Understanding the Role of Vaccine Programs in Reducing Antimicrobial Resistance

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Key Recommendations

Background

Very little evidence exists to help decision-makers understand the role that vaccines can play in reducing the global problem of antimicrobial resistance (AMR), particularly in resource-constrained settings such as the low- and middle-income countries (LMICs) served by organizations like Gavi, the Vaccine Alliance, which provides financing, capacity building and technical assistance support for national immunization programs (NIPs). In performing a landscape analysis and updating the Decade of Vaccine Economics Antibiotic Courses Averted by Vaccine Programs (DoVE ACAVP), which estimates the number of antibiotic courses averted by vaccine programs in 73 Gavi-supported LMICs, this report aims to understand the role vaccines can play in reducing the global problem of AMR.

Recommendations

- Because the three elements explored here - high AMR burden, weak immunization/health systems, and high potential for vaccine programs to reduce antibiotic use – very closely overlap, an approach that better integrates AMR prevention and control activities with immunization program strengthening is likely to be strategically important in reducing AMR in high-burden LMIC settings in Asia and Africa; this integration should be prioritized by each of the two key groups of stakeholders (those working in immunization and those working in AMR, respectively)
- The coordination/communication channels established as part of this project (between the VAC-AMR group within WHO and the Monitoring and Evaluation team at Gavi) should be continued and expanded as much as possible; additional coordination among other organizations – perhaps through existing or new structures (e.g., a new consortium), digital coordination efforts, advocacy hubs, etc., would also be helpful in ensuring effective global strategy moving forward
- International resources must continue to support the ongoing development of a robust global AMR data collection system, including both AMR burden reporting via the GLASS system as well as antimicrobial use data, and targeting both international/multilateral data collation (e.g., by WHO) and support for local data collection
- Resources should prioritize both data collection activities as well as understanding the various stakeholders' use cases of the collected data/analyses so as to support effective communication/dissemination of this critically important information
- Additional research needed to refine these early quantifications of the impact of immunization programs on AMR, and to fully understand and quantify the complex biological processes involved in the emergence of AMR as it relates to the use of vaccines.

Acknowledgements

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Abbreviations and definitions

AMR – Antimicrobial resistance

ARI – Acute respiratory infection

LMIC – Low- and middle-income country

NIP – National immunization program

GAP – Global Action Plan

NAP – National Action Plan

EPI – Expanded Programme on Immunization

DoVE ACAVP - Decade of Vaccine Economics Antibiotic Courses Averted by Vaccine Programs

Hib - *Haemophilus influenzae* type B

MenA – Meningococcal type A

PCV – Pneumococcal conjugate vaccine

Introduction

Antimicrobial resistance (AMR) has emerged as a top public health priority. AMR refers to the process by which antimicrobial substances such as antibiotics and antifungals lose effectiveness, because the microbes they target evolve mechanisms to resist/survive exposure. By 2050, it is estimated that uncontrolled AMR could kill over ten million people and cost the global economy over $450 billion annually.(1)

AMR emerged almost simultaneously with the development of the world's first antibiotics in the 1930s; as early as 1940, even before penicillin's widespread use as a therapeutic drug for bacterial infections, researchers had isolated penicillinase produced by bacteria exposed to it in lab settings.(2) Nearly a century later, AMR threatens the massive improvements in population health that have been achieved through widespread use of therapeutic antimicrobials. To effectively fight back against this threat, strategic analysis of the current landscape and a detailed understanding of the potential benefits of AMR interventions are required.

Background

In recent years, global health experts have established frameworks for addressing the problem of AMR, prioritizing the dual goals of reducing demand for antibiotics (and thereby reducing their overuse) while simultaneously increasing the supply of novel antimicrobial products. Within the broad goal of reducing the demand for antibiotics, at least seven strategies have been identified, including promoting the development and use of vaccines as disease-prevention tools.(3)

However, very little evidence exists to help decision-makers understand the role that vaccines can play in reducing the global problem of AMR, particularly in resource-constrained settings such as the low- and middle-income countries (LMICs) served by organizations like Gavi, the Vaccine Alliance, which provides financing, capacity building and technical assistance support for national immunization programs (NIPs).(4)

Since the acceptance of a World Health Assembly resolution on AMR in 2015, which urged UN Member States to develop and implement country-level plans modelled on a Global Action Plan (GAP), many member countries have developed individualized National Action Plans (NAPs) to tackle AMR.(5) WHO provides resources for the development of such NAPs, including guidance on GAP-derived Strategic Objectives, but does not offer clear program priorities, such as strengthening the WHO-coordinated Expanded Program for Immunization (EPI) or member country NIPs as part of the solution to AMR (6); these program priorities and their resourcing and implementation are left to country governments to sort out.

In order to better inform global and local decision-making, including the prioritization of programs and their resourcing and implementation, more evidence must be generated about the role vaccines can play in reducing the global problem of AMR.

Aims and Objectives

The report aims to understand the role vaccines can play in reducing the global problem of AMR by answering two overarching research questions, each with important policy implications:

1. Where is there potential for NIP strengthening to reduce AMR?
2. How much (i.e. by what magnitude) could immunization program strengthening activities reduce AMR?

Objective 1: Where is there potential for NIP strengthening to reduce AMR?

To understand where there is the most potential for NIP strengthening to reduce AMR and to inform key decision/policy makers, this analysis asks a series of distinct sub-questions:

A. Which countries have the most problematic AMR, e.g. highest burden?
B. Which countries have indications that vaccine programs have room for improvement, e.g. low coverage, poor financing, etc.?
C. Where do the two overlap (indicating a significant potential role for immunization program strengthening as part of AMR reduction strategies)?

The answers to the above questions are intended to reveal key insights about the regions and countries that could be opportune places for AMR reduction strategies to include significant NIP strengthening. This information can help guide decision-makers at the global (e.g. WHO and other multilateral institutions, global donors, international NGOs, etc.) and local (e.g. national and local governments) levels; here I have explored the policy implications of the analysis, with the goal of identifying actionable insights for key actors involved in AMR control activities, as well as those involved in planning and resourcing these activities. This exercise is also useful to inform further refinement of the Decade of Vaccine Economics Antibiotic Courses Averted by Vaccine Programs (DoVE ACAVP) model (see Objective 2).

Objective 2: How much (i.e. by what magnitude) could immunization program strengthening activities reduce AMR?

To understand how much (i.e. by what magnitude) immunization program strengthening activities can contribute to reductions in AMR, this analysis updates and expands the DoVE ACAVP model, an existing model that estimates the antibiotic courses averted by use of vaccines in Gavi countries. Specifically, I have updated data sources from 2015 to the latest available versions (requiring a significant restructuring of model inputs due to changes in WHO guidance for pneumonia treatment), and added the potential impact of use of rotavirus vaccines to the list of vaccines already included in the model (*Haemophilus influenzae* type B vaccine, Pneumococcal conjugate vaccine, Meningococcal vaccine, and measles-containing vaccines used in Gavi countries). Understanding the quantitative aspects of immunization's potential role in AMR control is critical to evaluating it against other potential strategies, and ultimately to informing effective approaches overall.

Methods

Objective 1: Where is there potential for NIP strengthening to reduce AMR?

To begin to understand where NIP strengthening efforts could significantly contribute to AMR solutions, I conducted a semi-qualitative landscape analysis of self-reported data on progress towards implementation of national action plans, global AMR burden data reported through WHO's Global Antimicrobial Resistance Surveillance System (GLASS), and data showing the strength of vaccine programs such as estimated global coverage/access and administrative data about immunization program financing.

Landscape analyses are widely used in organizational strategy development processes as a way to understand the wider landscape that a business or nonprofit operates in, and to devise strategic objectives and plans that take this economic/political landscape into consideration.(7) A key feature of these analyses is the incorporation of geographic data that allow organizations to understand where to focus limited resources for maximum effectiveness and efficiency. In recent years, landscape analyses have been applied in public health settings by multilateral institutions such as WHO and Gavi and have proved to be valuable decision support tools. For example, an analysis of the location and types of existing evidence about pneumococcal conjugate vaccine (PCV), along with PCV use and coverage, was important to the strategic planning of global funding for PCV impact research, particularly post-licensure ecological studies in low- and middle-income settings served by Gavi.(8)

The key objective of this landscape analysis was to determine the potential scope of the opportunity to leverage immunization programs to reduce AMR as described in the Aims and Objectives section above. To reach these Aims/Objectives, I collated information about AMR burden, immunization coverage and access, and immunization program financing and examined these data by geography, mapping according to WHO regional groupings. I conducted this analysis in Microsoft Excel using AMR burden data from GLASS, WUENIC immunization coverage estimates, estimates of population access to vaccines available on VIEW-hub.org, and Vaccine program financing information provided as part of the UNICEF/WHO Joint Reporting process, as detailed in Appendix A.

Objective 2: How much (i.e. by what magnitude) could immunization program strengthening activities reduce AMR?

To begin to estimate the potential benefits to AMR reduction that immunization program strengthening activities might have, I have made additions/refinements to a 2016 estimation of antibiotic courses and associated costs averted by vaccine programs in the 73 Gavi countries.

The Decade of Vaccine Economics Antibiotic Courses Averted by Vaccine Programs (DoVE ACAVP) model was preliminarily developed in 2016 for internal use by Gavi; it is an Excel model that estimates the amount and value of antimicrobial use averted

by vaccines by multiplying the cases of pneumonia, measles, and meningitis averted by vaccines used in Gavi countries, by the WHO recommended antibiotic treatment guidelines for those conditions. That is, for each vaccine-preventable disease, the model calculates:

$$\begin{aligned} &antibiotic\ courses\ averted \\ &\quad = cases\ averted\ by\ vaccine\ use \times proportion\ of\ cases\ that\ would\ have\ sought\ care \\ &\quad \times proportion\ of\ care\ seeking\ prevented\ cases\ that\ would\ have\ recieved\ antibiotics \end{aligned}$$

Using the number of courses averted and the cost per course (using median supplier costs from the 2015 International Drug Price Indicator Guide), the model also calculates:

$$antibiotic\ costs\ averted = courses\ averted \times cost\ per\ course$$

The DoVE ACAVP model uses estimates of cases of disease averted by use of vaccines modelled by Imperial College London researchers, as part of the work of the Gavi Vaccine Impact Modelling Consortium (VIMC). VIMC estimates of cases averted by vaccine use in Gavi countries are not publicly available, but are available for my use as part of a MOU between JHU and Imperial College London. Estimates of cases averted by Gavi-supported vaccine programs leverage Gavi Strategic Demand Forecast (SDF) calculations and assume immunization coverage rates targeted by Gavi are achieved for 2021-2030. The most recent SDF estimates cover the 73 Gavi countries (Appendix B) and include both routine (all Gavi-supported vaccines) and supplemental (Measles and meningococcal vaccines only) delivery strategies as shown in Appendix C. All model parameters except VIMC case estimates are publicly available, or where unavailable, are assumptions made with expert input (see Appendix F).

