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Michael Padget

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Michael Padget. Antibiotic resistance among children in low-income countries - Investigating community antibiotic consumption. Human health and pathology. Université Paris Saclay (COMUE), 2016. English. NNT: 2016SACLV130 . tel-01530745

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NNT : 2016SACLV130

THÈSE DE DOCTORAT  
DE  
L'UNIVERSITÉ PARIS-SACLAY  
PRÉPARÉE À  
L'UNIVERSITÉ VERSAILLES SAINT-QUENTIN EN YVELINES

Ecole doctorale 570  
Spécialité de doctorat : Santé Publique - épidémiologie  
Présentée par

**Michael PADGET**

**ANTIBIOTIC RESISTANCE AMONG CHILDREN IN LOW-INCOME COUNTRIES  
- INVESTIGATING COMMUNITY ANTIBIOTIC CONSUMPTION.**

*Thèse dirigée par Didier Guillemot et Elisabeth Delarocque-Astagneau*

Thèse présentée et soutenue à Institut Pasteur le 18 Novembre, 2016

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## Acknowledgements

This work would not have been possible without the contributions of a great number of people.

I would first like to thank my co-directors Didier Guillemot and Elisabeth-Delarocque Astagneau for giving me the opportunity to work on this thesis. Without their continued support and confidence in my abilities I would not be where I am today. Their guidance throughout the process was essential in developing the direction of the work and greatly improving its quality. In my time working with Didier, I learned about the importance of message, strategy, and most importantly shooting for the stars. Along with her constant support, Elisabeth taught me how to see the bigger picture in my work and to never forget the value of what I have done. I will carry these lessons with me.

I would like to thank my thesis readers including; Pierre Marie Girard, Francois Dabis for accepting to read my manuscript. I would also like to thank Martin Rottman, and Judith Muller for accepting to be members of my jury. I am honored that each has accepted to participate.

I would also like to thank the Principality of Monaco for their financial support without which this work would not have been possible.

A big thank you to the team in Madagascar including Perlinot, Tanjona, and Tanjona. Their coordination efforts, help with local administration, insights into local culture, and provision of data were indispensable. My time in Madagascar would not have been nearly as fruitful or rewarding without you and I thank you for your constant good humor, willingness to help, and friendship. Also, thank you to the field workers who provided countless hours of field investigation and data entry in difficult circumstances. You made every effort to collect clean data in a complicated environment. I'd like to thank Chiarella for sharing her local knowledge and insight into Madagascar drug use. I would also like to thank all the families who participated.

A big thank you also to Jeanne Tamarelle for her work in Senegal and with manuscript writing and data analysis. Her availability and help with this thesis went above and beyond what I could have hoped for. I appreciated your enthusiasm for a rather esoteric topic, rigor, and intellectual curiosity.

I would like to thank Bich-Tram both for her contributions to this work as well as her friendship. Your support and advice meant a lot to me and helped me navigate some of the more difficult moments. I would also like to thank Maud Seguy for her support and help getting my study from concept to the real world.

I would like to thank Laurence for her incredible attention to detail, her passion for statistics and survey methodology and most of all her good humor.

I would like to thank Fanny for laying much of the groundwork for my work in Madagascar. I couldn't have made such beautiful survey tools without stealing parts of yours.

A special thanks to Malamine for not only statistics help but for with sharing the thesis journey with me and listening to me complain. Thank you to all the PhEMI/B2PHI team for your good humor and friendless in the lab. Your support both personally and professionally helped to motivate me and push through to the end. To cite just a few; Anne F., Lulla, Helene, Clotilde, Maya, Felix, Lenaig, Anna, Annick, Anne T., and Mathieu along with many others.

Lastly, thank you to my family. Thank you to my French and American parents for your support from near and far. Thank you to Celestine for reminding me of what is important. And thank you to Maya for putting up with me these last few years, for everything you did to allow me to finish my work, and for your love and support.

## Publications

### **Main publications**

Huynh BT, Padget M, Garin B, Herindrainy P, Kermorvant-Duchemin E, Watier L, Guillemot D, Delarocque-Astagneau E. Burden of bacterial resistance among neonatal infections in low income countries: how convincing is the epidemiological evidence? *BMC Infect Dis*. 2015 Mar 15;15:127.

Michael Padget, Didier Guillemot, Elisabeth Delarocque-Astagneau Measuring antibiotic consumption in low-income countries: A systematic review and integrative approach. *International Journal of Antimicrobial Agents*. 2016 Jul;48(1):27-32.

Michael Padget, Jeanne Tamarelle, Perlinot Herindrainy, Awa Ndir, Fatoumata Diène Sarr, Vincent Richard, Patrice Piola, Didier Guillemot, Elisabeth Delarocque-Astagneau. A community survey of antibiotic consumption among children in Madagascar and Senegal: the importance of health care access and care quality. *Journal of Antibiotic Chemotherapy*. 2017 Feb;72(2):564-573.

### **Other works**

Chereau F, Herindrainy P, Garin B, Huynh BT, Randrianirina F, Padget M, Piola P, Guillemot D, Delarocque-Astagneau E. Colonization of extended-spectrum- $\beta$ -lactamase- and NDM-1-producing Enterobacteriaceae among pregnant women in the community in a low-income country: a potential reservoir for transmission of multiresistant Enterobacteriaceae to neonates. *Antimicrob Agents Chemother*. 2015;59(6):3652-5.

Bich-Tram Huynh, Michael Padget, Benoit Garin, Elisabeth Delarocque-Astagneau, Didier Guillemot on behalf of the BIRDY study group. Bacterial neonatal sepsis and antibiotic resistance in low-income countries. *Lancet*. Volume 387, No. 10018, p533–534, 6 February 2016

## Table of contents

<b>Acknowledgements</b> .....	<b>3</b>
<b>Publications</b> .....	<b>5</b>
<b>Table of contents</b> .....	<b>6</b>
<b>List of figures</b> .....	<b>10</b>
<b>List of tables</b> .....	<b>12</b>
<b>List of abbreviations</b> .....	<b>13</b>
<b>CHAPTER 1</b> .....	<b>14</b>
<b>1 General overview- Bacteria &amp; human health, antibiotics, and resistance</b> .....	<b>15</b>
<b>2 Current state of antibiotic resistance – consequences, measurement, and containment strategies</b> .....	<b>20</b>
Consequences of resistance .....	20
Resistance surveillance .....	21
Rise of resistance .....	21
Strategies to reduce antibiotic resistance .....	23
<b>3 Antibiotic resistance in low-income countries</b> .....	<b>24</b>
Bacterial disease burden in LICs .....	24
Bacteria involved in severe childhood infections in LICs.....	26
Evidence of resistance among children in LICs.....	26
Effects of resistance in LICs.....	26
Worldwide resistance spread and the role of LICs .....	27
<b>4 Antibiotic consumption</b> .....	<b>28</b>
Antibiotic consumption in humans.....	28
Antibiotic use in LICs.....	29
Lack of public health systems .....	29
Medical antibiotic misuse .....	29
Patient misuse/non-prescription use .....	30
Consequences of non-prescribed use and poor antibiotic prescription .....	31
Poor quality antibiotics .....	31
<b>Research questions and objectives</b> .....	<b>32</b>
Context.....	32
<b>CHAPTER 2 – Community burden of resistance among children in LICs</b> .....	<b>34</b>
<b>Introduction</b> .....	<b>34</b>
<b>Methods</b> .....	<b>35</b>
<b>Results</b> .....	<b>37</b>
<b>Neonatal results</b> .....	<b>37</b>
Laboratory methods and antibiotic susceptibility testing guidelines.....	39

Bacterial infection incidence estimates and pathogens.....	39
Antibiotic resistance .....	40
<b>Children under Two .....</b>	<b>44</b>
Design, recruitment settings, and study topics .....	44
Bacterial isolation rates .....	44
Laboratory methods and antibiotic susceptibility testing guidelines.....	45
Bacterial infection incidence rates and pathogens among children 28	
days to 2 years .....	45
Incidence estimates .....	45
Bacteremia.....	45
Meningitis .....	45
Invasive Pneumococcal Disease.....	46
<b>Antibiotic resistance among bacteria from children past the neonatal</b>	
<b>period (&gt;28 life days) .....</b>	<b>52</b>
Streptococcus pneumonia .....	52
Salmonella spp.....	53
<b>Discussion .....</b>	<b>56</b>
Neonatal bacteria and resistance .....	56
Under-two bacteria and resistance .....	57
Incidence rates.....	58
Lack of data .....	58
<b>Conclusion.....</b>	<b>59</b>
<b>Chapter 3 – Measurement of Community Antibiotic Consumption in LICs .....</b>	<b>60</b>
<b>Background .....</b>	<b>60</b>
Non-prescribed antibiotics .....	60
<b>Methods.....</b>	<b>62</b>
<b>Results and methodology review .....</b>	<b>62</b>
Pharmacy/hospital document reviews.....	63
Simulated client method.....	64
Observed prescribing encounters/patient exit interviews.....	65
Community surveys .....	66
<b>Discussion and integrating study techniques .....</b>	<b>66</b>
<b>Conclusion .....</b>	<b>70</b>
<b>Chapter 4 – Madagascar, Senegal Survey.....</b>	<b>71</b>
<b>Introduction .....</b>	<b>71</b>
Madagascar context .....	71
Senegal context.....	71
<b>Study Objectives.....</b>	<b>72</b>
<b>Methods.....</b>	<b>72</b>
Survey population.....	72
Household selection .....	72
Study size .....	73
Data gathered .....	73
Health care structures and pharmacies.....	74
Statistical analysis .....	74



Ethics.....	75
<b>Results .....</b>	<b>75</b>
Sociodemographic characteristics by site.....	75
Antibiotic consumption .....	80
Factors associated with antibiotic consumption .....	84
Antibiotic consumption and structural factors.....	85
<b>Discussion .....</b>	<b>88</b>
<b>Conclusion.....</b>	<b>91</b>
<b>Chapter 5 – General Discussion and Conclusions .....</b>	<b>92</b>
<b>Current work and resistance in LICs.....</b>	<b>92</b>
Research objectives and results .....	92
Non-prescription antibiotics.....	92
Strengths and weaknesses of this work.....	93
Challenges.....	94
Lessons from LIC context .....	94
Interventions in LICs .....	94
One health and animal use.....	95
<b>Antibiotic Resistance globally.....</b>	<b>95</b>
Future of resistance measurement .....	95
Future of antibiotic consumption measurement .....	96
Global responses to resistance .....	96
Future of this work .....	97
<b>Conclusion.....</b>	<b>98</b>
<b>References .....</b>	<b>99</b>
<b>Annex .....</b>	<b>110</b>
<b>Ch2 supplementary materials .....</b>	<b>110</b>
<b>Table S1. Neonatal infections in low-income countries (2000-May 2014).....</b>	<b>110</b>
<b>Ch3 supplementary material .....</b>	<b>115</b>
<b>Table S2. Studies of antibiotic consumption in the community in low-income countries.....</b>	<b>115</b>
<b>Ch4 supplementary material .....</b>	<b>120</b>
<b>S3. Results for Madagascar univariate and multivariate analysis. Dependent variable, antibiotic consumption in the last three months (1-Yes, 0-No).....</b>	<b>120</b>
<b>S4. Results for Senegal multivariate analysis. Dependent variable, antibiotic consumption in the last three months (1-Yes, 0-No) .....</b>	<b>120</b>
<b>S5. Antibiotic usage questionnaire for Madagascar and Senegal community survey ....</b>	<b>121</b>
<b>S6. Sample Fokontany map for Madagascar and Senegal community survey. ....</b>	<b>126</b>
<b>S7. Sample Household tracking sheet for Madagascar and Senegal community survey .....</b>	<b>127</b>
<b>S8. Sample antibiotic visuals for Madagascar and Senegal community survey. ....</b>	<b>128</b>
<b>S9. Local calendar for Madagascar and Senegal community survey. ....</b>	<b>129</b>

**Résumé substantiel en langue française. ....130**

**Published articles .....146**

**Résumé /Abstract .....175**

## List of figures

<b>Figure 1.</b> Global causes of under-five deaths in 2010.....	16
<b>Figure 2.</b> Crude death rate for infectious diseases –United States 1900-1996 per 100,000 population per year. ....	17
<b>Figure 3.</b> Timeline of antibiotic discovery and detection of antibiotic resistance. ....	18
<b>Figure 4.</b> Antibiotic targets and resistance mechanisms. ....	18
<b>Figure 5.</b> Antibiotic resistance of <i>Klebsiella Pneumoniae</i> in the United States. ....	22
<b>Figure 6.</b> Proportion of <i>Staphylococcus Aureus</i> isolates resistant to methicillin among invasive infections in 2014. ....	23
<b>Figure 7.</b> Regional causes of death among children under 5 in 2010. ....	25
<b>Figure 8.</b> Consumption of antibiotics in 2010 (A) and annual growth rate in antibiotic consumption from 2000 to 2010 (B).....	28
<b>Figure 9.</b> Flowchart of literature search including both the infection incidence and antibiotic resistance branches.....	37
<b>Figure 10.</b> Incidence and aetiology of neonatal sepsis/bacteremia for 1000 live births in developing countries. ....	40
<b>Figure 11.</b> Penicillin resistance among <i>Streptococcus pneumoniae</i> isolates along with pathology, study years, and country. ....	52
<b>Figure 12.</b> Frequency of non-prescription use of antimicrobials in the general population based on published works.....	61
<b>Figure 13.</b> Flowchart of literature search.....	63
<b>Figure 14.</b> Flowchart for integration of study types for antibiotic measurement and surveillance in LICs. ....	69
<b>Figure 15.</b> Segment selection steps in Antananarivo using the compact segment sampling method. ....	73
<b>Figure 16.</b> Distribution of symptoms and antibiotic consumption among children under 2 surveyed.....	83
<b>Figure 17.</b> Types of antibiotic classes used among children under 2 surveyed according to study sites.....	84

**Figure 18.** Antibiotic consumption estimates centers in study zone in Madagascar and Senegal per (a) number of public health structures and (b) number of pharmacies per 10k population. ....87

