74 Institute for Health Metrics and Evaluation. Epi Visualization | IHME Viz Hub. 2019; published online Oct. http://vizhub.healthdata.org/epi (accessed Oct 27, 2020).

75 Larsen K. Graphreader.com. Graphreader.com. http://www.graphreader.com/ (accessed Oct 27, 2020).

76 Parks T, Kado J, Miller AE, *et al.* Rheumatic Heart Disease-Attributable Mortality at Ages 5–69 Years in Fiji: A Five-Year, National, Population-Based Record-Linkage Cohort Study. *PLOS Neglected Tropical Diseases* 2015; **9**: e0004033.

77 Eberly LA, Rusingiza E, Park PH, *et al.* Understanding the Etiology of Heart Failure Among the Rural Poor in Sub-Saharan Africa: A 10-Year Experience From District Hospitals in Rwanda. *Journal of Cardiac Failure* 2018; **24**: 849–53.

78 Stewart S, Wilkinson D, Hansen C, *et al.* Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. *Circulation* 2008; **118**: 2360–7.