To calculate the proportion of cases that seek care for vaccine-preventable diseases, I used national Demographic and Health Survey data on care-seeking behavior for the three conditions corresponding to the syndromic case definitions included in the DoVE ACAVP model: the proportion of children with a fever who sought care, the proportion of children with diarrhea who sought care, and the proportion of children with ARI symptoms who sought care (Appendix D). Survey data were available for sixty-six of the seventy-three Gavi-supported countries, with some countries reporting partial care-seeking information. For missing care-seeking rates, the average care seeking rate (per syndrome) across all available Gavi countries was used.

In this analysis I have updated existing model inputs and added new parameters and parameter refinements as detailed in Appendix E. I performed a scoping (non-systematic) review of both peer-reviewed and gray literature, searching for information that could help refine existing but weak model parameters (hospitalization rates for pneumonia, measles and meningitis), as well as new parameters (the proportion of diarrhea cases prevented by RVV that would result in reduced antibiotic prescribing, along with the specific antibiotics and dosage information). The final sources used for this analysis are shown in Appendix F.

The original DoVE ACAVP model accounted for the use of three antibiotics used to treat vaccine-preventable diseases: ampicillin, gentamicin and amoxicillin. My

literature search identified three key additional model inputs that allowed the restructuring of the calculation of the proportion of cases prevented by vaccines that would have received antibiotic treatment: the rates of first line antibiotic failure for severe and very severe pneumonia, the rates of measles complications that require antibiotic treatment, and the proportion of rotavirus diarrhea cases that receive antibiotic treatment. The rates of first line antibiotic treatment failure allowed the addition of two previously ignored antibiotics used as second-line treatment for pneumonia: cloxacillin and ceftriaxone. The rates of measles complications allowed the addition of three previously ignored antibiotics used to treat these complications: tetracycline, benzylpenicillin and metronidazole. The proportion of rotavirus diarrhea cases receiving antibiotic treatment allowed for syndromic diarrhea cases prevented by rotavirus vaccine to be added to the model, as well as one associated antibiotic: ciprofloxacin.

All DoVE ACAVP model treatment parameters are derived strictly from WHO's Integrated Management of Childhood Illness (IMCI) and Pocket Book of Hospital Care for Children (2nd Edition), and do not include any additional treatment guidance/assumptions. These WHO guidelines were developed specifically for case management of common childhood illnesses in LMIC settings where resource constraints frequently require the symptomatic treatment of illnesses without robust diagnostic testing. Thus, the DoVE ACAVP model is built on syndromic (not etiologic) case definitions for the syndromes prevented by Gavi-supported vaccines against *Haemophilus influenzae* type b (Hib), measles, meningococcus serotype A (menA), pneumococcus (PCV) and rotavirus. These syndromes are: pneumonia, meningitis, diarrhea and measles (including the following complications, which are included in the model: pneumonia, diarrhea and otitis media). Other syndromes, including non-pneumonia non-meningitis (NPNM) conditions such as sepsis, are not included (except otitis media as a complication of measles as described above and shown in Appendix E).

Since the original creation of the DoVE ACAVP model, the WHO guidelines for pneumonia case management have significantly changed, requiring an overhaul of the calculation of the proportion of care-seeking pneumonia cases that receive antibiotic treatment (Appendix E). This new structure accounts for revisions to care guidance since 2015 as well as the additional antibiotics described above to account for the proportion of pneumonia, measles and diarrhea care-seeking cases that result in additional antibiotic use, such as failed first-line treatment and secondary bacterial infections after measles infection, as described above. No meningitis complications are accounted for, because the range of sequelae and frequency of their occurrence are not quantified in the literature in such a way as to allow calculation of the proportion of meningitis cases receiving additional antibiotics after initial ceftriaxone treatment (the proportion receiving initial ceftriaxone is assumed to be 100% of care-seeking cases as shown in Appendix E).

The addition of diarrhea to the DoVE ACAVP model was undertaken in the same way as existing syndromes: the total diarrhea cases averted by Gavi vaccine programs (as modeled in VIMC estimates) were multiplied by the proportion of these cases that seek care, and by the proportion of those care-seeking cases that would receive antibiotics. The proportion of care-seeking cases receiving antibiotics was derived from GEMS data, which included the total number of enrolled diarrhea

cases, the number of these cases that were PCR positive for rotavirus, and the proportion of these positive cases that received antibiotics. Although IMCI/Pocket Book guidelines recommend only one antibiotic (ciprofloxacin), and only for the subset of syndromic diarrhea that is bloody (dysentery), the GEMS data revealed a wide variety of additional antibiotics were prescribed for diarrhea cases. To understand how adherence to prescribing guidelines might affect model outputs, I used this antibiotic-specific data to perform an analysis of the difference in antibiotic courses averted assuming WHO prescribing guidelines are followed, versus the actual reported antibiotic prescribing rates per the GEMS data.

Results

Objective 1: Where is there potential for NIP strengthening to reduce AMR?

To answer the question of where NIP strengthening could significantly help reduce AMR, I collated and analyzed data to answer the following questions:

A. Which countries have the most problematic AMR, e.g. highest burden?
B. Which countries have indications that vaccine programs have room for improvement, e.g. low coverage, poor financing, etc.?
C. Where do the two overlap (indicating a significant potential role for immunization program strengthening as part of AMR reduction strategies)?

Overall, there are 52 countries reporting data to WHO's Global Antimicrobial Resistance Surveillance System (GLASS) as of 2017 (the most recent year with data available). This represents less than 30% of the 194 WHO member states.

Among the countries that do report data to GLASS, there is a wide range in the volume of isolates tested/reported and the proportion of tested isolates that are resistant. For this analysis, because Objective 2 focuses on vaccine programs in Gavi countries and therefore includes estimates of antibiotic courses averted by Gavi-supported PCV and rotavirus vaccines (plus measles and meningitis), I focus on the four pathogens and two specimens and that best align with these vaccines: pneumococcus, *E. coli*, *Salmonella* and *Shigella* species found in blood and stool samples.

Among the pneumococcal isolates reported to GLASS, the antibiotics with the highest resistance frequency are doripenem, carbapenems, levofloxacin and azitrhmycin, in descending order of frequency (Table 2). The antibiotics with the lowest resistance frequency are ciprofloxacin, fluoroquinolones, third generation cephalosporins and ceftriaxone, in ascending order of frequency. The proportion of isolates with resistance varies widely among antibiotics, from 99% (doripenem) to 15% (ciprofloxacin). There is some variability between WHO regions in the average proportion of isolates with resistance, varying from 20% (WPRO) to 50% (SEARO).

Among the enteric isolates reported to GLASS, the antibiotics with the highest resistance frequency are cefotaxime, oxacillin, and cotrimoxazole, in descending order of frequency. (Table 3). The antibiotics with the lowest resistance frequency are penicillins excluding penicillin G, sulfonamides/trimethoprim, and penicillin G, in

ascending order of frequency. The proportion of isolates with resistance varies widely among antibiotics, from 58% (cefotaxime) to 6% (penicillins excluding penicillin G). There is variability between WHO regions in the average proportion of isolates with resistance, varying from 32% (EMRO) to 54% (AFRO).

Table 2: Percent of GLASS pneumococcal isolates that are non-susceptible to common antibiotics, by WHO region

	Azithromycin	*Carbapenems*	*Cefotaxime*	*Ceftazidime*	*Ceftriaxone*	*Ciprofloxacin*	*Doripenem*	*Ertapenem*	*Fluoroquinolones*	*Imipenem*	*Levofloxacin*	*Meropenem*	*3rd gen cephalosporins*	*Total*
AFRO			43%	41%	4%	25%		43%	81%	37%	92%	26%	73%	**40%**
Madagascar				0%	0%	0%		0%		0%				**0%**
Malawi				0%	0%	0%								**0%**
South Africa				36%	8%	7%		39%		26%		26%		**22%**
Zambia			86%	87%	0%	81%		91%	81%	86%	92%		73%	**84%**
AMRO	69%		70%	59%	53%	3%		79%	4%	59%	84%	30%	51%	**46%**
Argentina	69%		70%	59%	79%	4%		79%	4%	59%	84%	59%	51%	**54%**
Canada				0%	0%	0%						0%		**0%**
EMRO	73%		59%	37%	20%	7%	99%	54%	7%	45%	70%	63%	6%	**31%**
Bahrain			99%		0%	0%				99%		98%		**59%**
Lebanon					0%	0%			3%	0%	0%	0%	0%	**1%**
Oman			82%	57%	15%	1%		94%	1%	73%	0%	73%	15%	**39%**
Pakistan					0%	0%			0%				0%	**0%**
Saudi Arabia	56%		41%	20%	30%	3%	99%	58%	3%	1%	52%	4%	1%	**27%**
Tunisia			7%	11%	0%	30%		11%	30%	7%	0%	96%	7%	**25%**
United Arab Emirates	91%		59%	48%	53%	17%		55%	16%	45%	88%	43%	12%	**46%**
EURO	97%	88%	35%	35%	63%	29%		57%	28%	59%	94%	54%	24%	**43%**
Finland		88%		0%	32%	1%		0%	1%			88%	32%	**40%**
Malta				0%	0%	0%		0%	0%	0%		0%	0%	**0%**
Norway				0%	0%	0%		0%	0%			0%	0%	**0%**
Poland			46%	85%	64%	95%		85%	95%	92%	100%	92%	23%	**78%**
Switzerland	97%		98%	81%	78%	67%		86%	65%	85%	91%	89%	69%	**81%**
SEARO	24%		100%	85%	41%	43%		0%	43%	65%			38%	**50%**
Bangladesh	24%			85%	19%	14%		0%	14%	65%			14%	**32%**
Thailand			100%	0%	85%	100%		0%	100%	0%			85%	**94%**
WPRO	41%		27%	21%	6%	3%		95%	5%	48%	63%	47%	5%	**20%**