## List of tables

<b>Table 1.</b> Search strategy and selection criteria for neonatal and young childhood infection and bacterial resistance articles in low-income countries (2000-May 2014).....	36
<b>Table 2.</b> Antibiotic resistance of bacteria isolated from invasive neonatal infections in developing countries (2000-May 2014) .....	42
<b>Table 3-</b> Articles included in analysis for children under two by region, subject, and design .....	47
<b>Table 4.</b> Antibiotic resistance of Salmonella and Shigella isolates from low-income countries (2000-May 2012) .....	54
<b>Table 5.</b> Capacity of four study types in responding to antibiotic consumption investigation needs in LICs .....	68
<b>Table 6.</b> Socio-demographic sample characteristics of children under 2 participating in a community survey in Madagascar and Senegal. ....	76
<b>Table 7.</b> Demographic and health history information sample characteristics of children under 2 participating in a community survey in Madagascar and Senegal. ....	79
<b>Table 8.</b> Population estimates of antibiotic consumption based on sample of children under 2 participating in a community survey in Madagascar and Senegal. ....	81
<b>Table 9.</b> Characteristics of antibiotic consumption episodes in the sample of children under 2 participating in a community survey in Madagascar and Senegal. ....	82
<b>Table 10.</b> Factors associated with antibiotic consumption in the last three months among children under 2 in Madagascar and Senegal. ....	86

## List of abbreviations

CA-MRSA - Community-associated MRSA

CSS- Compact segment sampling

DDD - Defined daily dose

ESBL- Extended spectrum beta-lactamase

HIB - *Haemophilus Influenzae* type b

KPC - *Klebsiella pneumoniae* carbapenemase

LIC - Low-income country

MIC - Minimum inhibitory concentration

MRSA – Methicillin resistance *Staphylococcus aureus*

NTS - Non-typhoid salmonella

PPS - Probability proportion to size

3rd GC - Third generation cephalosporins

## Chapter 1

Antibiotic resistance is a global issue. WHO has reported high levels of bacterial resistance across the globe including in both high-income and low-income countries (LICs).<sup>1</sup> Worryingly, bacteria are increasingly multi-drug resistant including to last line antibiotics, making them difficult or impossible to treat.<sup>2</sup>

These multi-resistant bacteria have been detected both inside and outside of hospital settings and include important disease causing pathogens such as carbapenemase producing *enterobacteriaceae*, and methicillin resistant *Staphylococcus Aureus*. The relative lack of new antibiotic research and discovery complicates this issue. Unlike past eras where doctors could count on development of new antibiotics to combat resistance, maintaining the activity of current antibiotics is critical. Rising resistance jeopardizes not only advances made in infectious disease morbidity and mortality but also many modern medical procedures.<sup>3</sup>

The increased burden of resistance is likely to disproportionately affect LICs. These countries are home to high rates of bacterial disease and often lack the diagnostic methods and access to second-line antibiotics necessary to combat the effects of resistance. Children are at particularly high risk as they bear the highest bacterial disease burden in LICs. In Africa alone, infectious disease accounts for over 75% of under-5 deaths.<sup>4</sup>

Despite the risks, resistance in LICs has been understudied due to resource limitations, lack of laboratory capacity, and the absence of surveillance systems. However, LICs are important elements in the global resistance dynamic and act as global reservoirs and amplifiers of resistance.<sup>5</sup> LICs are also sources of novel forms of resistance.<sup>6</sup>

Along with high transmission of bacterial disease, risk factors for the development and spread of resistance in LICs include: antibiotic consumption without a prescription, poor quality antibiotics from expired or counterfeit sources, and misuse or overuse of antibiotics due to lack of medical training or diagnostics.<sup>7</sup> In many countries children drive rates of antibiotic consumption and may play a key role in resistance development and spread.<sup>8</sup>

In order to combat resistance in LICs, particularly among vulnerable children, we need to first understand the dynamic of resistance. What is the real burden? Which bacteria cause childhood infection? What kinds of resistances profiles are prominent? Knowing how these bacteria and their resistance profiles compare to current treatment recommendations is also important.

Along with understanding the burden, controlling of antibiotic usage is needed in LICs where little controls exist. Antibiotic stewardship programs have proven to be successful in controlling or lowering resistance levels in both hospitals and community settings.<sup>9-11</sup>

To control usage, data are need about who uses antibiotics, which antibiotics are used, why they are used, and where they come from. These data can help to develop context-specific solutions to help maintain the effectiveness of current antibiotics and stem the tide of rising resistance.

## 1) General overview- Bacteria & human health, antibiotics, and resistance

### *Bacteria and human health*

Bacteria and humans have evolved together over centuries and humans cannot live or develop normally without the presence of bacteria. Commensal bacteria aid humans in numerous activities including digestion, protection from pathogens, and immune system development.<sup>12</sup>

Certain bacteria can also lead to disease in humans ranging from skin infections to diarrhea to serious invasive infections including sepsis and meningitis. Before causing disease, these pathogenic bacteria must first enter the human body through cuts or abrasions, contaminated food or water, or inhalation. Once they have gained access, these bacteria then damage human cells by secreting toxins or through direct damage via resource competition or reproductive techniques.

A large number of disease causing bacteria have been identified and include widespread pathogens such as: *Mycobacterium tuberculosis*, *Streptococcus*, *Staphylococcus*, *Salmonella*, and *Escherichia Coli*, among others. Bacteria can generally be classified as Gram-positive or Gram-negative according to the structure of their cell walls.

The incidence of bacterial disease varies greatly by region, type of infection, and pathogen but bacteria remain one of the largest causes of human mortality globally and particularly in LICs.<sup>13</sup> *Staphylococcus Aureus* (*S. Aureus*) is one example. This gram positive bacterium is commonly found on the skin or in the nares and is carried asymptomatically at least intermittently by up to 50% of healthy individuals.<sup>14</sup> *S. Aureus* is a common cause of skin and respiratory infections as well as a leading cause of serious bloodstream infections in both LICs and developed countries. Incidence estimates for *S. Aureus* bacteremia ranges from 4.31 to 38.22 per 100,000 person-years in the United States alone and rates as high as 100 cases of *S. Aureus* bacteremia per 100,000 person-years has been reported among children under 1 in Kenya.<sup>15,16</sup>

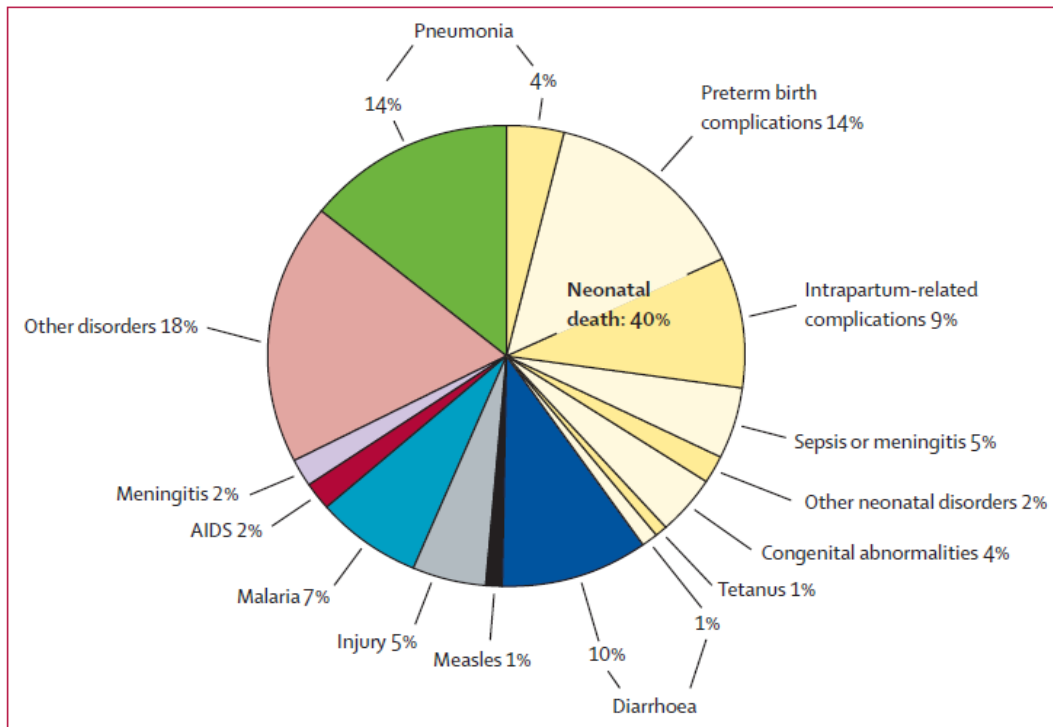
Another common disease causing pathogen is *Escherichia Coli* (*E. Coli*). This commensal bacterium is carried in the human gut and is a common cause of diarrhea including serious forms which can lead to kidney damage or even death. Reported incidence rates of *E. coli* caused diarrhea in 2004 ranged from .9 cases per 100,000 people in the USA to 22 cases per 100,000 children aged six to 48 months in Argentina. Undocumented incidence rates from low-income countries have the potential to be much higher.<sup>17</sup> *E. Coli* is also a common cause of bloodstream infections and is the number one cause of these infections in the community and the second leading cause in hospitals globally.<sup>18</sup>

### *Childhood bacterial burden*

Bacterial infections are particularly important causes of mortality among children who are more susceptible to infectious diseases. It is estimated that 37% of the global under-five mortality is due to infectious diseases caused either entirely or in part by bacteria including illnesses such as diarrhea, sepsis, and meningitis (Figure 1). Incidence of community-acquired bacteremia as high as 505 per 100,000 has been reported in Kenya for children under-5 and



diarrhea alone is responsible for an estimated 1 of every 9 under 5-child deaths worldwide. <sup>4</sup>  
16



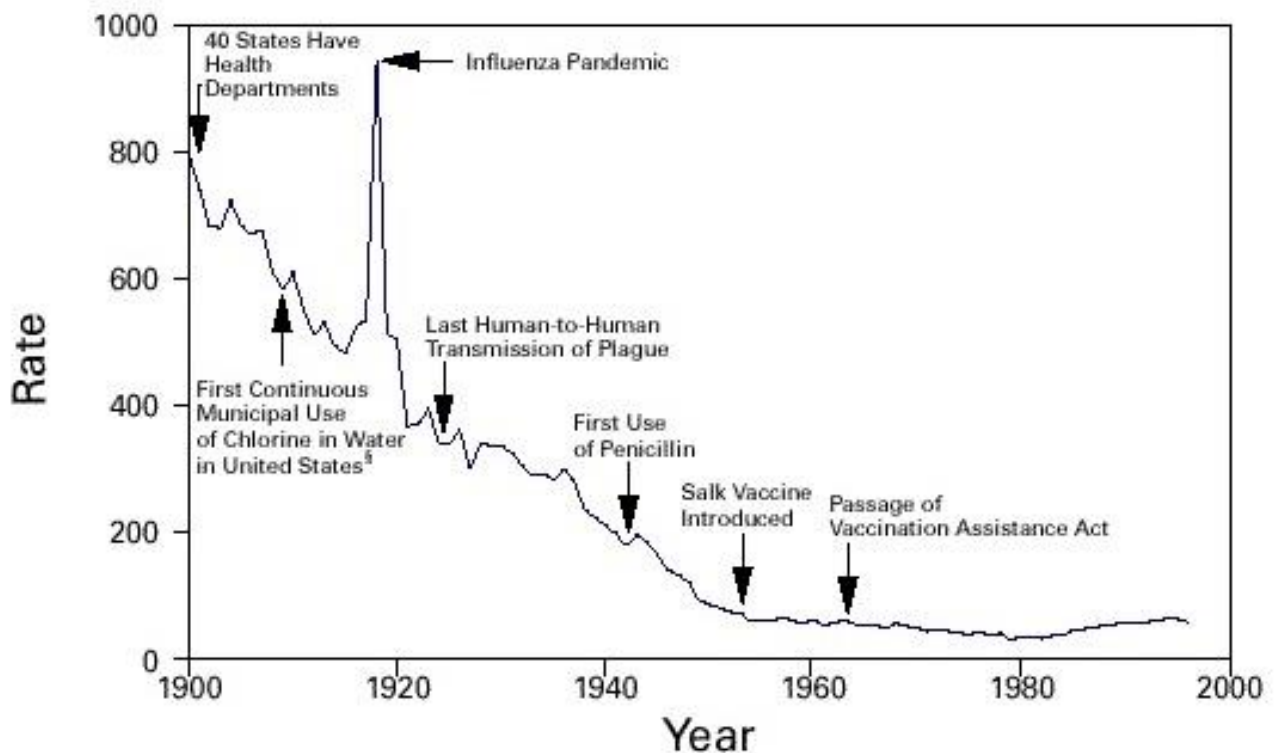
**Figure 1.** Global causes of under-five deaths in 2010. Source: [4]

### *What are antibiotics?*

Antibiotics are antimicrobial substances used to treat bacterial infection by killing bacteria or preventing their growth. A large number of different antibiotics exist with diverse mechanisms of action. These include Penicillins which inhibit bacterial cell wall synthesis, Quinolones which inhibit bacterial DNA synthesis, and Tetracyclines which inhibit bacterial protein synthesis. Antibiotics can be classified as wide-spectrum meaning they are active against a wide range of bacteria, or narrow-spectrum meaning they are effective against a limited range of bacteria.<sup>19</sup>

### *History of antibiotics*

Following their introduction as therapeutic agents in the 1940's, antibiotics were hailed as "miracle drugs". Long-feared diseases such as tuberculosis, bacterial pneumoniae, and sepsis suddenly became easily treated with antibiotics leading to greatly improved survival and patient outcomes. Along with improved measures in public health, the number of deaths due to infectious and bacterial diseases plummeted in most developed nations following World War II (see Figure 2).