Japan			0%	0%		0%				0%		0%		**0%**
Lao PDR					0%	0%			0%				0%	**0%**
Malaysia			86%	86%	1%	8%		95%	8%	94%	0%	94%	1%	**41%**
Philippines	82%		24%	0%	17%	8%		0%	8%	98%	63%	0%	15%	**32%**
Republic of Korea			0%	0%		0%				0%				**0%**
GLOBAL	**60%**	**88%**	**45%**	**40%**	**26%**	**15%**	**99%**	**58%**	**20%**	**49%**	**80%**	**51%**	**21%**	**35%**

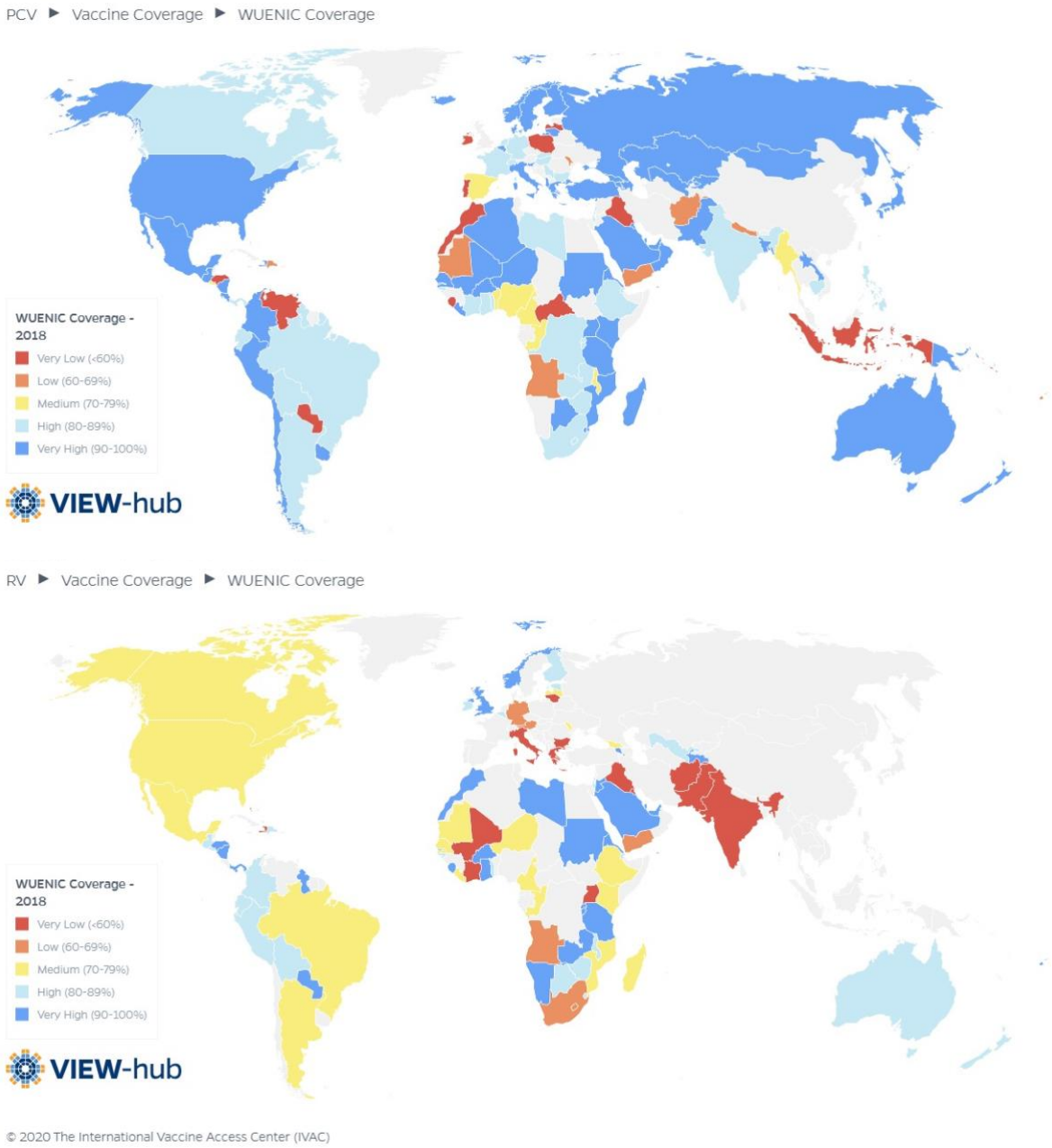
Table 3: Percent of GLASS E. coli, Salmonella sp. and Shigella sp. isolates that are non-susceptible to common antibiotics, by WHO region

Region	*Cefotaxime*	*Ceftriaxone*	*Co-trimoxazole*	*Oxacillin*	*Penicillin G*	*Penicillins*	*Sulfonamides and trimethoprim*	*3rd gen cephalosporins*	*Total*
AFRO		92%	26%		44%			70%	**54%**
Malawi			0%		0%				
Nigeria		100%	0%		100%			100%	**100%**
South Africa		0%	28%		28%			28%	**28%**
Uganda		83%	50%		50%			83%	**67%**
AMRO	70%	13%	22%	43%				60%	**35%**
Argentina	70%	13%	22%	43%				60%	**35%**
EMRO	46%	22%	34%	84%	30%			16%	**32%**
Cyprus						0%			**0%**
Lebanon								20%	**20%**
Oman	82%	3%	39%		55%			3%	**36%**
Pakistan		33%	6%		41%			32%	**28%**
Saudi Arabia	28%	20%	40%	70%	13%			13%	**30%**
Tunisia	0%							0%	**0%**
United Arab Emirates	75%	31%	49%	98%	43%			30%	**54%**
EURO	77%	16%	79%	75%	24%	6%	47%	16%	**33%**
Austria						0%			**0%**
Bosnia and Herzegovina	26%	21%	100%	100%	0%	0%		21%	**38%**
Croatia						0%			**0%**
Czech Republic						0%			**0%**
Finland			47%		18%	18%	47%		**32%**
France						0%			**0%**
Georgia	100%	0%	100%	100%	100%	100%		0%	**71%**
Germany						0%			**0%**

Ireland						0%			**0%**
Latvia	90%	5%	10%		10%			5%	**24%**
Lithuania						0%			**0%**
Luxembourg						0%			**0%**
Macedonia	50%	50%	100%	0%	50%	0%		50%	**43%**
Malta		0%			0%			0%	**0%**
Netherlands						0%			**0%**
Norway						0%			**0%**
Poland						0%			**0%**
Russian Federation	100%	0%	100%	100%	0%	0%		0%	**43%**
Sweden			0%			0%			**0%**
Switzerland	92%	34%	100%	74%	11%	4%		34%	**50%**
United Kingdom						0%			**0%**
SEARO	46%	97%	19%	11%	5%			43%	**37%**
Thailand	46%	97%	19%	11%	5%			43%	**37%**
WPRO	53%	44%	13%	39%	12%		0%	59%	**33%**
Japan	23%	14%		100%	0%				**34%**
Lao PDR			13%	13%	13%				**13%**
Malaysia	90%	63%	15%	45%	32%			63%	**51%**
Philippines	100%	100%	11%		16%			56%	**57%**
Republic of Korea	0%	0%		0%	0%		0%		**0%**
GLOBAL	**61%**	**35%**	**45%**	**58%**	**24%**	**6%**	**23%**	**32%**	**35%**

Vaccine coverage rates are indicators of NIP performance and strength, highlighting where countries and subnational regions need to improve delivery and uptake of vaccines to ensure populations have access to them. WUENIC estimates of PCV and rotavirus vaccine coverage show that while Gavi programs have made enormous progress towards increasing vaccine access in LMIC settings, there are still pockets of low coverage in many countries (Figure 1). These coverage gaps tend towards low-income countries in Asia and Africa, as well as middle-income countries around the world, where governments do not have access to Gavi financial or logistical support to improve vaccine programs.

Figure 1: WUENIUC estimates of PCV and rotavirus vaccine coverage

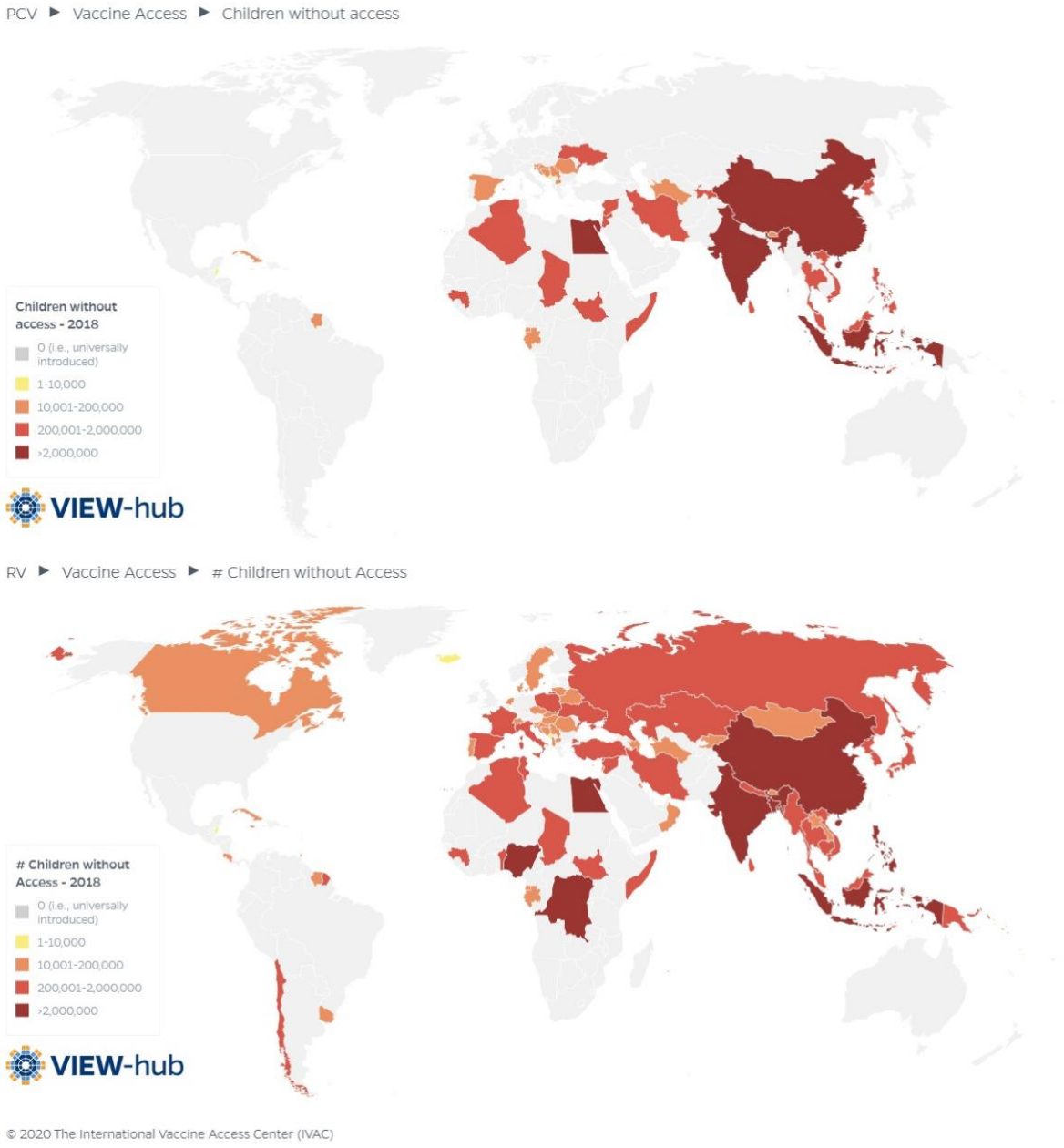


Another key consideration for vaccine program performance globally is the number of children with access to vaccines. While coverage rates are important to make

comparisons between countries on performance, absolute numbers showing where the highest number of children are missing out on vaccines is also important for global decision-makers to understand and prioritize strategies that will impact the most children.

The vast majority of children without access to PCV and rotavirus vaccines are children living in Gavi-supported LMIC countries in Africa and Asia (Figure 2) – regions and income groups that align with the settings with the highest resistance rates among isolates reported to GLASS.

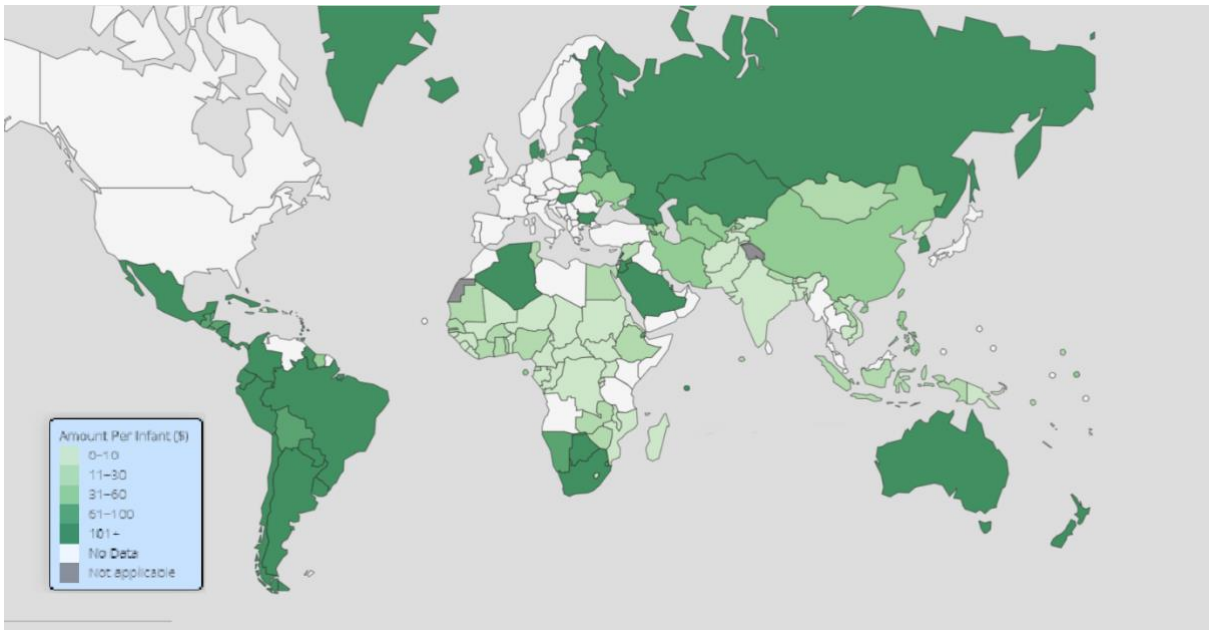
Figure 2: Number of children without access to PCV and rotavirus vaccine



Finally, a key indicator of vaccine program strength is the financial resources allocated to NIPs on a per child basis. Globally, this spending ranges from under $10

per child in most of sub-saharan Africa to over $101 in middle- and high-income countries in Europe and the Americas (Figure 3).

Figure 3: Government expenditures on NIPs in 2017, per child



Objective 2: How much (i.e. by what magnitude) could immunization program strengthening activities reduce AMR?

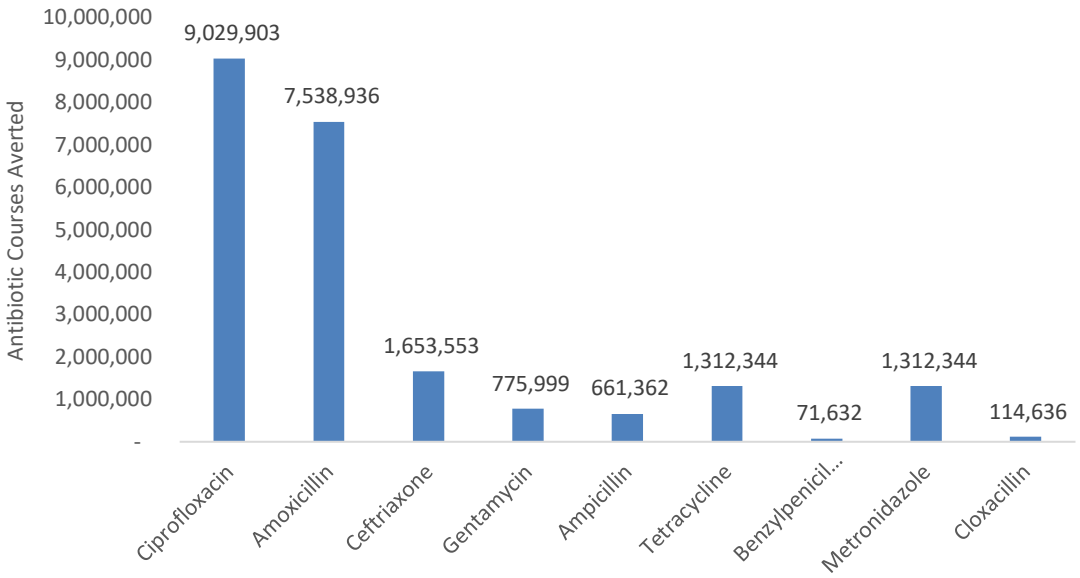
After assessing the current landscape of immunization programs globally, I proceeded to update and refine the DoVE ACAVP model as described above. In total, the updated and improved DOVE ACAVP model now suggests that over 40 million antibiotic courses and over $30 million in total antibiotic costs will be averted by Gavi-supported use of vaccines by 2030 (Table 4).

Table 4: Antibiotic courses and costs averted by Gavi-supported Hib, Pneumococcal, Rotavirus, Measles and MenA vaccine programs, 2001-2030

	ANTIBIOTIC COURSES AVERTED				
	2001-2010	**2011-2015**	**2016-2020**	**2021-2030**	**Total**
PNEUMONIA	522,237	1,470,250	2,829,545	5,361,445	10,183,477
MENINGITIS	305,572	1,846,684	1,382,317	1,591,826	5,126,399
MEASLES	36,199	1,382,352	4,853,067	6,720,841	12,992,458
ROTAVIRUS	20,391	543,280	2,620,194	8,796,598	11,980,463
TOTAL	**884,399**	**5,242,566**	**11,685,122**	**22,470,710**	**40,282,797**
	ANTIBIOTIC COSTS AVERTED (2015 USD)				
	2001-2010	**2011-2015**	**2016-2020**	**2021-2030**	**Total**
PNEUMONIA	$ 355,505	$ 1,000,852	$ 1,926,173	$ 3,649,729	$ 6,932,260
MENINGITIS	$ 1,105,330	$ 6,679,918	$ 5,000,187	$ 5,758,033	$ 18,543,468
MEASLES	$ 19,298	$ 472,782	$ 1,519,510	$ 2,095,446	$ 4,107,036
ROTAVIRUS	$ 1,870	$ 54,936	$ 290,945	$ 1,007,907	$ 1,355,658
TOTAL	**$ 1,482,004**	**$ 8,208,489**	**$ 8,736,815**	**$ 12,511,114**	**$ 30,938,422**