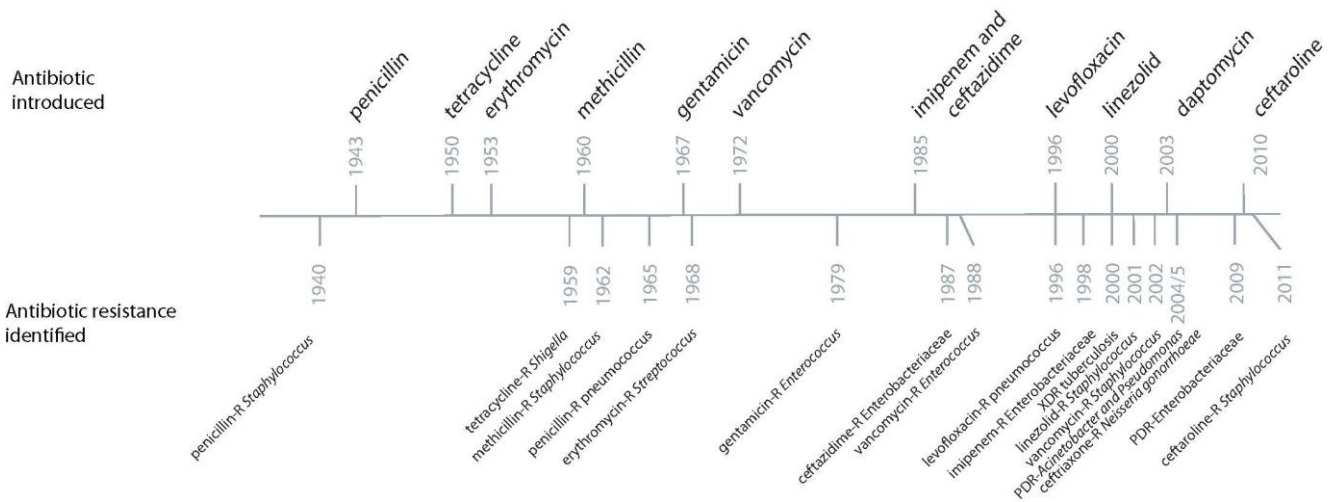
**Figure 2.** Crude death rate for infectious diseases –United States 1900-1996 per 100,000 population per year  
Source: [20]

Along with falling infectious disease mortality, this period was considered the “golden age” of antibiotic discovery and a number of important and effective antibiotics were discovered including: various beta-lactams, aminoglycosides, and macrolides.<sup>21</sup> The effectiveness, few side effects, and cheap costs associated with these drugs led to their wide usage and antibiotic prescription became standard treatment for a number of common illnesses. Antibiotics have since become a cornerstone of modern medicine used not only to treat episodes of bacterial infection but also in a prophylactic capacity allowing for complicated modern medical procedures such as chemotherapy, organ replacements, and other invasive surgeries.<sup>22</sup>

#### *History of resistance in humans*

Almost as soon as new antibiotics were discovered however, bacteria capable of resisting their effects emerged (see Figure 3). Only one year after the discovery of Tetracycline, a powerful broad spectrum drug, did resistant clinical isolates start to appear.<sup>23</sup> Similarly, only three years after the discovery of methicillin, a drug designed to treat penicillin resistant *S. Aureus*, were methicillin resistant strains discovered.<sup>21</sup>

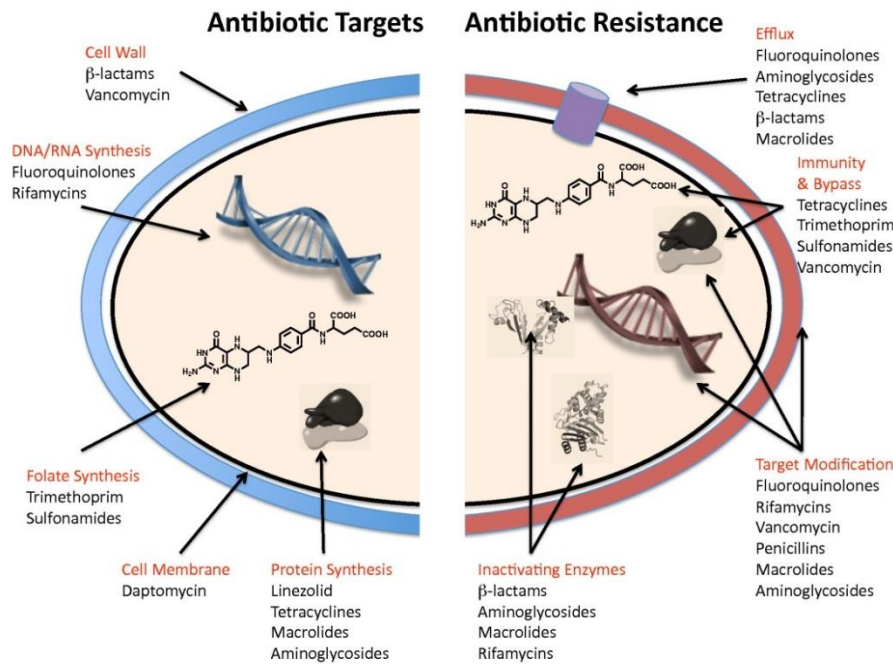
Famously, resistance to penicillin had been discovered even before the introduction of this drug as a therapeutic agent.<sup>21</sup> As new antibiotics were developed and used so did bacteria become resistant to their effects. The accumulation of these mechanisms eventually led to an increase of multi-resistant bacteria capable of resisting multiple antibiotics.



**Figure 3.** Timeline of antibiotic discovery and detection of antibiotic resistance. Adapted from [24]

### Types of resistance

A number of techniques exist for bacteria to avoid the effects of antibiotics. Some bacteria simply pump the antibiotic out of the cell wall before it reaches its target using efflux pumps. This technique is used by both gram positive and gram negative bacteria and can be effective against a range of antibiotics. Another resistance strategy involves modification of the antibiotic target. For example, some bacteria may alter the proteins that Penicillin binds to rendering this antibiotic ineffective. Common antibiotic targets and resistance mechanisms can be seen in Figure 4.



**Figure 4.** Antibiotic targets and resistance mechanisms. Source [25]

### *Antibiotic resistance development*

The development of antibiotic resistance is a classic example of Darwinian survival of the fittest. Acquisition of antibiotic resistance gives bacteria a survival advantage in environments where antibiotics are present allowing them to survive and reproduce.

Bacteria can acquire antibiotic resistance either through spontaneous mutations or through acquiring resistance genes from other bacteria. This second method is much more efficient and includes horizontal gene transfer through conjugation, transformation, transduction, or gene transfer agents.<sup>26</sup> This gene transfer has played a large role in resistance spread particularly through the exchange of mobile genetic elements. Mobile elements including plasmids or transposons are capable of transmitting powerful multi-drug resistance genes such as extended spectrum beta-lactamases (ESBLs) or carbapenemases and can be exchanged between different bacterial strains, species, or even genera.

Antibiotic exposure increases the frequency of gene transfer including antibiotic resistant genes. Levels as low as 100 times below minimum inhibitory concentrations (the lowest levels of antimicrobial concentration needed to inhibit bacterial growth) have been found to induce a stress response in bacteria provoking increased horizontal gene transfer.<sup>27</sup> These low levels of exposure are particularly dangerous as they increase the chance of resistance gene transfer without killing the bacteria allowing them to survive and reproduce.

This selective pressure and gene transfer can occur in any situation where multiple bacteria are found in the presence of antibiotics. The human gut, home to an estimated 1000 species of bacteria, is one such environment. Oral antibiotics, and especially non-lethal doses, taken for one type of infection will affect all bacteria in the gut stimulating gene transfer without killing the bacteria. Similar dynamics can be found in environmental contexts such as water treatment plants, antibiotic contaminated soil, or any other area where large numbers of bacteria are exposed to antibiotics.<sup>28, 29</sup> Limiting unnecessary antibiotic exposure in these contexts is thus an important component in combatting rising resistance rates.

### *Resistance origins*

Bacterial antibiotic resistance is not a recent phenomenon and bacteria from as many as 30,000 years ago have been found to contain antibiotic resistant genes.<sup>30</sup> Like resistance genes today these ancient genes played an important role in bacterial survival.

Microorganisms are continuously competing with each other for space and food and have developed a number of mechanisms to aid in their survival. These mechanisms include the production of antibiotics to kill or slow the growth of competing organisms including bacteria. In order to counter these antibiotics bacteria rely on effective gene activation and exchange including antibiotic resistance genes. Over the centuries, this continuous struggle has resulted in a deep reservoir of antibiotic resistant genes that bacteria may access when necessary. This global collection of resistance genes or antimicrobial resistome is thus much older than human discovery of antibiotics and very diverse.<sup>22</sup> The heavy use of antibiotics by humans in both human and animal medicine use over the past 70 years has created a

powerful selection pressure for bacteria to develop resistance and has greatly accelerated the access of this resistome resulting in the high levels of resistance seen today.

### *Bacterial and antibiotic resistance identification*

A number of methods exist for identifying bacteria and detecting the presence of antibiotic resistance and can include both phenotypic and genotypic methods. Phenotypic identification of bacteria is the classic approach based on observable physical or metabolic characteristics. This can include microscopic or colony morphology, straining results, or environmental requirements for bacteria growth. When detecting antibiotic resistance using these methods, disk-diffusion is often used. In this method isolated bacteria are grown in petri dishes and disks of selected antibiotics are placed on the plate. The activity of the antibiotic is measured as the zone around the antibiotic where bacterial growth is inhibited.<sup>31</sup>

Bacteria can also be identified using genotypic methods. These methods use bacterial RNA or DNA to identify specific genes unique to each bacterium. This approach is highly specific and often highly sensitive. These methods also have the advantage of being much quicker than phenotypic methods which require bacterial growth but are often much more expensive. Antibiotic resistance detection using genotypic includes looking for the presence of specific antibiotic resistance genes.<sup>31</sup> Expression of these resistance genes may vary however, so their presence does not always equate to antibiotic resistance.

## 2 – Current state of antibiotic resistance – consequences, measurement, and containment strategies

### *Consequences of resistance*

Resistant bacteria can have dramatic effects on patient outcomes compared to non-resistant infections. Bacteremia cases due to Methicillin resistant *S. Aureus* (MRSA) have been shown to double the probability of death and were associated with longer hospital stays and higher costs when compared to Methicillin sensitive *S. Aureus* infections.<sup>32, 33</sup> These associations remain even when adjusting for related factors including disease severity.<sup>34</sup> Infections due to ESBL-producing *Enterobacteriaceae* are associated with treatment failure and higher mortality in bacteremia cases. Infection with penicillin non-susceptible pneumococci has been associated with a fourfold increase in complications.<sup>35</sup> The CDC estimates that over 20,000 people currently die each year in the US alone due to antibiotic resistance. In France this figure was estimated at 12,500 in 2012.<sup>36</sup>

Antibiotic resistance also comes with an economic cost. A study of surgical site infections found that patients with a methicillin sensitive *S. Aureus* infection cost \$29,455 on average for hospitals while the cost of this same infection due to MRSA was \$52,791. This extra cost was driven by longer hospital stays, along with additional diagnostics and treatment costs.<sup>37</sup>

The rapid increases in antibiotic resistance seen in many countries over the last few years including the emergence of many multi-drug resistant bacteria have many scientists fearing a return to a pre-antibiotic era where relatively minor infections could result in death and many of the advances made in modern medicine are reversed.<sup>1</sup>

If not controlled, the impacts of resistance will continue to grow. A recent report estimated that by 2050 over 10 million people will die due to antibiotic resistance each year worldwide costing over 100 trillion dollars unless solutions are found.<sup>38</sup>

### *Resistance surveillance*

To measure resistance a number of surveillance studies have been conducted around the world including a few ongoing surveillance systems.<sup>39</sup>

EARS-Net is a European surveillance system run by the European Centre for Disease Prevention and Control. Data are collected systematically from national networks of European member countries. These networks include over 900 clinical laboratories across Europe. Surveillance data gathered includes resistance profiles for specific pathogens and antibiotics and are available by year and country from 1998 to present.

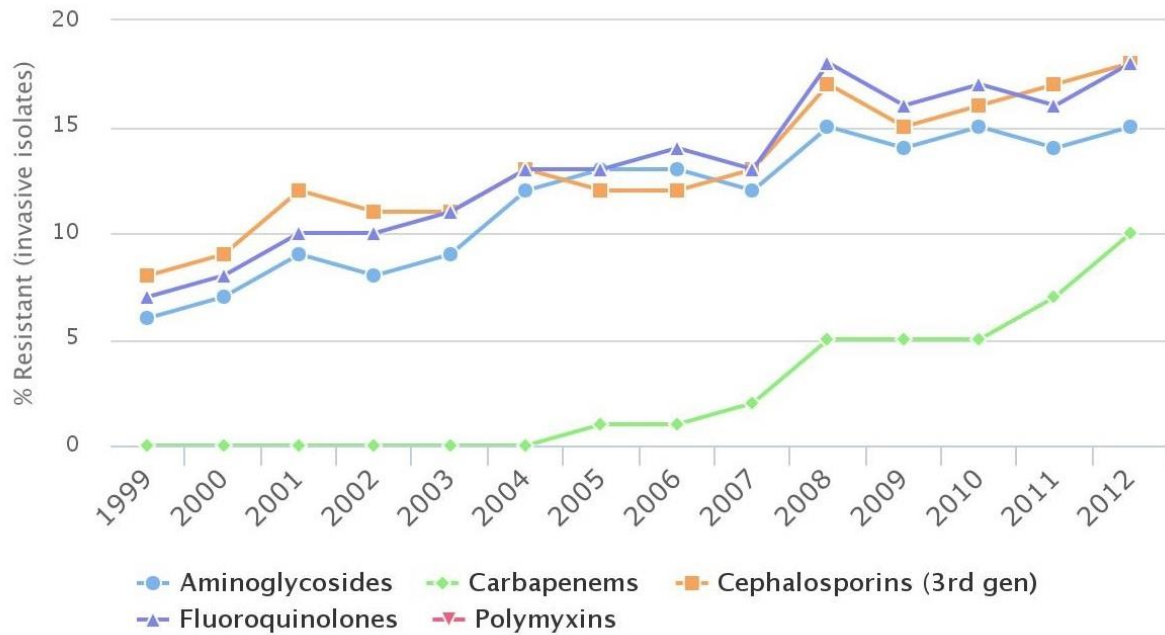
In the U.S., The Surveillance Network plays a similar role. This surveillance system also includes data from 1998 to present and collects data on all clinically encountered bacterial pathogens, all available antimicrobial agents, and includes data from over 300 participating healthcare institutions from all regions of the country.

These surveillance systems are particularly important to track resistance trends, identify emerging forms of resistance, and for creating and monitoring programs to control antibiotic resistance. Unfortunately, these programs exist almost exclusively in high-income countries where lab facilities capable of delivering suitable, high-quality data are available.

### *Rise of resistance*

Rates of antibiotic resistance may fluctuate from year to year depending on which bacteria/antibiotic pair is being measured. Measurement issues such as changing definitions may also play a role. Once measurement issues have been controlled for, a wide variety of factors can influence rates including changing epidemiologic trends or changing antibiotic consumption patterns.

Despite these fluctuations, a clear trend of rising resistance globally can be observed and resistance has reached critical levels for many important pathogens including high levels of multi-drug resistance. Resistance among *K. Pneumoniae* isolates in the United States can be seen in Figure 5.

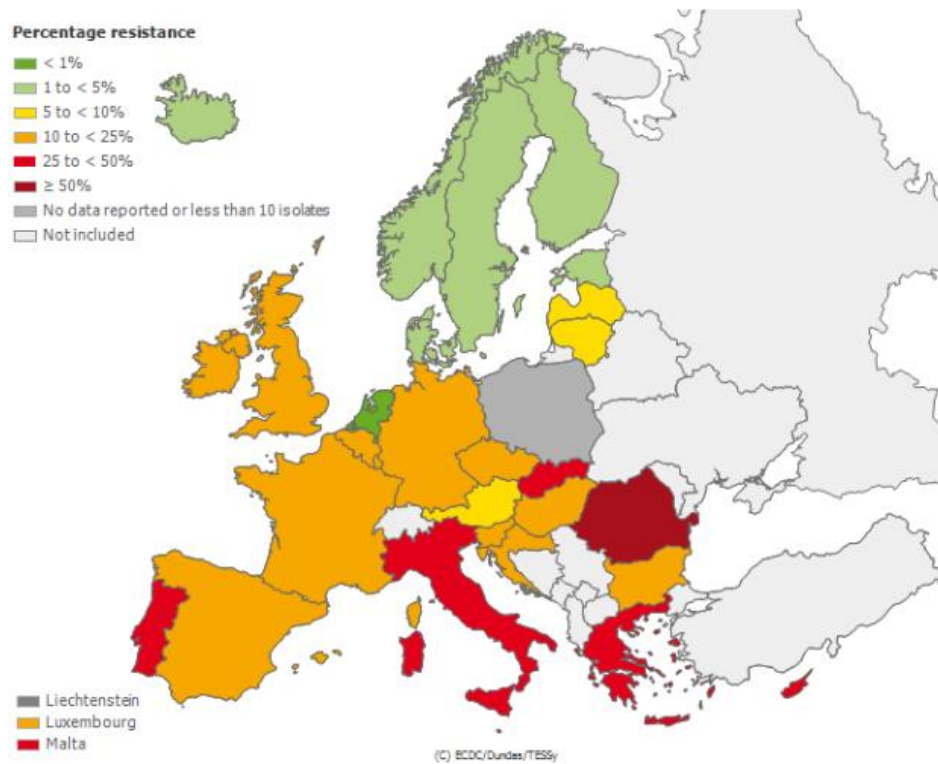


**Figure 5.** Antibiotic Resistance of *Klebsiella Pneumoniae* in the United States.

Source: Center for Disease Dynamic, Economics & Policy

Another well-known multi-drug resistant bacterium is MRSA. In 2008 MRSA represented 44% of resistance bacteria responsible for nosocomial infections in Europe.<sup>40</sup> Increasingly, MRSA is also reported in community acquired infections, often with increased virulence factors.<sup>21</sup>

In Europe, the proportion of *S. Aureus* isolated from invasive infections resistant to methicillin is highly variable (See Figure 6) with rates as high as 56% in Romania in 2014.



**Figure 6.** Proportion of *Staphylococcus Aureus* isolates resistant to methicillin among invasive infections in 2014.  
Source: ECDC - EARS-Net surveillance system.

### *Strategies to reduce antibiotic resistance*

Like global warming, antibiotic resistance is an example of a “problem of the commons” where individual users behaving in their own self-interest deplete a common resource.<sup>41</sup> In the case of antibiotics, the benefit of antibiotic use outweighs the risk of global development of resistance on the individual level. This aspect is one of the principal difficulties in tackling antibiotic resistance and must be taken into account when determining measures to limit resistance.

Additionally, discovery of new antibiotics has become difficult and expensive for pharmaceutical companies in recent years and no widely used antibiotics have been commercialized. A number of pharmaceutical companies have left the development of these drugs entirely in favor of more lucrative chronic disease drug research.<sup>42</sup>

Because of these issues, several novel solutions have been proposed to treat resistance bacteria. These approaches include: antibodies, new vaccines, and the use of bacteriophages among others. While some of these approaches have shown promise their future remains uncertain. The development process for these techniques is often long and expensive and the majority is limited to specific pathogens. Furthermore, these strategies are designed not to replace antibiotics but to be used in conjunction meaning that the problem of resistance may persist.<sup>43</sup> Even with the technological capability, replacing antibiotics in human health



would require tremendous efforts and fundamental changes to health care making this option difficult.

Retaining the effectiveness of current antibiotics is another important approach. A number of strategies designed to do this include changing or controlling antibiotic use. The use of antibiotic cycling or using narrow spectrum antibiotics to avoid unnecessary selection pressure are among these proposed strategies however evidence for their effectiveness remains limited. Other strategies are focused on reducing antibiotic use overall often with a particular focus on reducing unnecessary use.<sup>44</sup> Numerous hospital based studies have reported success with antibiotic stewardship programs in reducing antibiotic resistance infections.<sup>9, 11</sup> In the community setting, clear correlations between resistance and overall consumption can be seen from country-level data and certain community interventions have also shown success in reducing overall resistance.<sup>10, 45</sup>

### 3 - Antibiotic resistance in low-income countries

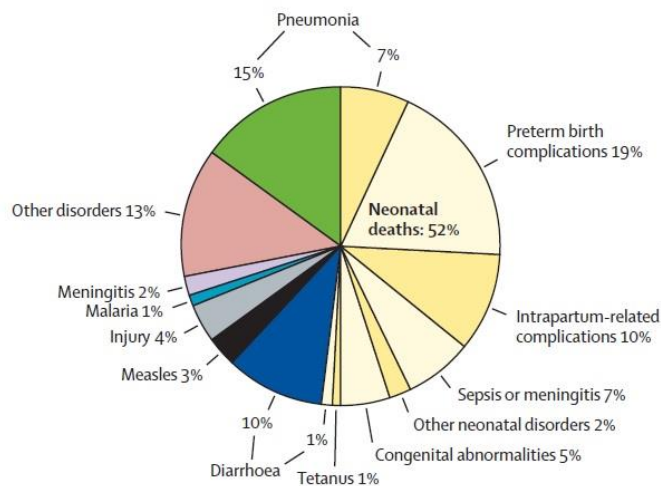
Antibiotic resistance has been widely studied in developed countries where strong surveillance systems exist and large research efforts have been undertaken in both hospitals and community settings.<sup>46, 47</sup> Data from low-income countries on the other hand is often hard to come by or of questionable quality. This lack of data exists despite the fact that low-income countries are home to a number of factors which make them high risk environments for the development and transmission of resistance including: misuse and overuse of antibiotics, use of poor quality antibiotics, and lack of public health and hygiene measures. Some of these same factors also make populations in LICs those most vulnerable to the added burden of antibiotics resistance. The large burden of bacterial disease in LICs is one particularly important factor in both the spread of resistance and the increased burden of resistance in these countries.

#### *Bacterial disease burden in LICs.*

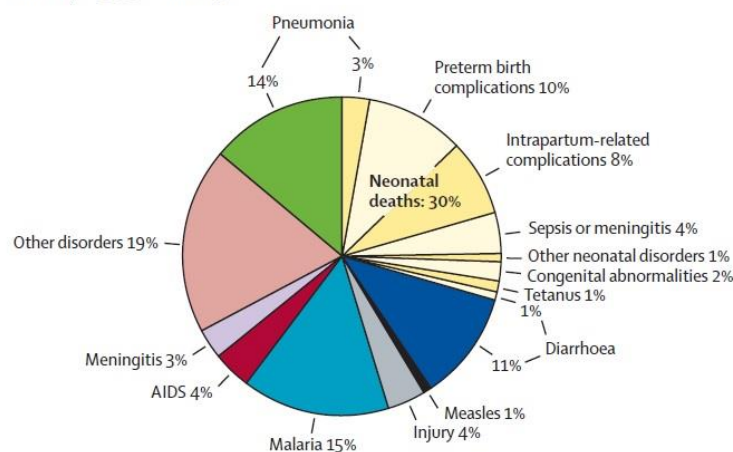
Infectious disease is the leading cause of death and disability in LICs which are home to 80% of the world's population.<sup>48</sup> Among the poorest populations, infectious diseases are responsible for 58.6% of deaths and 64% of lost disability-adjusted life-years (as opposed to 7.7% and 11% among the world's richest countries respectively).<sup>49</sup>

Children and infants in LICs represent a particularly vulnerable population and bear a heavy burden of infectious disease including a large proportion of bacterial disease. Over 99% of the almost 8 million infant and early childhood deaths occur in LICs with the majority of these deaths found in Sub-Saharan Africa (3.6 million) and Southeast Asia (2.1 million). In Africa alone, infectious disease accounts for over 76% of under-5 deaths and according to estimates, 36% of neonatal deaths worldwide are directly attributable to severe infections.<sup>4, 50</sup> Bacterial infections, including sepsis, pneumonia, tetanus, meningitis and diarrhea, are the leading cause of these severe infections.<sup>51, 52</sup> (Figure 7)

Southeast Asia (N=2.096 million)



Africa (N=3.552 million)



**Figure 7.** Regional causes of death among children under 5 in 2010. Source [4]

In the poorest regions, in which neonatal mortality rates may exceed 50 per one thousand births (versus only 4 per thousand in developed countries), the proportion of deaths attributable to severe infections can be as high as 50% and high mortality rates for neonatal infections are found in both community and hospital settings. These mortality rates are particularly striking in the context of other global health issues. Results of a prospective cohort study of children in Tanzania presenting systemic signs of infection showed mortality rates attributable to gram-negative bacillus infections that were twice as high as those for malaria (44% versus 20%).<sup>53</sup>

Along with high impacts, serious bacterial disease is also common in LICs. A study conducted in Kenya among children admitted to the hospital found incidence estimates of community-acquired bacterial infections ranging from 505 per 100,000 children under 5 to 1457 per 100,000 children under one.<sup>16</sup>

*Haemophilus Influenzae* type b (HIB) alone is responsible for an estimated 31 cases of meningitis per 100,000 children under 5 worldwide (22) while *Streptococcus pneumoniae* (*S. Pneumoniae*) an estimated 17 cases per 100,000 children under five (14). The combination of

*S. pneumoniae* and Hib is estimated to cause five million cases of pneumoniae or sepsis along with 215,000 deaths among children under five in India.<sup>54 55</sup>

Compared to industrialized countries, the number of neonatal infections among hospital-born babies have been estimated to be 3–20 times higher in LICs including a majority of bacterial infections.<sup>56</sup>

#### *Bacteria involved in severe childhood infections in LICs*

A number of important pathogens are involved in the serious bacterial infections among children in LICs and worldwide. A study conducted between 1998 and 2002 in Kenya included blood cultured on admission from over 19,000 in-patients and found that among children under 60 days old, roughly 13% had bacteremia.<sup>16</sup> Important pathogens included *E. coli* and Group B Streptococci. Six percent of children over 60 days included in the study also had bacteremia. Important pathogens among this group included *S. pneumoniae*, non-typhoidal *Salmonella* species, *Haemophilus influenzae*, and *E. coli*.

A review of neonatal bacterial infections in LICs found that the most commonly isolated pathogens included: *K. pneumoniae*, *E. coli*, *Pseudomonas* spp., *Acinetobacter* spp., and *S. aureus*.<sup>56</sup>

#### *Evidence of Resistance among children in LICs*

While extensive data is lacking, high rates of resistance have been reported in LICs including resistance to first line treatment among major disease causing pathogens.

A review of neonatal infections in LICs found high rates of cefotaxime resistance among gram negative bacteria including 46% among *E. coli*, and 51% among *Klebsiella*. Results also suggested widespread dissemination of resistance including ESBLs. High rates of methicillin resistance were found for isolates of *S. Aureus* particularly in South East Asia with reported resistance as high as 56%.<sup>56</sup> Importantly, as much as 70% of bacteria isolated from neonatal infections in LICs would not be covered by an empiric regimen of ampicillin and gentamicin recommended by WHO. Thus, the need to adapt treatment recommendations remains a particularly pressing issue in LICs.<sup>57</sup>

A review on community acquired bacterial neonatal infections in LICs found poor susceptibility to almost all commonly used antibiotics for pathogens such as *S. aureus* and *Klebsiella* spp. Only *S. pneumoniae* exhibited good susceptibility to all antibiotics other than cotrimoxazole. However, the scarcity of data prevented drawing any firm conclusions beyond the need for more studies to address this issue in the developing world.<sup>58</sup>

#### *Effects of resistance in LICs*

The effects of bacterial resistance have been shown to lead to important negative patient outcomes in developed countries. In resource constrained LICs resistance has the potential

to have even greater impacts. Whereas in high income countries the effects of resistance may include mostly increased morbidity and economic costs, resistance in LICs may translate directly into increased mortality.<sup>59</sup> A study among children in Tanzania showed that taking treatment that was ineffective due to antibiotic resistance was an independent risk factor for death. Other factors included HIV-positive status, malnutrition, the presence of underlying infections, and the isolation of gram-negative bacilli.<sup>53</sup>

Increased incidence and severity of bacterial disease, coupled with lack of access to second-line antibiotics make LICs vulnerable to rising resistance rates. This is particularly true for children in these environments who bear the highest infectious disease burden including serious infections. Complicating factors such as malnutrition or co-infections with HIV which are common in LICs make the issue of bacterial infections and antibiotic resistance particularly problematic.