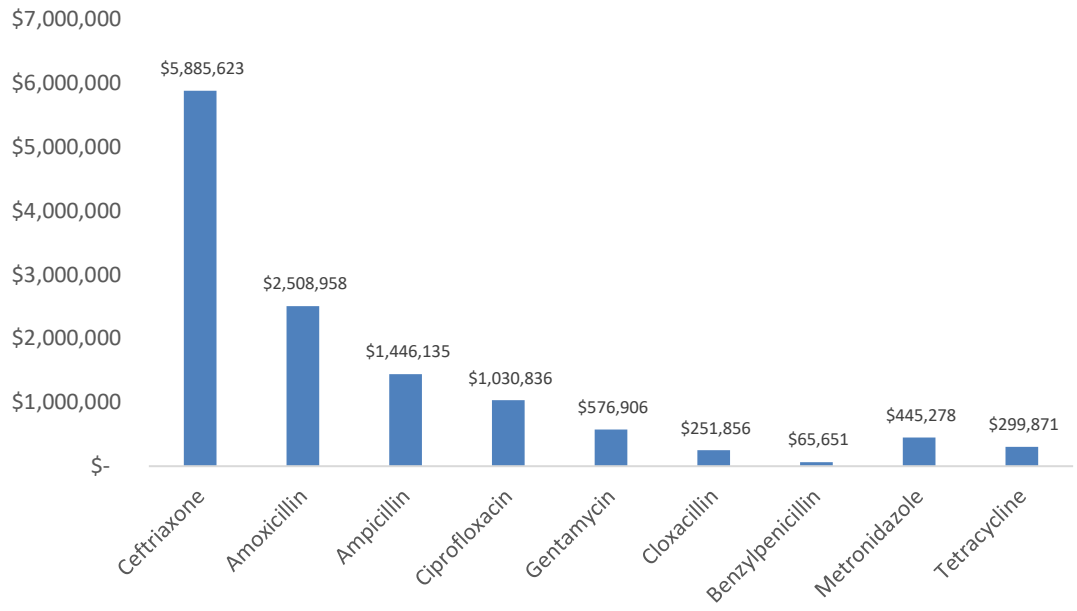
At over 9 million courses averted from 2021-2030 (Figure 4), ciprofloxacin represents the antibiotic that will most frequently be averted by vaccine programs in Gavi countries. It is the first-line antibiotic prescribed for diarrhea (and the only one specifically recommended in WHO IMCI/Pocket Book guidelines), which is the syndrome that will be most prevented by Gavi-supported vaccines over the next decade, with an estimated 155 million cases averted. Diarrhea is also a measles-related syndrome (as an estimated 8% of measles cases will be complicated by diarrhea), with Gavi-supported vaccines averting another approximately 3.2 million cases (9). The antibiotic with the second most averted courses in the next decade will be amoxicillin, with approximately 7.5 million courses averted by Gavi-supported vaccine programs.

Figure 4: Antibiotic use averted by Gavi-supported vaccine programs, 2021-2030



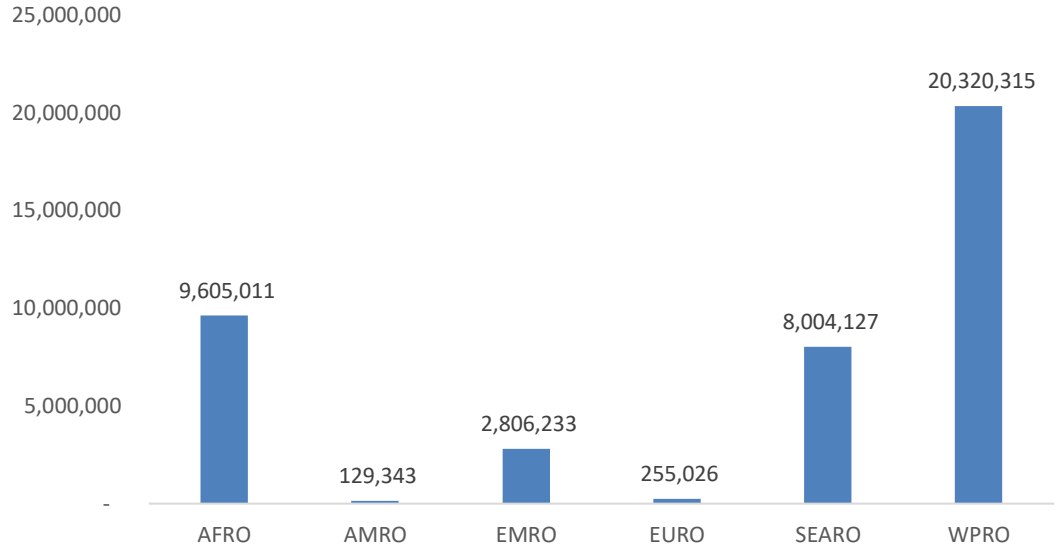
Vaccine programs in Gavi-supported countries will avert nearly $30 million in antibiotic product costs by 2030, with most (over $12 million) of these savings occurring in the next decade (2021-2030). The antibiotic with the highest cost savings between 2021 and 2030 is ceftriaxone which is used to treat meningitis, followed by amoxicillin, ampicillin and ciprofloxacin.

Figure 5: Antibiotic costs averted by Gavi-supported vaccine programs, 2021-2030



In keeping with the geographic focus of the landscape analysis performed to achieve Objective 1, I examined the antibiotic use averted by Gavi programs by WHO region. This stratification revealed that the regions with the most courses averted by Gavi-supported vaccine programs are in Africa and Asia (Figure 6), with WPRO, AFRO and SEARO with approximately 20 million, 10 million, and 8 million courses averted, respectively. These regions overlap with the highest resistance rates among isolates reported to GLASS (Tables 2 and 3), as well as with the poorest-performing/resourced NIPs (Figures 1-3).

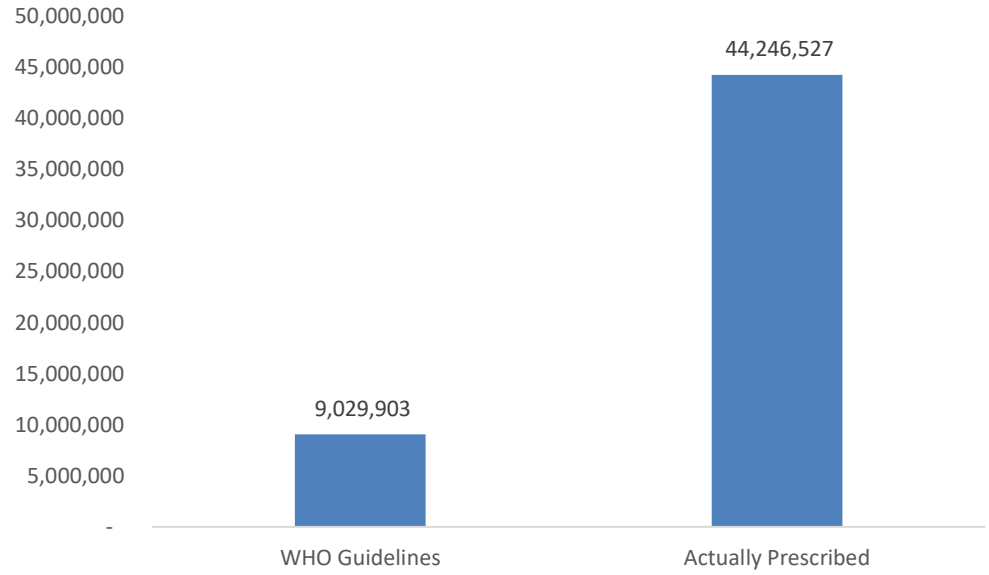
Figure 6: Antibiotic use averted by Gavi-supported vaccine programs, by region, 2021-2030



The DOVE ACAVP model assumes that care-seeking cases prevented by Gavi vaccine programs would have been treated according to the guidelines outlined in the 2014 WHO IMCI/Pocket Book guidelines, as described in the Methods section above. However, there is frequently at least some divergence between treatment

guidelines and actual treatment provided at health facilities, especially those in LMIC settings where healthcare supply chains are weaker and stockouts of key commodities such as antibiotics are common. Even in high-income settings, antibiotic product choice varies widely, and overuse is widespread.(10) This is evident in the diarrhea treatment data used to populate the DOVE ACAVP's proportion of cases receiving antibiotics parameter: although 10% of care-seeking cases enrolled in the multicenter study received the only antibiotic recommended in the WHO guidelines (ciprofloxacin), the percent of enrolled diarrhea cases receiving any antibiotic was nearly five times as high – 49%. Using this parameter in the DOVE ACAVP model, the estimated ciprofloxacin courses averted by Gavi vaccine programs between 2021 and 2030 rises to over 44 million (Figure 7).

Figure 7: Antibiotic courses averted by rotavirus vaccination, by adherence to treatment guidelines



Discussion

Objective 1: Where is there potential for NIP strengthening to reduce AMR?

Although AMR is problematic all over the world, many LMIC settings are particularly vulnerable to both increased likelihood of the development of AMR pathogens (due to less stringent antibiotic prescribing requirements/practices, less water and sanitation infrastructure and infection control capacity, etc.) and fewer resources to treat AMR infections when they happen. This is borne out in the limited data showing slightly increased rates of AMR in regions with more LMICs (Africa and Asia) as compared to higher-income regions. While this is an informative preliminary analysis of this available data, it is critical that continued international resources are specifically directed to continue to support the development of a robust global AMR data collection system. With limited countries reporting, only one year of data available (much of which is incomplete), and continued refinement of the reporting process/technology use itself (making it difficult to access and triangulate where the

most updated AMR surveillance data are available), there is certainly room for improvement in the amount and quality of global AMR burden data.

The continued limited availability of robust global AMR data is an important takeaway with clear policy implications. While the need for this data has been apparent for decades and began to be addressed in the aftermath of the release of the O'Neil report, slow progress has been made towards a truly effective system for monitoring AMR globally.(3) There is still an urgent need for better data collection to inform a more robust understanding of the burden of AMR, particularly on a national and subnational basis.(11)

International donors and multilateral institutions should prioritize providing resources and support for these programs as well as supporting the effective communication and use of the data to/by key stakeholders. Increased communication and collaboration between organizations/groups collecting and using the data can support the effective refinement of the GLASS system. It's critical for those collecting data (WHO) to not only improve the quality by supporting individual countries reporting it, but to also understand how key stakeholders such as Gavi could use it.

Taken together with data on NIP strength and resourcing, the early GLASS data make it clear that there are distinct regions where the need for both AMR control activities and NIP strengthening overlap. These settings – mostly LMICs in Africa and Asia – also happen to be the targets for existing vertical and horizontal health programming. It would therefore be beneficial for organizations and groups currently working in siloed spaces (namely those working in immunization, separately from those working on AMR issues) would align their activities and strategies. There are likely to be meaningful and productive synergies between both workstreams, and efficiencies to be gained in collaboration.

Objective 2: How much (i.e. by what magnitude) could immunization program strengthening activities reduce AMR?

While the results of the Objective 1 analysis reveal a geographical overlap in AMR burden and weak immunization systems in WHO regions in Asia and Africa, particularly in the LMIC settings served by Gavi, the DoVE ACAVP model updates confirm the logical third dimension of overlap in these regions: the potential for NIP strengthening activities to significantly reduce antibiotic use. Above all else, the triangulation of these three elements – high AMR burden, weak immunization/health systems, and high potential for vaccine programs to reduce antibiotic use – suggest that an approach that better integrates AMR prevention and control activities with immunization program strengthening is likely to be strategically important in reducing AMR in LMIC settings in Asia and Africa.

This is among the first analyses attempting to quantify the potential impact of vaccine use on AMR and/or antibiotic use. In connection to ongoing activities of WHO's Value Attribution Framework For Vaccines Against Antimicrobial Resistance Working Group (VAC-AMR), alternate, recently published estimates of the impact of pneumococcal and rotavirus vaccines on episodes of antibiotic disease approached the question differently, using DHS data from select LMICs to perform a case-control analysis and evaluate the odds of previous vaccination among children under five

years of age with diarrhea or acute respiratory infection (ARI) treated with antibiotics, as well as the incidence of ARI and diarrhea-related antibiotic use.(12) Using these data, the researchers calculated vaccine effectiveness against antibiotic-treated infection, and modeled the vaccine-type attributable fractions of these cases. By multiplying the incidence rate estimates by pathogen-specific attributable fractions, the group arrived at the number of antibiotic-treated ARI and diarrhea cases prevented by PCV and rotavirus vaccines. The results suggest that annually PCVs prevent approximately 57 million antibiotic-treated ARI episodes, while rotavirus vaccines prevent approximately 48 million antibiotic-treated diarrhea episodes. While a simple extrapolation of these figures over the next decade would result in an estimate of approximately 750 billion antibiotic treatment episodes averted by just these two vaccines (which is substantially higher than the estimates presented here), this simple linear extrapolation is likely inappropriate. More importantly, methodological differences such as the countries included in the analysis, timeline studied, vaccine products included, and syndromic versus etiologic approaches prohibit robust comparison of the two figures. These differences in approach reveal a key limitation of the DoVE ACAVP model and this related analysis: it is based on Gavi-specific data and therefore largely limited to the 73 Gavi countries.

Despite this, both estimates of at least millions – if not billions – of antibiotic doses averted by immunization programs by 2030 clearly show vaccines can play a meaningful role in curbing AMR, and further leveraging of this link to best effect will require a cooperative effort among the key players in these two global health issues. One key mechanism for collaboration could be an intentional/structured linkage between Gavi teams, especially those working on Gavi-supported health system strengthening activities and larger Gavi organizational strategic planning, and the international institutions working on AMR. As part of my work on this project, I have connected individuals and teams at the VAC-AMR group within WHO and the Monitoring and Evaluation team at Gavi; it is my strong suggestion that these linkages continue to be cultivated and that the two groups remain in close contact as additional evidence is generated that could inform effective strategy within both organizations. Additional coordination among other organizations – perhaps through existing or new structures such as consortia, digital coordination efforts, advocacy hubs, etc., would also be helpful in ensuring effective global strategy.

In my antibiotic-specific analysis, the two antibiotics expected to be most frequently averted by Gavi-supported vaccine programs are ciprofloxacin (approximately 9 million courses averted) and amoxicillin (approximately 7.5 million courses averted). As some of the most prescribed antibiotics on earth, both are important contributors to antibiotic resistant disease, and are likely to contribute to bacterial ecosystems and resistomes in such a way as to encourage clinically problematic resistance. Thus the contribution of Gavi-supported vaccine programs to the prevention AMR is likely to be particularly impactful globally, since these programs result in the reduced prescription of some of the antibiotics most likely to be implicated in the emergence of AMR worldwide.

For both amoxicillin – which is a key first-line antibiotic for syndromic pneumonia cases of unknown etiology – as well as other pneumonia-related antibiotics included in the DOVE ACAVP model, preventing bacterial Hib and pneumococcal pneumonia through the use of Gavi-supported vaccines is clearly a strategic way to reduce

AMR. However, even the measles vaccine (against a viral disease) is likely to significantly reduce the use of amoxicillin and other antibiotics because measles cases are frequently complicated by secondary bacterial infections that require antibiotic treatment.

The use of these antibiotics is complicated by several factors – most of which are likely to make the DoVE ACAVP estimates of antibiotic use averted by vaccine programs significantly lower than in reality (that is, vaccine programs are likely to reduce antibiotic use and subsequent AMR by orders of magnitude greater than the magnitude estimated here).

One factor in the under-estimation provided here is the syndromic treatment approach reflected in WHO IMCU/Pocket Book guidelines and used in many of the LMIC settings that Gavi programs support. Without diagnostic tools that can identify the definitive etiologic origins of diarrhea cases in resource-constrained settings, guidelines that recommend antibiotic use based on clinical presentation are necessary but likely to result in inappropriate prescriptions for cases that are in fact caused by non-bacterial pathogens. In the example of rotavirus diarrhea, data used in the DOVE ACAVP (derived from the Global Enteric Multicenter Study (GEMS) case-control study), suggest that approximately 10% of rotavirus-positive diarrhea cases in LMIC settings receive antibiotic treatment with ciprofloxacin – even though these viral cases are unlikely to benefit from antibiotic therapy.(13) Thus, preventing rotavirus cases in the first place through the use of vaccines has the potential to greatly reduce inappropriate use of ciprofloxacin.

Indeed, analysis using the GEMS data showed that the inappropriate treatment of rotavirus diarrhea (i.e. the use of antibiotics including ciprofloxacin as well as other products not included in WHO treatment guidelines) could result in nearly five-fold rates of antibiotic use – a key indicator that this analysis is not reflective of actual antibiotic use that could be averted by vaccines. The fact that data from the GEMS study shows a difference in prescribing rates of nearly five times shows that the potential differential between guidance and reality is large. However, the GEMS data are only a small piece of the puzzle of antibiotic prescribing rates – for a true understanding of how actual prescribing differs from medical guidelines, comprehensive surveillance data on the use of these products is required. The ongoing efforts by WHO to stand up a global antimicrobial use surveillance system will help address this issue, and future use of these data should include additional analyses better quantifying the magnitude of actual courses averted by NIP programs supported by Gavi (as opposed to the magnitude of courses averted by programs assuming treatment guidance is always followed).

Use of ciprofloxacin (and likely other antibiotics) in LMIC settings is also often complicated by the problem of fraudulent or low-quality drug products, which are further likely to contribute to AMR.(14) In these settings in particular, then, there are multiple factors compounding the problem of AMR and solutions that are preventative, such as vaccines, are likely to offer the most success.

Another key consideration likely to increase the real-world impact of vaccine use on AMR (as compared to the conservative estimates presented here) is the biological ways by which bacteria actually acquire resistance. Take for example ciprofloxacin resistance, which has been increasing for at least the past decade, especially in

developing countries. As a broad-spectrum fluroquinolone, the antibiotic is frequently prescribed for a variety of infections, including urinary tract infections (UTIs) caused by species such as *E. coli*, which are often present in healthy human microbiomes without causing harm. Because these species naturally inhabit human hosts, the use of antibiotics such as ciprofloxacin to treat vaccine-preventable enteric disease such as rotavirus infection may cause the unintended consequence of increasingly resistant microbiome bacteria within individuals being treated. Because UTIs are frequently treated with the same broad spectrum antibiotics as diarrhea, the results of sustained levels of diarrhea within a population are likely increasing rates of treatment failure in opportunistic infections such as UTIs caused by pathogens like *E. coli* (15).

Ciprofloxacin resistance (as an example) is also important for pathogens that are not opportunistic – that is, that do not inhabit the human microbiome and thereby evolve resistance via syndromic treatment for infections with other pathogens, as exemplified in the above discussion of rotavirus diarrhea treatment with ciprofloxacin that likely contributes to ciprofloxacin-resistant UTIs. For bacteria that are not typically part of the human microbiome (and therefore unlikely to be present within hosts receiving antibiotic treatment for vaccine-preventable diseases), there are still potential mechanisms for the development of antibiotic resistance that could be mitigated by the use of vaccines. The genes encoding resistance to fluroquinolones are known to emerge from both selective pressure on a bacterial population (as would happen with a population's exposure to ciprofloxacin because of diarrhea treatment), as well as horizontal gene transfer via plasmids. These mobile gene elements do not require evolutionary pressure to infiltrate a bacterial population, and although they do not immediately or directly cause clinical resistance, they do substantially accelerate the acquisition of clinical resistance once present in the extrachromosomal bacterial genome (16).