Along with increased morbidity and mortality rising costs are also a problem. Increased treatment failure and complications due to resistance may add unsustainable economic demands on already insufficient health care budgets.<sup>60</sup> The real cost of treating an infection caused by an antibiotic-resistant bacterium in LICs has been estimated at more than two times that of an infection caused by susceptible bacteria.<sup>44</sup>

#### *Worldwide resistance spread and the role of LICs*

LICs have been shown to play critical roles in the global dynamic of antibiotic resistance as both important sources of new resistance and amplifiers of existing resistance.<sup>61</sup> Besides the danger antibiotic resistance poses locally in LICs, the dissemination of resistance does not stop at borders and poses a threat to all countries regardless of income level. Like other infectious diseases, antibiotic resistance can be transmitted quickly around the globe through international travel. Over the last 20 years global travel has increased significantly particularly to and from developing economies such as India and China. This travel increase has coincided with a rapid exchange and dissemination of resistant bacteria globally including common ESBLs. CTX-M genes, one of the most common and clinically important ESBLs, are spread via mobile genetic elements and are thought to have originated in developing countries. These countries also act as reservoirs for resistance genes. A recent study of international travellers returning to Sweden found much higher levels of ESBL carriage among travellers from countries such as Egypt and India as opposed to European destinations.<sup>62</sup> The effects of travel have led to introduction of resistance into remote areas of the world without antibiotic selection pressure.<sup>63</sup> More recently, the NDM-1 gene which was first discovered in patients travelling to India has spread rapidly across the globe with developing countries and India specifically acting as a reservoir for this gene.<sup>6</sup>

While developing countries have added much to the spread of resistance, the global nature of resistance makes this a multidirectional problem. The *K. pneumoniae* carbapenemase (KPC) is an example of this. Strains of KPC were originally detected in North Carolina, USA in 1996 and are now found in high levels among populations in Israel, Columbia, and China.<sup>5</sup> A major concern in this dynamic is that once new resistance has become introduced into developing countries, the specific risk factors leading to resistance dissemination in these

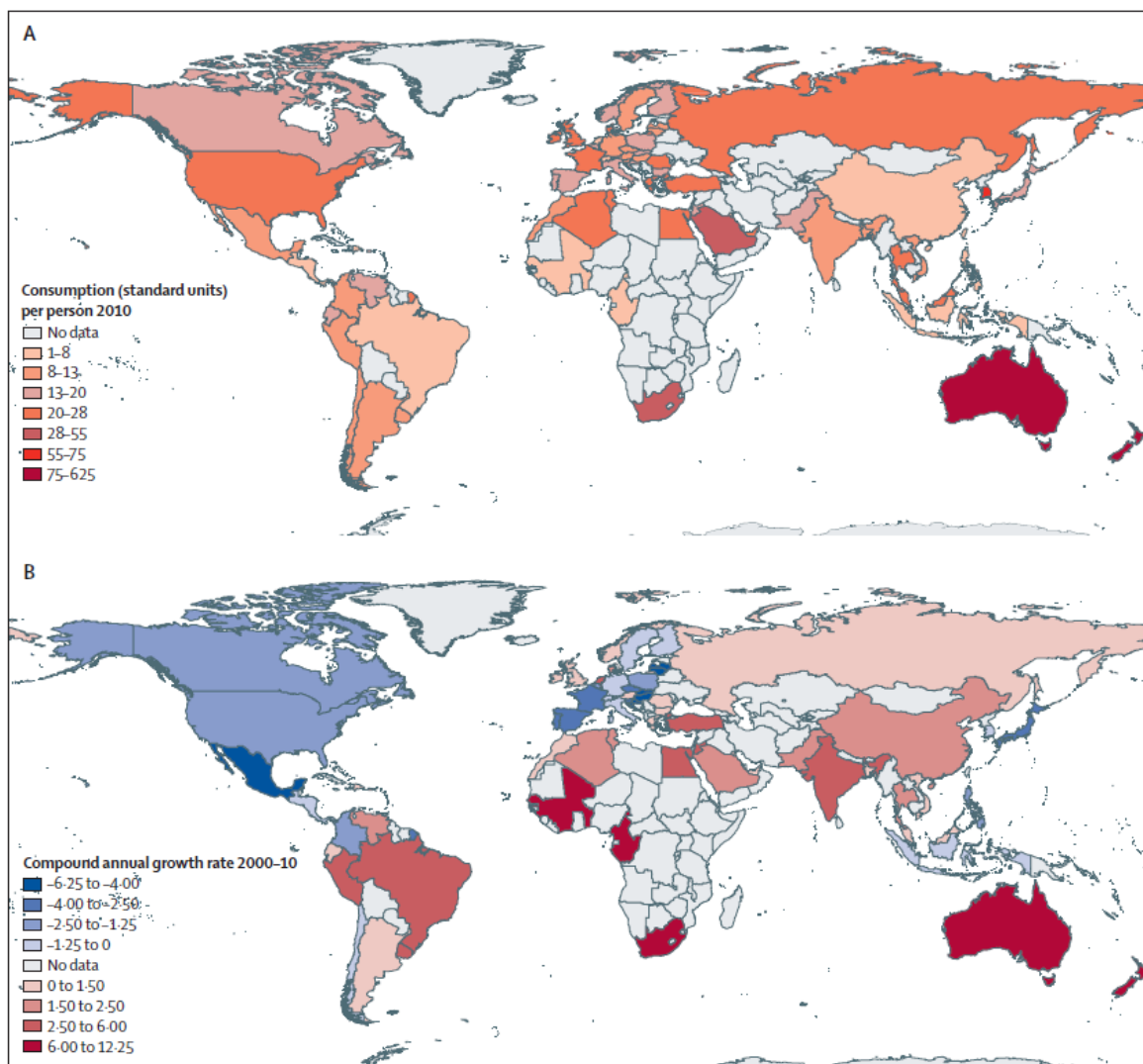
countries will greatly amplify its local spread transforming it into a reservoir for further global spread.

Solutions to the spread of resistance must include global solutions including both high and low-income countries.

#### 4 - Antibiotic consumption

##### *Antibiotic consumption in humans*

The exact contribution of human use versus use in animals or environmental exposure in the rise in resistance is still unknown. However, human consumption is clearly associated with a rise in resistance among human pathogens.<sup>45</sup> As global antibiotic resistance rates are growing, so is global antibiotic consumption, particularly in emerging economies.<sup>64</sup> (See Figure 8). This increasing exposure constitutes a global pressure for the development of resistant bacteria.



**Figure 8.** Consumption of antibiotics in 2010 (A) and annual growth rate in antibiotic consumption from 2000 to 2010 (B). Source [64]

In addition to a general rise in antibiotic consumption, certain types of exposure may represent a higher risk of resistant development. These include use of wide-spectrum agents, use of poor quality or counterfeit drugs with non-lethal doses, and prescription non-compliance. Ironically, rising antibiotic resistance has also led to examples of higher use of wide-spectrum antibiotics creating a vicious circle.<sup>65</sup>

#### *Antibiotic use in LICs*

Along with high rates of infectious disease, antibiotic usage and particularly misuse in LICs is a major risk factor for the development and dissemination of antibiotic resistance in these countries. Antibiotic usage in LICs is poorly understood due to the lack of surveillance systems and the multitude of antibiotic sources available in LICs.<sup>55</sup> Data is needed however, in order to develop systems to control unnecessary antibiotic use, combat resistance, and optimize access and use for those who need it.

Data that do exist show that antibiotic consumption is high in LICs and rapidly rising particularly in former LICs with growing economies. In a review of pharmacy and hospital databases, data showed that consumption of antibiotic drugs worldwide increased by 36% from 2000 and 2010. Three quarters of this increase was due to increases in Brazil, Russia, India, China, and South Africa. Importantly, there was increased consumption of carbapenems (45%) and polymyxins (13%), two last-resort classes of antibiotic drugs.<sup>64</sup> Data also show increasing use of broad-spectrum antibiotics.<sup>19</sup>

#### *Lack of public health systems*

One significant factor leading to high rates of antibiotic usage is the lack of public health infrastructure in many LICs. Without systems in place to ensure proper sanitation, vaccination, or other public health measures, the increased burden of infectious disease is often met by an increased use of antibiotics.<sup>41</sup> Prophylactic use of antibiotics in the absence of disease is one example of this dynamic common in LICs.<sup>66</sup> India, the world's largest consumer of antibiotics per capita in 2010 lagged behind countries such as Brazil, China, and Indonesia in public health system indicators showing markedly lower levels of immunization rates and access to sanitation facilities.<sup>67</sup> This combination of disease spread and high antibiotic use due to poor public health is a leading factor in the high levels of Carbapenem resistance observed in India.<sup>64</sup>

#### *Medical antibiotic misuse*

Inappropriate or unnecessary antibiotic use is common in medical practice in LICs. The form of misuse can vary depending on context as LICs often contain both "developed" and "non-developed" areas where populations, access to health care, and health care provider training can differ greatly.<sup>19</sup> In higher-income areas, access to hospitals and trained doctors is possible. In these settings medical antibiotic misuse mirrors that of developed countries where consumption may be a result of patient pressure for antibiotics, or a prescription for non-bacterial illness such as viral upper respiratory infections.<sup>48</sup> There is also a general notion common across all populations and income levels including LICs that antibiotics are

not harmful and even an unnecessary prescription will not harm the patient. Patient demand can therefore play a strong role in prescribing.<sup>68</sup>

In the less developed areas where access to quality health care is limited, misuse is more likely to come as a result of lack of training or lack of diagnostic tools. Well trained doctors in LICs are scarce and poor training has been associated with higher levels of antibiotic prescribing.<sup>48</sup> Furthermore, information that doctors do possess may come directly from pharmaceutical companies who have a financial interest in antibiotic sales.<sup>7</sup> Poorly formed providers are more likely to choose the wrong antibiotic, wrong duration, or not properly explain the importance of finishing courses of antibiotics leading to low compliance.<sup>48</sup>

Lack of diagnostic testing is also problematic in low-income areas and is linked to incorrect antibiotic prescription.<sup>55</sup> In cases of uncertainty, doctors are more likely to rely on antibiotic prescriptions and particularly wide-spectrum or last-line antibiotics. Many South Asian hospitals lacking diagnostic testing use carbapenems, often reserved as a last-line drug, as first line treatment.<sup>41</sup> Because of these issues one antibiotic course taken in an LIC does not necessarily equal one taken in a high-income country in terms of risk of resistance development and spread.

Overprescription in LICs may also be a result of financial incentives. Indeed, many doctors or hospitals in LICs are paid to prescribe antibiotics or rely on the sale of medication including antibiotics as a source of income.<sup>64, 69</sup>

#### *Patient misuse / non-prescription use*

Antibiotics in LICs may come from multiple sources including those outside of the medical sphere and available without a prescription. These sources might include markets or unlicensed street vendors, or even pharmacies. These sources of non-prescribed antibiotics can account for as much as 100% of antibiotic consumption in certain populations.<sup>70</sup>

Unsurprisingly, self-medication with antibiotics has a number of negative characteristics. It has been linked to unnecessary use, overuse, wrong molecule choice, and inadequate treatment durations which increase the risk for resistance development and spread. The purchase of small samples for example, is exceedingly common among those who buy without prescription.<sup>7</sup>

Non-prescribed antibiotics mean that the antibiotic 'advisor' is often not a medical professional and false beliefs about the usefulness of antibiotics can play a powerful role in shaping usage patterns and pushing unnecessary consumption.<sup>7, 69</sup>

Many patients in a Chinese survey believed that antibiotics were a cure-all to be used in almost any situation. These beliefs may push patients to request and consume antibiotics increasing self-medication.<sup>71</sup>

Even when obtaining non-prescribed antibiotics from traditional sources including pharmacies, courses dispensed are often unnecessary and the choice of drug incorrect. Furthermore, pharmacists or pharmacy attendants providing non-prescription drugs rarely explain the proper duration and patient compliance with full courses is poor.<sup>48</sup>

#### *Consequences of non-prescription use and poor antibiotic prescription*

Because of high risk for the development and spread of antibiotic resistance associated with non-prescription use, high rates of antimicrobial-resistant bacteria have been observed in communities with frequent non-prescription use.<sup>70</sup>

Other safety issues associated with non-prescription use include adverse reactions and the masking of underlying infectious processes.<sup>70</sup>

Non-prescription sales of antibiotics in markets or by unlicensed vendors is also related to poor quality antibiotics.<sup>70</sup>

### *Poor quality antibiotics*

Poor quality antibiotics can fall into one of three categories. The first category includes antibiotics with normal levels of antibiotic activity which due to time or poor storage conditions have lost their antibacterial activity. In LICs, antibiotics are often stored in poor conditions including extreme heat and/or humidity which may reduce effectiveness of the active ingredient of these pills. Pills are also often taken out of packages to be sold individually further exposing them to disruptive elements.<sup>7</sup> A second category of poor quality antibiotics are those considered as “substandard”. Substandard antibiotics are defined by the WHO as “a product with genuine packaging with incorrect quantity of ingredient” which is not deliberate.<sup>72</sup> The poor quality found in these antibiotics comes from initial poor manufacturing without the intention to deceive. Lastly, poor quality antibiotics may be considered as counterfeit. WHO defines counterfeit pharmaceuticals as “a product that is deliberately and fraudulently mislabeled with respect to identity and/or source”. These can include “products with correct ingredients, wrong ingredients, without active ingredients, with incorrect quantity of active ingredient or with fake packaging.”<sup>73</sup> All type of poor antibiotics may be purchased and distributed by pharmacists or other distributors either knowingly or unknowingly in LICs.<sup>74</sup>

Unfortunately, these three categories of poor quality drugs are common in LICs as governments often do not have the capacity to enforce drugs standards and drugs often come from a number of different sources including various laboratories or even donations.<sup>66</sup>

Numerous examples have been found of high rates of poor quality antibiotics in LICs. A drug study in Cambodia including antibiotics found that 13% of the 230 drugs sampled failed quality testing. 10% of drugs were considered counterfeit and 3% were considered substandard.<sup>75</sup>

In India, fake drugs are estimated to represent 13–30% of the pharmaceutical market.<sup>76</sup> In Myanmar and Vietnam 35% of chloramphenicol samples, 19% of co-trimoxazole samples, and 15% of ampicillin/amoxicillin samples failed pharmacopoeia tests in a WHO led study in the region.<sup>72</sup> A study purchasing and testing antibiotic from local pharmacies in Nigeria found that 55% of all antibiotics tested were outside British pharmacopoeia limits.<sup>77</sup> Because of the sheer number of antibiotic courses consumed worldwide, even a small percentage of poor quality antibiotics may result in millions of individuals being affected.<sup>76</sup>



## Research questions and objectives

Antibiotic resistance is a global threat particularly in LICs. The first step in responding to this threat is quantifying the burden of resistance. These critical data are necessary for a number of important objectives including allowing researchers to situate the problem in the context of major global health issues such as HIV, malaria, and tuberculosis. Large international financing systems have been put in place for these issues and substantial progress has been made in part due to better data. Data are also necessary to allow for a baseline measurement to determine changing resistance or burden patterns as well as facilitate the measurement of intervention impacts. Understanding which pathogens are involved in bacterial infections in LICs and their resistance profiles can help in updating treatment guidelines. Because of health care access and treatment seeking patterns in LICs, information on the community level burden is particularly important. The first objective of this work was to quantify the burden of antibiotic resistance in the community among children under two in LICs. This burden included determining incidence of community-acquired invasive bacterial infections among children under two in LICs as well as determining the pathogens involved in these infections and their antibiotic susceptibility based on published scientific literature.

Along with determining the burden of resistance in LICs, techniques responding to this issue are needed. A number of tools have proven to be effective in responding to the threat of antibiotic resistance threat. The majority of these tools rely on changing antibiotic usage patterns through interventions such as awareness campaigns, doctor trainings, or even technological methods. Choosing between these interventions and identifying targets necessitates data on antibiotic consumption patterns and related factors. These data however can be difficult to obtain in LICs where sources of antibiotics are numerous and few surveillance systems exist. The second objective of this work was to review current techniques used to measure antibiotic consumption in LICs from published literature and propose an adapted solution to this issue.

Using this adapted solution, the third objective was to investigate patterns of antibiotic consumption and related factors among children under two in two African LICs. This investigation was designed to fill data gaps on consumption in LICs and respond to questions necessary to implement techniques to measure and adapt antibiotic consumption among these populations.

### *Context*

The work was undertaken in the context of a large international cohort study, the BIRDY program. The BIRDY program seeks to estimate the burden and understand the development and transmission of antibiotic bacteria among children in LICs. The study recruits pregnant women living in defined geographic areas and follows their child from birth to two years by using both active and passive follow-up. Resistant bacteria are identified through systematic sampling including during episodes of infectious disease. The main goal is to assess the burden of severe childhood and neonatal infections caused by antibiotic resistant bacteria in low-income countries. The study will also assess the economic burden of

antibiotic resistant bacterial infections in LICs and help to set public health priorities and guide public health measures necessary to combat resistance. The study is currently active among sites in the Institut Pasteur International Network including Madagascar, Senegal, and Cambodia.

## Chapter 2 – Community burden of resistance among children in LICs

### Introduction

Reliable data on the burden of resistance in LICs is a necessary first step in controlling resistance and mitigating its effects.<sup>78</sup> Importantly, these data are needed for tracking resistance trends and updating treatment recommendations based on local aetiology and resistance profiles. Information is also needed in order to generate the political will to deal with this issue and set international priorities.

Because of differences in health care seeking and access, an understanding of the population-level burden of antibiotic resistance in the community in LICs is critical. This understanding includes: incidence rates, responsible pathogens, and resistance profiles.<sup>79</sup> These data are important particularly for children in LICs who bear the highest infectious disease burden. However, obtaining the components necessary to estimate these data can be difficult and a number of methodological and statistical difficulties must be taken into account.<sup>65</sup> The calculation of incidence rates for example may be difficult in these settings as estimates for both the number of cases and the size of the reference population can be biased or incomplete.

Reports of resistance in LICs often present resistance profiles for bacterial isolates from a specific lab or labs. Relying on these reports to determine incidence numerators may introduce bias as lab reports often lack epidemiological data needed to link results to specific populations and to allow for strict case definitions. These missing epidemiologic data might include the type of sample taken, the clinical diagnosis, and patient characteristics. Without knowledge of these data it is impossible to determine the number of disease cases for a given population. These difficulties can also apply to bacterial infections in general regardless of presence of resistance.

Laboratory quality issues in LICs can affect the quality of data and the number of cases when working with lab reports. A WHO report in 2014 compiled data on resistance worldwide and noted that labs used various detection methods along with heterogeneous definitions of resistance which hurt comparability both within and among countries.<sup>1</sup> Along with a lack of uniform methods, untrained staff, common in many LICs, may lead to contaminated or biased results and quality control remains problematic.

Determining a reference population to be used as an incidence denominator from laboratory studies can also be difficult as lab samples may come from numerous sources including patients from various geographic areas or lower-level labs.

Calculating incidence rates from studies examining resistance from the patient level can also be problematic in LICs. Determining the number of community-acquired infections based on studies recruiting patients in the hospital in LICs may be imprecise as not all the local population may have access to the health care system meaning that many infectious episodes are missed. Along with lack of access, high usage of traditional medicine or home care mean that a majority of populations in some LICs do not seek care in hospitals.<sup>7</sup> A study in India showed that Medical advice was sought for just under one-third of children with symptoms of pneumonia.<sup>55</sup> Additionally, patients admitted to the hospital may have been treated with antibiotics prior to admission which can lower the chances of a positive blood

culture and increase the proportion of antibiotic resistant bacteria isolated. Determining inclusion criteria in these contexts is difficult and biases may affect results.

Like lab studies, determining the size of the source population for hospital studies may be difficult particularly due to lack of population data.

A review of pathogens associated with community-acquired neonatal sepsis in LICs conducted by Zaidi et al. found that *Klebsiella* species, *E. coli*, and *S. aureus* were major pathogens in the first week of life while *S. aureus*, group B streptococcus, *S. pneumoniae* and non-typhoidal *Salmonella* species predominated after the first week up to 90 days.<sup>80</sup> While important data, these findings were based on children presenting at hospitals and the range of pathogens identified is probably different than that of infants and young children sick or dying at home, or in lower-level structures.

One solution to these issues is to include community recruitment of patients. With active community level recruitment the source population is more easily defined and the chance of missed cases or biased samples is diminished. An investigation of bacterial disease in young children in Bangladesh included home visits from health workers.<sup>81</sup> This study reported bacteraemia rates of 3 per thousand live births, with a pathogen profile slightly different than that found by Zaidi et al., with *S. aureus* being the principal pathogen (30%).

In addition to these considerations, variations within the country must be taken into account when estimating global burden. In LICs there can be wide variations in socioeconomic status, lifestyles, health care access, health care seeking behaviour, and other factors related to antibiotic resistance between urban and rural areas. This dynamic should be investigated when addressing health questions in LICs including ATB resistance.

To investigate the evidence for the burden of bacterial infection and antibiotic resistance among young children in the community in LICs, we examined published literature on these topics among children under two. Evidence was then analysed from an epidemiological perspective including potential biases.

## Methods

We searched PubMed for studies published in 2000 or later (last search April 30th, 2014). To overcome a potential lack of studies dealing with both topics simultaneously, our search was divided into two branches including 1) community-acquired bacterial infections among infants in LICs (BI), and 2) antibiotic resistance among community-acquired infections in LICs (AR). LICs were identified as “least developed”, “other low income”, or “lower middle income” by the World Bank or as “low human development” or “medium human development” by the United Nations.<sup>64, 65</sup> We also screened reference lists of relevant articles for further publications.

Before paper selection, duplicates from the BI and AR lists were eliminated. Detailed PubMed search and inclusion criteria are shown Table 1. Abstracts were screened for full text reading by two of three reviewers and a third reviewer was called upon as needed. Information was extracted from selected articles including: study year, study location, urban vs. rural location, hospital recruitment vs. other, community or nosocomial infections, study

design and microbiology methods (bacterial isolation methods and antibiotic susceptibility testing). Articles were then re-evaluated by two reviewers as before.

An effort was made to restrict the selection to community-acquired infections, and all articles presenting exclusively nosocomial infections were eliminated. Results were divided into two periods: neonatal, and children under two not including the neonatal period.

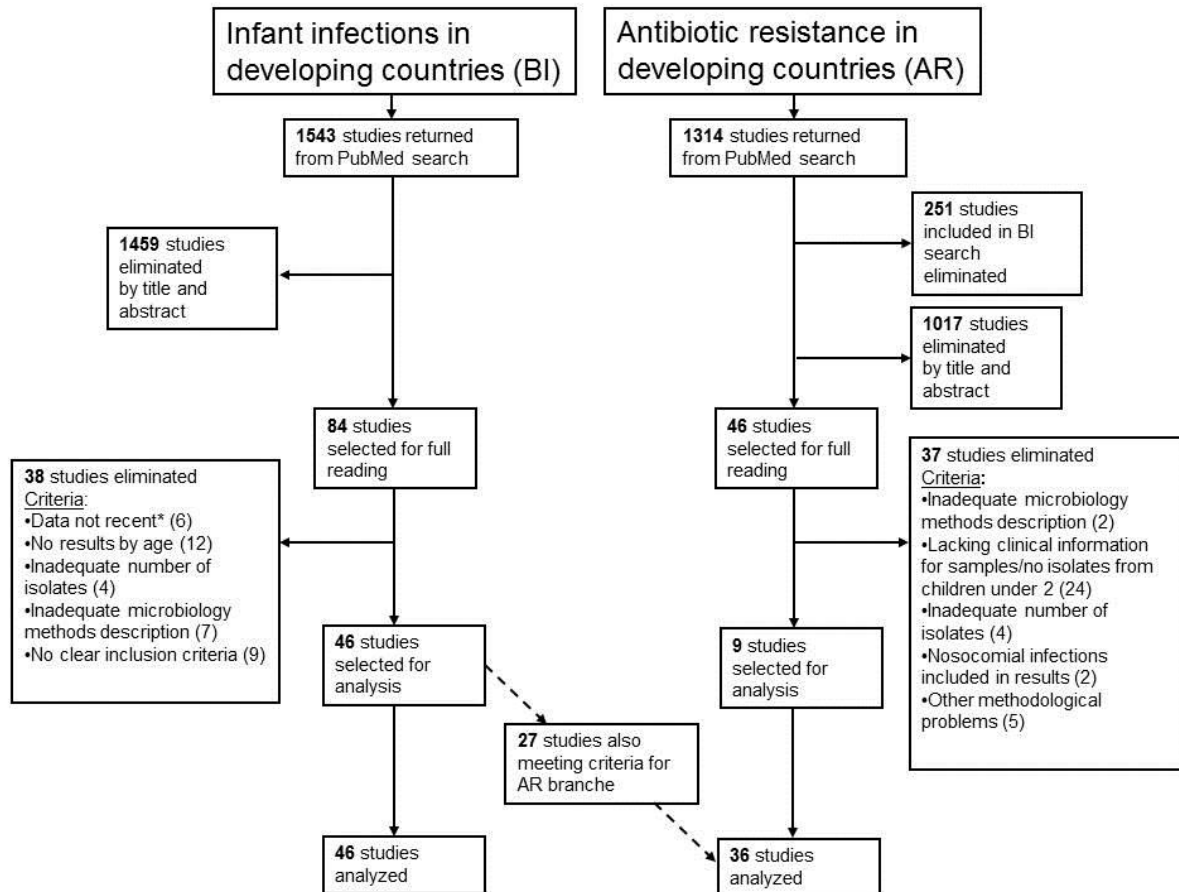
Disease incidence estimated including children over two were reported when incidence estimates limited to children under two was unavailable and data presented in the article showed that the majority of disease cases occurred before the age of two.

**Table 1.** Search strategy and selection criteria for neonatal and young childhood infection and bacterial resistance articles in low-income countries (2000-May 2014)

<b>Search strategy</b>	
<p>For the BI search, each LIC was cross-linked with search terms “Bacterial Infections” OR “Sepsis” OR “bacter*” AND “epidemiology”. For the AR search, each LIC was cross-linked with “Drug resistance, bacterial” OR (“antibiotic resistance” AND “bacter*”) AND “epidemiology”. Both searches were restricted to English language articles and the BI search was restricted to the PubMed “infant” age category (birth-23 months). Both searches were also limited by excluding the keywords and MeSH terms “travel”, “candida”, “HIV infection”, “leprosy”, “tuberculosis”, “tetanus”, “malaria”, “cholera”, or “helicobacter”. The BI search was further limited by excluding the keywords “immunization”, “immunization program”, and “vaccination”.</p>	
<b>Inclusion criteria</b>	
<b>Infant infection search (BI)</b>	<b>Resistance search (AR)</b>
<ul style="list-style-type: none"> <li>• Information on bacterial infections including either etiology or disease burden/incidence</li> <li>• Community acquired infections</li> <li>• Methodologically sound including clear inclusion criteria</li> <li>• Sound microbiological methods/citation of guidelines used</li> <li>• Neonatal specific information presented</li> </ul>	<ul style="list-style-type: none"> <li>• Bacterial pathogens</li> <li>• Community acquired infections</li> <li>• Information on antibiotic resistance profile of pathogen (proportion resistance/susceptible, etc.)</li> <li>• Sound microbiological methods/citation of guidelines used</li> <li>• Information on pathogen source and/or clinical information</li> </ul>
<b>Exclusion criteria</b>	
<b>Both Branches</b>	
<ul style="list-style-type: none"> <li>• Review study or expert opinion</li> <li>• Outside of developing country list</li> <li>• Purely nosocomial infections or no possibility to extract only community acquired infections from data</li> <li>• Pathogen not in the restricted list, including <i>Neisseria gonorrhoeae</i>, <i>Campylobacter</i>, <i>Helicobacter</i>, <i>Vibrio</i>, <i>Clostridium tetani</i>, or any Mycobacteria</li> <li>• Obvious methodological weakness including sampling methods</li> <li>• Insufficient number of isolates/insufficient number of isolates for follow-up period (minimum 10 isolates per year)</li> <li>• Data collection done principally before 2000</li> </ul>	
<b>Infant infection search (BI)</b>	<b>Resistance search (AR)</b>
<ul style="list-style-type: none"> <li>• Ages outside of range of interest or ages of interest non-extractable</li> </ul>	<ul style="list-style-type: none"> <li>• Insufficient epidemiological info on sample source/patients/no. of bacteria isolated from neonates or children under 2</li> </ul>

## Results

Of the 1543 and 1314 studies returned from the BI and AR searches, 84 and 46 were selected for full reading, respectively (Figure 9). Ultimately, 46 BI studies and 9 AR studies were retained for a total of 55 studies included in the final analysis. Of the 46 BI studies selected, 27 also met the selection criteria for inclusion in AR studies and thus a total of 36 articles were included in the resistance analyses. 21 studies, including 20 BI and 1 AR, had information regarding neonatal infections or resistance. Two studies had both neonatal and under-two information.



**Figure 9.** Flowchart of literature search including both the infection incidence and antibiotic resistance branches.

\*Data was considered not recent if data collection took place principally before 2000.

### **Neonatal results**

A majority of neonatal studies came from Sub-Saharan Africa (n=10) or the Indian subcontinent (n=8) (Table S1 Appendix).

Of the 21 neonatal articles analyzed, 17 used either a cross-sectional or surveillance study design.<sup>82-98</sup> Four studies were conducted in rural settings<sup>81, 89, 93, 96</sup> with the remaining 17 conducted in urban settings.

Nineteen of 21 studies recruited participants in large district or university hospitals. Only two studies used active community recruitment.<sup>81, 99</sup> Sixteen of the 17 urban studies recruited uniquely at large hospitals.

Thirteen of the 20 neonatal BI articles reported bacteremia rates. Excluding one study from Georgia with an isolation rate of 67%<sup>86</sup>, isolation rates ranged from 5.8% to 48% (median=22.4%). No difference in rates was noted between urban and rural studies.<sup>81, 83-87, 90-93, 95-98, 100, 101</sup> Only one study reported bacterial isolation rates from cerebrospinal fluid cultures, with a 4% positivity rate.<sup>96</sup> Of all BI articles, two reported antibiotic use prior to blood culture, with 16% and 67% exposure rates, respectively<sup>81, 82</sup> and two studies excluded those with prior antibiotic exposure.<sup>87, 88</sup>

### *Laboratory methods and antibiotic susceptibility testing guidelines*

Two of the 19 neonatal BI studies with blood cultures reported taking two blood samples from patients.<sup>86, 87</sup> Of these 19 studies, 13 reported blood quantity taken.<sup>81-85, 87-91, 93, 95, 97</sup> Overall, ten of 12 studies retained in the AR analysis cited the use of established guidelines for resistance interpretation<sup>83, 84, 91, 92, 96-101</sup> with the majority referring to the Clinical and Laboratory Standards Institute (CLSI) methods. Two studies cited external quality control measures<sup>81, 96</sup> and only Darmstadt et al.<sup>81</sup> sent samples to a reference lab for confirmation.