More importantly, plasmid-mediated horizonal gene transfer is known to occur between different gram-negative bacterial species, making it theoretically possible that a resident, harmless microbiome bacterium such as *E. coli* could acquire resistance genes at one point in time, and then later pass them on to an infectious bacterial species that subsequently infects the same host – even if the second infection is not actually treated by antibiotics (17). This theoretical new, resistance plasmid-containing infectious species would then be more likely to become clinically resistant as it further spreads throughout a human population. Because there are limited treatment options for gram negative infections, they can become particularly difficult to treat cases of severe/invasive disease. Ciprofloxacin in particular has been recently highlighted as a potentially effective treatment for gram-negative infections such as bacteremia, but the growth of ciprofloxacin resistance in gram-negative species – which may be accelerated by both vertical and horizontal gene transfer as a result of ciprofloxacin use – may limit the effectiveness of this strategy in the long term.(18) The larger value of vaccine use to slow the horizontal transfer of antibiotic resistance genes is an important consideration that further underlines the value of rolling out newly-supported vaccines such as rotavirus vaccine in Gavi-supported countries, as exemplified by the case of ciprofloxacin – which also happens to be the product most frequently saved from use by effective Gavi-supported vaccine programs according to this analysis. While quantifying the dynamics of the vertical and horizontal antibiotic resistance gene transfer is beyond the scope of this

analysis, it is a key question that should be addressed as soon as possible, in order to better prioritize the interventions that can address the sharing of genetic information conferring resistance among bacterial populations and biomes.

This crude calculation of antibiotic costs averted by Gavi supported vaccine programs reveals a standout product with the highest costs averted: ceftriaxone, which in the DoVE ACAVP model is used to treat meningitis cases. Although the number of cases of meningitis averted by Gavi programs in the next decade is projected to be relatively low, the total antibiotic cost per case of averted meningitis was by far the highest among all the syndromes included in this model at over $3 per case (Appendix E) – much higher than the 10 cent cost per case for the lowest-cost product, ciprofloxacin. In addition to the oversimplification of extremely complex (and as yet not fully understood or quantified) biological processes conferring resistance as described above, another key limitation of the model is the inclusion of only direct product costs in estimating the costs of antibiotics averted by vaccine programs in Gavi-supported countries. While further cost data collection or analysis was beyond the current scope, this was at least a start at a micro-costing approach to quantifying the potential total costs averted by NIPs in LMICs. Additional work to fully understand these costs would be a valuable next step; ultimately the goal of such exercises should be to provide national and local decision-makers with the evidence they need to strategically decide how to allocate limited resources to different AMR control programs and strategies.

Taken together, these results suggest an important and potentially critical role for NIP strengthening activities to prevent and reduce AMR, particularly in the LMIC settings supported by Gavi and identified as countries where there is a relatively high AMR burden. While additional work is required to fully understand and strategically prioritize NIP strengthening among other AMR interventions and programs, this preliminary exercise reveals that the impact of prioritizing immunization program strengthening as a means to reduce AMR is likely to be significant.

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Appendix A: Landscape Analysis (Objective 1) research questions, analyses and sources

Research Sub-Question	Data/Analysis	Source	Rationale for Use
Which countries have the most problematic AMR situations/responses?	AMR Burden: proportion of patients with non-susceptible results, by pathogen and antibiotic	Global Antimicrobial Resistance Surveillance System (GLASS) (19)	Most comprehensive, publicly available global AMR burden data
	Self-reported AMR control progress: • Development/funding of national action plan (5 point scale) • Strength of policies for optimal antimicrobial use in human health (5 point scale) • Training and professional education on AMR in the human health sector (5 point scale)	Global Database for Antimicrobial Resistance Country Self Assessment (20)	Most comprehensive, publicly available global data on AMR reduction progress/approaches[1]
Which countries have indications that vaccine programs have room for improvement?	Coverage: PCV and Rotavirus vaccine	WUENIC (21)	Indicator of NIP strength
	Access: number of children with access to immunization	VIEW-hub (22)	Indicator of NIP strength
	Financing: proportion of total expenditure (from all sources of financing) on vaccines used in routine immunization	JRF/WHO (21)	Indicator of NIP resourcing
Where do the two questions above overlap, indicating significant potential role for immunization program strengthening as part of AMR reduction strategies?	Mapping, including stratification by WHO region, where the two questions above overlap.	n/a	Helps global decision makers prioritize areas for attention/resources that integrate NIP strengthening in AMR control plans

[1] A preliminary review of national AMR plans publicly available via the WHO AMR portal revealed that these plans have little indication of the specific role immunization programs are/will play in national AMR reduction strategies/activities. Most NAPs follow the same format as the WHO's GAP, recycling similar language and revealing little about specific implementation activities, progress towards goals, or other meaningful information. Thus this survey data was chosen as a more robust indicator of national progress towards AMR reduction.

Appendix B: The 73 Gavi Countries

COUNTRY	WHO REGION	WORLD BANK INCOME GROUP
AFGHANISTAN	EMRO	LIC
ANGOLA	AFRO	UMIC
ARMENIA	EURO	LMIC
AZERBAIJAN	EURO	UMIC
BANGLADESH	SEARO	LMIC
BENIN	AFRO	LIC
BHUTAN	SEARO	LMIC
BOLIVIA	AMRO	LMIC
BURKINA FASO	AFRO	LIC
BURUNDI	AFRO	LIC
CAMBODIA	WPRO	LIC
CAMEROON	AFRO	LMIC
CENTRAL AFRICAN REPUBLIC	AFRO	LIC
CHAD	AFRO	LIC
COMOROS	AFRO	LIC
CONGO, DEMOCRATIC REPUBLIC	AFRO	LIC
CONGO, REPUBLIC	AFRO	LMIC
COTE D IVOIRE	AFRO	LMIC
CUBA	AMRO	UMIC
DJIBOUTI	EMRO	LMIC
ERITREA	AFRO	LIC
ETHIOPIA	AFRO	LIC
GAMBIA	AFRO	LIC
GEORGIA	EURO	LMIC
GHANA	AFRO	LMIC
GUINEA	AFRO	LIC
GUINEA-BISSAU	AFRO	LIC
GUYANA	AMRO	LMIC
HAITI	AMRO	LIC
HONDURAS	AMRO	LMIC
INDIA	SEARO	LMIC
INDONESIA	SEARO	LMIC
KENYA	AFRO	LMIC
KIRIBATI	WPRO	LMIC
KOREA DPR	SEARO	LIC
KYRGYZSTAN	EURO	LMIC
LAO PDR	WPRO	LMIC
LESOTHO	AFRO	LMIC
LIBERIA	AFRO	LIC
MADAGASCAR	AFRO	LIC
MALAWI	AFRO	LIC
MALI	AFRO	LIC
MAURITANIA	AFRO	LMIC

MOLDOVA	EURO	LMIC
MONGOLIA	WPRO	UMIC
MOZAMBIQUE	AFRO	LIC
MYANMAR	SEARO	LMIC
NEPAL	SEARO	LIC
NICARAGUA	AMRO	LMIC
NIGER	AFRO	LIC
NIGERIA	AFRO	LMIC
PAKISTAN	EMRO	LMIC
PAPUA NEW GUINEA	WPRO	LMIC
RWANDA	AFRO	LIC
SAO TOME AND PRINCIPE	AFRO	LMIC
SENEGAL	AFRO	LMIC
SIERRA LEONE	AFRO	LIC
SOLOMON ISLANDS	WPRO	LMIC
SOMALIA	EMRO	LIC
SRI LANKA	SEARO	LMIC
SUDAN - NORTH	EMRO	LMIC
SUDAN - SOUTH	AFRO	LIC
TAJIKISTAN	EURO	LMIC
TANZANIA	AFRO	LIC
TIMOR-LESTE	SEARO	LMIC
TOGO	AFRO	LIC
UGANDA	AFRO	LIC
UKRAINE	EURO	LMIC
UZBEKISTAN	EURO	LMIC
VIETNAM	WPRO	LMIC
YEMEN	EMRO	LMIC
ZAMBIA	AFRO	LMIC
ZIMBABWE	AFRO	LIC

Appendix C: Vaccines included in the DoVE ACAVP model

Antigen	Delivery Strategy	
	Routine	Supplementary Immunization Activities
Haemophilus influenzae type b (Hib)	✓	
Measles (second dose and SIA)	✓	✓
Meningococcal conjugate serotype A (MenA)	✓	✓
Pneumococcal conjugate (PCV)	✓	

Appendix D: DHS care-seeking behavior for fever, acute respiratory infections (ARI), and diarrhea*

*Blue highlights indicate missing DHS data and are average care seeking among all Gavi countries with data, per syndrome.

	FEVER CARE SEEKING		ARI CARE SEEKING		DIARRHEA CARE SEEKING	
COUNTRY	Proportion of children	Reference	Proportion of children	Reference	Proportion of children	Reference
AFGHANISTAN	0.64	2015 DHS	0.69	2015 DHS	0.64	2015 DHS
ANGOLA	0.52	2015-16 DHS	0.5	2015-16 DHS	0.49	2015-16 DHS
ARMENIA	0.72	2015-16 DHS	0.94	2015-16 DHS	0.41	2015-16 DHS
AZERBAIJAN	0.42	2006 DHS	0.33	2006 DHS	0.35	2006 DHS
BANGLADESH	0.83	2014 DHS	0.89	2014 DHS	0.77	2014 DHS
BENIN	0.53	2017-18 DHS	0.46	2017-18 DHS	0.43	2017-18 DHS
BHUTAN	0.63		0.76	Bennett et al. 2015	0.57	
BOLIVIA	0.61	2003 DHS	0.61	2008 DHS	0.57	2008 DHS
BURKINA FASO	0.74	2017-18 MIS	0.64	2010 DHS	0.58	2010 DHS
BURUNDI	0.7	2016-17 DHS	0.62	2016-17 DHS	0.59	2016-17 DHS
CAMBODIA	0.88	2014 DHS	0.94	2014 DHS	0.78	2014 DHS
CAMEROON	0.61	2018 DHS	0.59	2018 DHS	0.52	2018 DHS
CENTRAL AFRICAN REPUBLIC	0.38	Bennett et al. 2015 [29]	0.37	Bennett et al. 2015	0.57	
CHAD	0.42	2014-15 DHS	0.45	2014-15 DHS	0.49	2014-15 DHS
COMOROS	0.53	2012 DHS	0.45	2012 DHS	0.5	2012 DHS
CONGO, DEMOCRATIC REPUBLIC	0.57	2013-14 DHS	0.55	2013-14 DHS	0.56	2013-14 DHS
CONGO, REPUBLIC	0.67	2011-12 DHS	0.71	2011-12 DHS	0.56	2011-12 DHS
COTE D IVOIRE	0.6	2011-12 DHS	0.6	2011-12 DHS	0.52	2011-12 DHS
CUBA	0.63		0.96	Bennett et al. 2015	0.57	
DJIBOUTI	0.66	Bennett et al. 2015	0.76	Bennett et al. 2015	0.57	
ERITREA	0.63		0.27	Bennett et al. 2015	0.57	
ETHIOPIA	0.36	2016 DHS	0.32	2016 DHS	0.45	2016 DHS
GAMBIA	0.65	2013 DHS	0.71	2013 DHS	0.71	2013 DHS
GEORGIA	0.63		0.74	Bennett et al. 2015	0.57	
GHANA	0.69	2019 MIS	0.75	2014 DHS	0.68	2014 DHS
GUINEA	0.62	2018 DHS	0.83	2018 DHS	0.68	2018 DHS
GUINEA-BISSAU	0.42	Bennett et al. 2015	0.62	Bennett et al. 2015	0.57	
GUYANA	0.65	2009 DHS	0.73	2009 DHS	0.65	2009 DHS
HAITI	0.47	2016-17 DHS	0.43	2016-17 DHS	0.38	2016-17 DHS