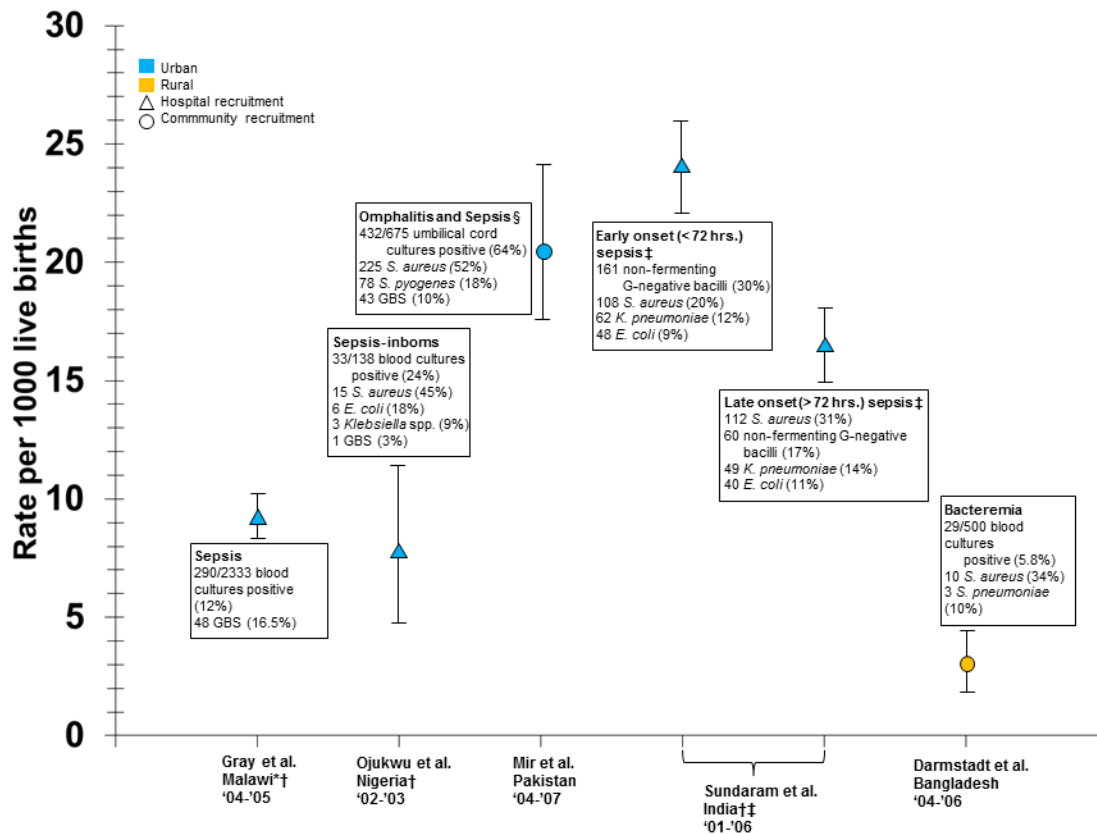
### *Bacterial infection incidence estimates and pathogens*

Of the 20 studies of BI in neonates, five reported an incidence rate for invasive bacterial infection (Figure 10).<sup>81, 90, 95, 99, 100</sup> Incidence rates per 1000 live births ranged from 2.9 (95% CI 1.9–4.2) for bacteremia among neonates in Bangladesh<sup>81</sup> to 24 (95% CI 21.8–25.7) for early onset sepsis (<72 hours) in India.<sup>95</sup> Along with Darmstadt et al.<sup>81</sup>, Mir et al.<sup>99</sup> used community recruitment and reported an incidence of 20.4 (95% CI 17.3–24.0) in Pakistan for neonatal omphalitis with sepsis.<sup>99</sup> Studies based on hospital recruitment reported sepsis incidence rates of 9.2 (95% CI 8.2–10.3) in Malawi<sup>100</sup> and 7.8 (95% CI 4.4–11.5) in Nigeria<sup>90</sup> per 1000 live births. A third study using hospital recruitment in India reported rates of 24 (95% CI 21.7–25.7) for early onset sepsis (<72 hours), and 16 (95% CI 14.0–18.1) for late onset sepsis (>72 hours).<sup>95</sup>

Among the 20 neonatal studies reporting full bacterial etiology, *S. aureus* was reported in all but two, accounting for 3% to 63% (median=32.5%) of pathogens. Other common pathogens included *Klebsiella* spp., reported in 16 studies and ranging from 8% to 66% (median=22%) of pathogens, and *E. coli*, reported in 14 studies and ranging from 5% to 23% (median=12%) of isolated pathogens. Sundaram et al.<sup>95</sup> reported that non-fermenting Gram-negative bacteria were the most common isolates in early-onset sepsis (first 72 hrs. of life) representing 30% of isolates, followed by *S. aureus* (20%), *K. pneumoniae* (12%), and *E. coli* (9%), whereas *S. aureus* predominated in late-onset sepsis (31%), followed by non-fermenting Gram-negative bacteria (17%), *K. pneumoniae* (14%), and *E. coli* (11%)<sup>95</sup>. Blomberg et al.<sup>82</sup> and Mhada et al.<sup>83</sup> reported results for early-onset sepsis defined as 0-7 days. Both studies found early onset sepsis was due primarily to *Klebsiella* spp. (33% and 32% respectively), *S. aureus* (29%, 11%) and *E. coli* (19%, 11%) with late-onset sepsis, defined as 7-28 days and 7-30 days respectively, due mostly to *S. aureus* (55%, 16%), *Klebsiella* spp. (23%, 23%), and *E. coli* (18%, 10%).

Twelve neonatal studies reported Group B *streptococcus* isolates. Percentages were low overall, representing between 1% and 20% (median=4.5) of blood culture isolates in eleven studies.<sup>81-83, 85-87, 90, 93, 96, 97, 99, 100</sup>





**Figure 10.** Incidence and aetiology of neonatal sepsis/bacteremia for 1000 live births in developing countries.

Sources;<sup>81, 90, 95, 99, 100</sup> The figure shows point estimates, 95% confidence intervals, and aetiology of neonatal infections along with recruitment strategy and setting. Studies represented in blue were conducted in urban areas. Studies represented in orange were conducted in rural areas. Studies represented by a triangle used hospital recruitment. Studies represented by a circle used community recruitment.

GBS (Group B streptococcus).

\*The Incidence estimate was calculated from the number of isolates and births presented.

†CI estimated from data presented in the article.

‡The two estimates were taken from the same study.

§ Each case had both omphalitis and clinically defined sepsis.

### Antibiotic resistance

The 12 studies with relevant antibiotic resistance information for selected neonatal pathogens are presented in Table 3. Seven of the 12 studies were conducted before 2008. Resistance to penicillin/ampicillin among Gram-negative bacteria (not including *Klebsiella* spp.) ranged from 55% (95% CI 26%-84%) among *E. coli* isolates in Georgia<sup>86</sup> to 100% among *E. coli* isolates in Uganda.<sup>87</sup> Resistance to gentamicin among Gram-negative bacteria ranged from 0% for *Pseudomonas* and *E. coli* in Pakistan<sup>99</sup> and for *K. pneumoniae* in Nepal<sup>92</sup> to 100% for *K. pneumoniae* in India.<sup>97</sup> Among Gram-negative bacteria, resistance to third generation cephalosporins (3<sup>rd</sup> GC) ranged from 6% for *E. coli* isolates in Uganda<sup>87</sup> to 97% among *K. pneumoniae* isolates in India.<sup>97</sup> Only two studies tested for ESBL production in *Enterobacteriaceae*. One reported ESBL production in 87% of *Klebsiella* spp. isolates, 73% of *Enterobacter* spp. isolates, and 65% of *E. coli* isolates.<sup>98</sup> The second found 32% ESBL

production among *K. pneumoniae* isolates.<sup>97</sup> Resistance of *S. aureus* isolates to methicillin was reported in five studies and ranged from 0% to 67%.<sup>86, 91, 96, 99, 101</sup>

**Table 2.** Antibiotic resistance of bacteria isolated from invasive neonatal infections in developing countries (2000-May 2014)

Study, year	Location, Setting	Pathogen	Resistant % (95% CI)			
			Penicillin/ampicillin	Gentamicin	3rd generation cephalosporins	% ESBL*
Mugalu et al. <sup>87</sup> 2002	Uganda, urban	17 <i>E. coli</i> †, ‡	100§	29 (7-51)	6 (0-17)	--
		7 Group B <i>Streptococcus</i> †	14 (0-40)	57 (20-94)	--	NA
Gray et al. <sup>100</sup> 2004-2005	Malawi, urban	57 Group B <i>Streptococcus</i> †	0§	--	0§	NA
Shitaye et al. <sup>91</sup> 2006-2007	Ethiopia, urban	30 <i>S. aureus</i>	67% (50-84) resistance to meticcillin			NA
Talbert et al. <sup>96</sup> 2001-2009	Kenya, rural	48 <i>Acinetobacter</i> spp.†,	56 (42-70)	27 (14-39)	35 (22-48)	--
		49 <i>K. pneumoniae</i> †	96 (91-100)	49 (35-63)	43 (29-57)	--
		39 <i>S. pyogenes</i> †	0§	--	--	--
		41 <i>E. coli</i> †	78 (65-91)	10 (1-19)	17 (5-29)	--
		55 <i>S. aureus</i> †	0% resistance to meticcillin§			NA
Mhada et al. 2009-2010	Tanzania, urban	22 <i>Klebsiella</i> spp.	100§	77 (57-90)	18 (7-39)	--
		41 <i>E. coli</i>	93 (69-99)	43 (21-67)	14 (4-40)	--
Kruse et al. <sup>101</sup> 2009-2010	Vietnam, urban	78 <i>Klebsiella</i> spp. †,	100§	85 (75-91)	86 (76-92), 71 (60-79) ¶	--
		58 <i>Acinetobacter</i> spp. †,	85 (73-92)	50 (38-62)	82 (71-80), 71 (58-81) ¶	--
		21 <i>E. coli</i> †	86 (65-95)	57 (37-76)	58 (37-76), 42 (24-63) ¶	--
		16 <i>Enterobacter</i> spp. †,	93 (72-99)	62 (39-82)	62 (39-82), 50 (28-72) ¶	--
		6 <i>Pseudomonas</i> spp. †,	100§	48 (19-81)	83 (44-97), 33 (10-70) ¶	--
		11 <i>S. Aureus</i> †	55% (28-79) resistance to meticcillin			--
Jain et al. <sup>98</sup> 2001-2002	India, urban	86 <i>Klebsiella</i> spp.	100§	89 (82-96)	63 (53-73), 49 (38-60) ¶	87 (80-94)
		80 <i>Enterobacter</i> spp.	100§	93 (87-99)	64 (53-75), 54 (43-65) ¶	73 (63-83)
		49 <i>E. coli</i>	96 (91-100)	90 (72-98)	65 (52-78), 41 (27-55) ¶	65 (52-78)
Zakariya et al. <sup>97</sup> 2004-2006	India, urban	33 <i>K. pneumoniae</i> †	--	100§	97(85-99), 97(85-99) ¶	32 (20-50)
Mir et al. <sup>99</sup> 2004-2007	Pakistan, urban	52 <i>Pseudomonas</i> spp. †,	--	0§	--	--
		12 <i>Klebsiella</i> spp.†,	--	8 (0-23)	8 (0-23)	--
		9 <i>E. coli</i> †	--	0§	11 (0-31)	--
		304 <i>S. aureus</i> †	4% (2-6) resistance to meticcillin			--
Gyawali et al. <sup>84</sup> 2009-2010	Nepal, urban	82 Enterobacteriaceae ?	94 (87-97)	70 (59-78)	83 (73-90), 79 (69-87), 87 (78-92) ¶	--
		21 <i>Pseudomonas</i> spp.	--	37 (21-59)	47 (28-68), 71 (50-86), 67 (45-82) ¶	--
		30 <i>Acinetobacter</i> spp.	--	56 (39-73)	53 (36-70), 65 (46-78), 73 (56-86) ¶	--
Shresta et al. <sup>92</sup>	Nepal, urban	8 <i>K. pneumoniae</i>	38 (14-69)	0§	--	--

2011-2012

Macharashvili et al. <sup>86</sup>	Georgia, urban	45 <i>Klebsiella</i> spp. †,‡,	98 (94-100)	11 (2-20)	16 (5-27), 18 (7-29) ¶	--
2003-2004		11 <i>E. coli</i> †,‡	55 (26-84)	18 (0-41)	9 (0-26), 9 (0-26) ¶	--
		15 <i>S. aureus</i>	40% (15-65) resistance to meticillin			

\*Extended-spectrum beta-lactamase.

† Results were presented for sensitivity, resistance calculated as 100 minus % sensitive.

‡ Penicillin results based on amoxicillin.

§ Calculation of a CI was impossible.

|| Pathogens marked spp. means no further characterization was presented.

¶ Multiple 3GCs were tested.

## ***Children under Two***

Twenty-seven studies treating “infant infections” and eight studies treating “antibiotic resistance” among children from 1 month to 2 years old were retained for a total of 36 studies included in the final analysis (Figure 9). Of the 27 BI branch results, 19 studies also met the selection criteria for the AR branch and thus a total of 27 articles were included in the resistance analyses.

Overall, 33 of the 36 studies were conducted prior to 2008.

Like neonatal studies, the majority of all studies came from either Sub-Saharan African (n=17) or the Indian subcontinent including Bangladesh, Nepal, and Pakistan (n=13). Five studies came from Southeast Asia, with one study coming from Central America. None of the studies were from either South America or the Middle East (Table 3).

### *Design, recruitment settings, and study topics*

Study design, recruitment settings, and study topics can be seen in Table 3. Out of all articles, 31 used either a cross-sectional or surveillance study design.<sup>82, 93, 102-130</sup> Four studies used a prospective cohort design,<sup>131-134</sup> one a case-control design.<sup>135</sup> Only 11 of all studies were conducted in rural areas or included rural areas.<sup>93, 103, 104, 107, 110, 114, 121, 122, 124, 128, 132</sup> Of the studies conducted in both urban and rural environments only one<sup>114</sup> presented results broken down by area allowing for comparison of results by this factor.