HONDURAS	0.64	2011-12 DHS	0.67	2011-12 DHS	0.55	2011-12 DHS
INDIA	0.81	2015-16 DHS	0.85	2015-16 DHS	0.77	2015-16 DHS
INDONESIA	0.9	2017 DHS	0.92	2017 DHS	0.8	2017 DHS
KENYA	0.72	2015 MIS	0.73	2015 MIS	0.66	2015 MIS
KIRIBATI	0.63		0.66		0.57	
KOREA DPR	0.63		0.66		0.57	
KYRGYZSTAN	0.45	2012 DHS	0.33	2012 DHS	0.56	2012 DHS
LAO PDR	0.57	Bennett et al. 2015	0.57	Bennett et al. 2015	0.57	
LESOTHO	0.72	2014 DHS	0.72	2014 DHS	0.55	2014 DHS
LIBERIA	0.78	2016 MIS	0.73	2013 DHS	0.7	2013 DHS
MADAGASCAR	0.59	2016 MIS	0.48	2008-09 DHS	0.39	2008-09 DHS
MALAWI	0.54	2017 MIS	0.78	2015-16 DHS	0.66	2015-16 DHS
MALI	0.53	2018 DHS	0.71	2018 DHS	0.49	2018 DHS
MAURITANIA	0.16	2000-01 DHS	0.45	2000-01 DHS	0.33	2000-01 DHS
MOLDOVA	0.55	2005 DHS	0.6	2005 DHS	0.42	2005 DHS
MONGOLIA	0.63		0.87	Bennett et al. 2015	0.57	
MOZAMBIQUE	0.69	2018 MIS	0.61	2015 AIS	0.59	2015 AIS
MYANMAR	0.67	2015-16 DHS	0.7	2015-16 DHS	0.66	2015-16 DHS
NEPAL	0.8	2016 DHS	0.85	2016 DHS	0.64	2016 DHS
NICARAGUA	0.7	2001 DHS	0.66	2001 DHS	0.47	2001 DHS
NIGER	0.62	2012 DHS	0.65	2012 DHS	0.6	2012 DHS
NIGERIA	0.73	2018 DHS	0.75	2018 DHS	0.65	2018 DHS
PAKISTAN	0.81	2017-18 DHS	0.84	2017-18 DHS	0.71	2017-18 DHS
PAPUA NEW GUINEA	0.5	2016-18 DHS	0.63	2016-18 DHS	0.38	2016-18 DHS
RWANDA	0.56	2017 MIS	0.61	2014-15 DHS	0.53	2014-15 DHS
SAO TOME AND PRINCIPE	0.72	2008-09 DHS	0.79	2008-09 DHS	0.53	2008-09 DHS
SENEGAL	0.53	2018 DHS	0.59	2018 DHS	0.46	2018 DHS
SIERRA LEONE	0.72	2016 MIS	0.77	2016 MIS	0.71	2016 MIS
SOLOMON ISLANDS	0.63		0.66		0.57	
SOMALIA	0.18	Bennett et al. 2015	0.32	Bennett et al. 2015	0.57	
SRI LANKA	0.63		0.66		0.57	
SUDAN - NORTH	0.42	Bennett et al. 2015	0.64	Bennett et al. 2015	0.57	
SUDAN - SOUTH	0.42	Bennett et al. 2015	0.64	Bennett et al. 2015	0.57	
TAJIKISTAN	0.44	2017 DHS	0.69	2017 DHS	0.49	2017 DHS
TANZANIA	0.75	2017 MIS	0.85	2015-16 DHS	0.71	2015-16 DHS
TIMOR-LESTE	0.58	2016 DHS	0.71	2016 DHS	0.65	2016 DHS
TOGO	0.56	2017 MIS	0.68	2013-14 DHS	0.5	2013-14 DHS
UGANDA	0.87	2018-19 MIS	0.8	2016 DHS	0.69	2016 DHS
UKRAINE	0.63		0.94	Bennett et al. 2015	0.57	

UZBEKISTAN	0.63		0.66		0.57	
VIETNAM	0.8	Bennett et al. 2015	0.84	Bennett et al. 2015	0.6	Bennett et al. 2015
YEMEN	0.63	2013 DHS	0.63	2013 DHS	0.57	2013 DHS
ZAMBIA	0.77	2018 DHS	0.76	2018 DHS	0.69	2018 DHS
ZIMBABWE	0.51	2015 DHS	0.56	2015 DHS	0.41	2015 DHS

Appendix E: DoVE ACAVP Model Parameters, 2016 and Present

2016 Model Parameters

Condition	% of care-seeking cases receiving antibiotics	Drug
Meningitis	100%	Ampicillin
		Gentamicin
Severe pneumonia	15%	Ampicillin
		Gentamicin
Severe measles	25%	Ampicillin
		Gentamicin
Non-severe pneumonia	85%	Amoxicillin

2020 Model Parameters

	Case Definition	% of care seeking cases treated	% care seeking source	Antibiotic	Daily Dose per kg	Daily dose unit	Duration (days)	Total dose per case	Total cost per case
SEVERE PNEUMONIA	Any general danger sign or Stridor in calm child.	15%	Assumption/correspondence with L. Lee	Ampicillin	200	mg	5	13000	$ 2.19
		15%		Gentamycin	7.5	mg	5	487.5	$ 0.74
		3%	Webb et al., 2013*	Cloxacillin	200	mg	5	13000	$ 2.20
		3%		Gentamycin	7.5	mg	5	487.5	$ 0.74
		1%	Webb et al., 2013**	Ceftriaxone	80	mg	5	5200	$ 2.07
PNEUMONIA	Chest indrawing or Fast breathing.	85%	Assumption/correspondence with L. Lee	Amoxicillin	80	mg	5	5200	$ 0.33
MENINGITIS		100%	Assumption	Ceftriaxone	100	mg	7	9100	$ 3.62
SEVERE COMPLICATED MEASLES	Pneumonia	6%	CDC Pink Book, Measles	Amoxicillin	80	mg	5	5200	$ 0.33
	Otitis Media	7%	CDC Pink Book, Measles	Amoxicillin	80	mg	5	5200	$ 0.33
	Diarrhea	1%	CDC Pink Book, Measles***	Ciprofloxacin	30	mg	3	1170	$ 0.10
MEASLES WITH EYE OR MOUTH COMPLICATIONS	Pus draining from the eye	5%	CDC Pink Book, Measles****	Tetracycline	5	g	1	5	$ 0.23
	Mouth Ulcers	5%	CDC Pink Book, Measles****	Benzylpenicillin	200000	U	5	13000000	$ 0.92
		5%		Metronidazole	22.5	mg	5	1462.5	$ 0.34
SEVERE PERSISTENT DIARRHOEA	Diarrhea 14 days or more with dehydration			none					

PERSISTENT DIARRHOEA	Diarrhea 14 days or more without dehydration			none					
DYSENTERY	Blood in stool	10%	GEMS	Ciprofloxacin	30	mg	3	1170	$ 0.10

*Calculation of 17% unimprovement rate (Webb et al.) x 15% Severe/very severe rate
**Calculation of 9% failure rate (Webb et al.) x 15% Severe/very sever rate
*** Calculation of 8% complication rate (pink book) x 10% cipro rx rate (GEMS)
**** Calculation of 30% total complication rate minus pneumonia, OM and Diarrhea, apportioned evenly between conjunctivitis and mouth ulcers

Appendix F: DoVE ACAVP Model Parameter Sources, 2016 and Present

Model Input	2016 Source	Updated/Added Source	Data use permission
Cases averted by vaccine programs in Gavi countries	Health impact modelled estimates from Gavi contracted modeling teams, based on Gavi Strategic Demand Forecast (SDF) models, v12	Update: Health impact estimates from Gavi contracted modeling teams (VIMC), based on SDF v16	MOU between JHU and Imperial College
Antibiotic treatment course per outcome	2012 WHO Integrated Management of Childhood Illness (IMCI) and 2013 Pocket Book guidelines (23, 24)	Update: 2014 WHO IMCI and 2012 Pocket Book guidelines (24, 25)	Publicly available
Country-specific proportion of cases that seek care, by syndrome	Demographic and Health Surveys (DHS) Program data (various years) (26)	Update: DHS 7 (2013-2018) data (26)	Publicly available
Proportion of care-seeking cases that are treated with antibiotics	Pneumonia: • Vaccine probe study (Indonesia) (27) • IMCI validation study (Kenya) (28) Measles: • Compiled measles and rubella-related cost data (29) Meningitis: • Expert-suggested assumptions Diarrhea: • Not included	Additions: Pneumonia: • First line antibiotic failure study (Kenya) (30) Measles: • CDC Pink Book (9) Diarrhea: • Global Enteric Multicenter Study (GEMS) (13)	Peer-reviewed publications
Antibiotic cost per dose	Management Sciences for Health's 2014 International Drug Price Indicator Guide (31)	Update: Management Sciences for Health's 2015 International Drug Price Indicator Guide (32)	Publicly available