The majority of all studies (22 of 36) used large hospitals, including district or university hospitals for recruitment. Eight of the studies used hospitals or health centers of various sizes.<sup>103, 105, 114, 117, 123, 126, 128, 130</sup> Only six studies used any form of active community recruitment, either as the sole means of recruitment (n=4)<sup>104, 132-134</sup> or in addition to recruitment at the hospital (n=2).<sup>102, 131</sup> Out of the 25 urban studies, 20 recruited uniquely at large hospitals.

Among the most common invasive bacterial infections studied were sepsis (or bacteremia) (n=9), meningitis (N=10), and invasive pneumococcal disease (n=7).

### *Bacterial isolation rates*

Ten of the 27 infant infection articles reported isolation rates of pathogens from blood cultures. This rate ranged from 2.5% to 19% (median=5.7%) for the six studies conducted in urban areas<sup>82, 108, 113, 129, 131, 134</sup> and from 2% to 39% (median=14%) for the four studies conducted in rural areas respectively.<sup>93, 104, 107, 124</sup> The number of samples taken was reported by only three studies.<sup>82, 93, 124</sup> No studies reported taking two or more blood samples from patients.

Among the six urban studies reporting, cerebrospinal fluid isolation rates varied between 3% and 45% (median=13%).<sup>105, 106, 109, 117, 129, 130</sup> One rural site reported an isolation rate of 7%<sup>122</sup> while two mixed sites (both urban and rural) reported isolation rates of 7% and 25%.<sup>114, 121</sup>

Among the eight studies reporting, prior antibiotic use ranged from 10% to 67%.<sup>82, 102, 105, 120, 125, 130, 133</sup>

#### *Laboratory methods and antibiotic susceptibility testing guidelines*

Overall 14 out of 27 studies retained for resistance information cited the use of established guidelines for resistance interpretation including guidelines from The Clinical and Laboratory Standards Institute (n=11),<sup>82, 93, 115, 116, 118, 124, 129-133</sup> and the Antibiogram Committee of the French Microbiology Society (n=3).<sup>106, 126, 127</sup> Other measures of quality control during pathogen identification included; verification of results in reference labs (n=4),<sup>103, 108, 110, 128</sup> continuous internal quality control (n=1),<sup>114</sup> use of a control strain (n=1),<sup>112</sup> and use of WHO guidelines (n=2).<sup>121, 125</sup> Five studies did not mention any form of quality control or use of guidelines.<sup>119, 120, 122, 123, 135</sup>

### ***Bacterial infection incidence rates and pathogens among children 28 days to 2 years***

#### *Incidence estimates (Table 3)*

Twenty infection articles reported an incidence rate. Demographic surveillance systems were used for population estimates in four studies<sup>93, 104, 107, 122</sup> and government statistics in eleven<sup>102, 105, 108, 109, 114, 117, 121, 125, 128-130</sup>. Five studies based incidence on person-time in study cohorts.<sup>110, 131-134</sup>

#### *Bacteremia*

Three studies reported an incidence estimate for bacteremia. Estimates ranged from 1,108 (95% CI 953–1,282) per 100,000 child-years in Gambia to 2,469 (95% CI 1,480–3,946) per 100,000 child-years for children 12-23 months in Kenya (see Table 4).<sup>93, 107, 110</sup> Three studies reported *Salmonella* specific bacteremia incidence estimates ranging from 97 (95% CI 40–203) per 100,000 child-years for children 12 to 25 months in Bangladesh to 1,050 (95% CI 680–1550) for children under 5 also in Bangladesh.<sup>132-134</sup>

Overall *S. pneumoniae* was the most common pathogen representing between 11% and 50% of isolated pathogens among 4 studies reporting.<sup>93, 107, 110, 113</sup> In two studies, non-typhoid *Salmonella* accounted for 23% and 26% of isolates<sup>93, 110</sup> while in one study *Salmonella* Typhi accounted for 30% of all isolates.<sup>113</sup> *S. aureus* was reported in two studies representing 6% and 13% of isolates.<sup>82, 113</sup>

In Ghana, 128 of 208 bacteria (62%) isolated from blood cultures from children 2 months to 2 years with suspected pneumonia were non-typhoid *Salmonella*.<sup>124</sup>

#### *Meningitis*

Three studies presented incidence rates of bacterial meningitis. Incidence estimates for 100,000 child-years ranged from 68 among children under 5 in Mongolia to 1078 (95% CI 484–2400) in children under two months in Mozambique.<sup>105, 117, 122</sup>

Seven studies reported incidence for meningitis due to *Haemophilus Influenzae* (*H. influenzae*) type B with incidence estimates ranging from 20.1 per 100,000 child-years for

children under 5 in Sri Lanka to 290 (95% CI 145–579) for children 2 to 11 months in Mozambique.<sup>102, 105, 109, 117, 121, 122, 130</sup> Both studies were conducted prior to introduction of the *H. influenzae* type b conjugate vaccine. Seven studies also reported incidence estimates for meningitis due to *S. pneumoniae* ranging from 2.7 (95% CI 0.9–5.9) per 100,000 child-years among children under 5 in Pakistan to 108 (95% CI 35–337) among children 2-11 months in Mozambique.<sup>108, 114, 117, 121, 122, 128, 130</sup>

An additional seven studies reported isolated pathogens without an overall incidence estimate.<sup>102, 106, 109, 114, 121, 128, 130</sup> The most common pathogens isolated were *H. influenzae* and *S. pneumoniae*. Among nine studies, *H. influenzae* made up 28% to 58% of isolated pathogens and *S. pneumoniae* ranged from 21% to 78%.<sup>105, 106, 109, 114, 117, 121, 122, 128, 130</sup> *Neisseria meningitidis* (*N. meningitidis*) was reported in six studies and represented 4% to 23% of pathogens.<sup>109, 117, 121, 122, 128, 130</sup> *Salmonella* was also reported in two studies and represented 8% and 18% of isolated pathogens.<sup>106, 114</sup>

### *Invasive Pneumococcal Disease*

Five studies reported rates for invasive pneumococcal disease. Case definitions of invasive pneumococcal disease were heterogeneous (Table 3). Incidence rates for 100,000 child-years ranged from 34 among children under 5 in Nepal to 447 among children under 5 in Bangladesh.<sup>129, 131</sup>

**Table 3-** Articles included in analysis for children under two by region, subject, and design

Author, country, and study year	Study Disease and Age	Study design	Incidence Age	Incidence per 100,000 child years (95% CI), pathogen
<b>Sub-Saharan Africa</b>				
Blomberg et al. <sup>82</sup> Tanzania 2001-2002	<i>Bacteremia</i> <7 yrs	urban, hospital recruitment		
Brent et al. <sup>107</sup> Kenya 2003	<i>Bacteremia</i> < 5 yrs	rural, hospital recruitment	0-11 mo 12-23 mo	2412 (1040-4748) 2469 (1480-3946)
Enwere et al. <sup>110</sup> Gambia 2000-2004	<i>Bacteremia</i> 6 weeks - 29 mo	rural, hospital recruitment	6 wks - 29 mo 6-11 mo	1108 (953-1282) 1464 (1120-1880)
Sigaúque et al. <sup>93</sup> Mozambique 2001-2006	<i>Bacteremia</i> < 15 yrs	rural, hospital recruitment	< 1 yr	1738 (1525-1981)
Schwarz et al. <sup>124</sup> Ghana 2007-2009	<i>Non-typhoid Salmonella</i> <i>bacteraemia</i> 2 mo - 2 yrs	rural, hospital recruitment		
Parent du Chatelet et al. <sup>121</sup> Burkina Faso 2002-2003	<i>Meningitis</i> all ages	urban and rural, hospital recruitment	< 1 yr	95 (65-125) <i>S. pneumoniae</i> 105 (73-136) <i>H. influenzae</i> type B 77 (50-105) <i>N. meningitidis</i>
Bercion et al. <sup>106</sup> Central African Republic 2004-2005	<i>Meningitis</i> < 16 yrs	urban, hospital recruitment		



Kisakye et al. <sup>114</sup> Uganda 2001-2006	<i>Pneumococcal meningitis</i> < 5 yrs	urban and rural, hospital Recruitment	< 5 yr	3–20 <i>S. pneumoniae</i> (urban area) 28-42 <i>S. pneumoniae</i> (rural area)
Traore et al. <sup>128</sup> Burkina Faso & Togo 2002-2006	<i>Pneumococcal meningitis</i> all ages	urban and rural, hospital Recruitment	< 1 yr 1-2 yr	77 <i>S. pneumoniae</i> 28.9 <i>S. pneumoniae</i>
Cissé et al. <sup>109</sup> Senegal 2003-2007	<i>Haemophilus influenzae type B</i> <i>Meningitis</i> < 5 yrs	urban, hospital recruitment	< 1 yr	33 HIB (measured in 2003-2005) 11 HIB (measured in 2006) 1.4 HIB (measured in 2007)
Roca et al. <sup>122</sup> Mozambique 2006-2007	<i>Bacterial meningitis</i> < 15 yrs	rural, hospital recruitment	< 2 mo 2-11 mo	1078 (484-2400) 507 (300-856) 290 (145-579) <i>H. influenzae</i> type B 108 (35-337) <i>S. pneumoniae</i>
Campbell et al. <sup>108</sup> Mali 2002-2003	<i>Pneumococcal infections</i> < 15 yrs	urban, hospital recruitment	0-11 mo	84.0 (58.3–109.7) 43.0 (24.6–61.4) <i>S. pneumoniae</i> meningitis
Holliman et al. <sup>112</sup> Ghana 2002-2005	<i>Invasive pneumococcal disease</i> all ages	urban, hospital recruitment		
Falade et al. <sup>111</sup> Nigeria 2005-2006, 2006-2007	<i>Invasive pneumococcal disease</i> 2 mo - 2 yrs	urban, hospital recruitment		
Nitiema et al. <sup>120</sup> Burkina Faso 2009-2010	<i>Diarrhea</i> < 5 yrs	urban, hospital recruitment		
Sire et al. <sup>127</sup> Senegal 2004-2006	<i>Escherichia coli</i> all ages	urban, hospital recruitment		

Sire et al. <sup>126</sup>  
Senegal 2004-2006  
*Shigella*  
all ages  
urban, hospital recruitment

### SE Asia

Anh et al. <sup>102</sup>  
Vietnam 2000-2002  
*Haemophilus influenzae type B*  
*Meningitis*  
< 5 yrs  
urban, hospital and community  
Recruitment  
< 5 yr  
133 (111-158) suspected  
88 (71-109) probable  
12 (7-22) confirmed and probable HIB

Mendsaikhan et al. <sup>117</sup>  
Mongolia 2002-2005  
*Bacterial meningitis*  
2 mo - 5 yrs  
urban, hospital recruitment  
2 mo -5 yr  
68  
28 (40 adjusted) *H. influenzae* type B  
11 (15 adjusted) *S. pneumoniae*  
13 (17 adjusted) *N. meningitidis*

Meng et al. <sup>135</sup>  
Cambodia 2004-2006  
*Diarrhea*  
3 mo - 5 yrs  
urban, hospital recruitment

Nickerson et al. <sup>119</sup>  
Thailand 2006-2007  
*Staph bacteremia*  
all ages  
urban, hospital recruitment

Baggett et al. <sup>103</sup>  
Thailand 2005-2007  
*Pneumococcal bacteremia*  
all ages  
rural, community recruitment

### India subcontinent

Baqui et al. <sup>104</sup>  
Bangladesh 1999-2001  
*Lower respiratory infections*  
< 5 yrs  
rural, communitiy recruitment  
< 5 yr  
5020  
1-5 mo  
10890

Batuwanthudawe et al. <sup>105</sup>  
Sri Lanka 2004  
*H. influenzae type B meningitis*  
< 5 yrs  
urban, hospital recruitment  
< 5 yr  
90.5  
20.1 *H. influenzae* type B

Zaidi et al. <sup>130</sup>  
*Pneumococcal meningitis*  
urban, hospital recruitment  
< 1 yr  
11 (3.6-26.2) *S. pneumoniae*

Pakistan 2005-2006	< 5 yrs				22 (10.8-41.3) <i>H. influenzae</i> type B
Shah et al. <sup>125</sup>	<i>Invasive pneumococcal disease</i>	urban, hospital recruitment	< 5 yr	52.4	
Nepal 2004-2007	2 mo - 5 yrs				
Brooks et al. <sup>131</sup>	<i>Invasive pneumococcal disease</i>	urban, hospital and community	< 5 yr	447	
Bangladesh 2004-2006	< 5 yrs	Recruitment			
Williams et al. <sup>129</sup>	<i>Invasive pneumococcal disease</i>	urban, hospital recruitment	< 5 yr	34	
Nepal 2005-2006	2 mo - 5 yrs				
Arifeen et al. <sup>132</sup>	<i>Invasive pneumococcal disease</i>	rural, community recruitment	1-11 mo	265 (151-434) * <i>S. pneumoniae</i> bacteremia	
Bangladesh 2004-2007	< 5 yrs		12-24 mo	151 (70-288) * <i>H. influenzae</i> type B bacteremia	
				146 (72-270) * <i>S. pneumoniae</i> bacteremia	
			1-11 mo	97 (40-203) * <i>Salmonella</i> Typhi bacteremia	
			12-24 mo	265 (151-434) * IPD	
				146 (72-270) * IPD	
Saha et al. <sup>123</sup>	<i>Invasive pneumococcal disease</i>	mostly urban, hospital recruitment			
Bangladesh 2005-2007	< 5 yrs				
Kelly et al. <sup>113</sup>	<i>Invasive bacterial infections</i>	urban, hospital recruitment			
Nepal 2005-2006	< 12 yrs				
Naheed et al. <sup>133</sup>	<i>Typhoid and paratyphoid fever</i>	urban, community recruitment	< 5 yr	1050 (680-1550) <i>Salmonella</i> Typhi bacteremia	
Bangladesh 2003-2004	all ages			40 (20-80) Non-typhoid <i>Salmonella</i> bacteremia	
Owais et al. <sup>134</sup>	<i>Typhoid bacteremia</i>	semi-urban, community recruitment	< 2 yr	443 (193.8-876.5) <i>Salmonella</i> Typhi	
Pakistan 2007-2008	< 5 yrs				
Nandy et al. <sup>118</sup>	<i>Shigella</i>	urban, hospital recruitment			

India 2001-2007

< 5 yrs

Kumar et al.<sup>115</sup>

*Salmonella*

urban, hospital recruitment

India 1999, 2002, 2005

all ages

### **Latin America**

Matute et al.<sup>116</sup>

*Urinary tract infections*

urban, hospital recruitment

Nicaragua 2002

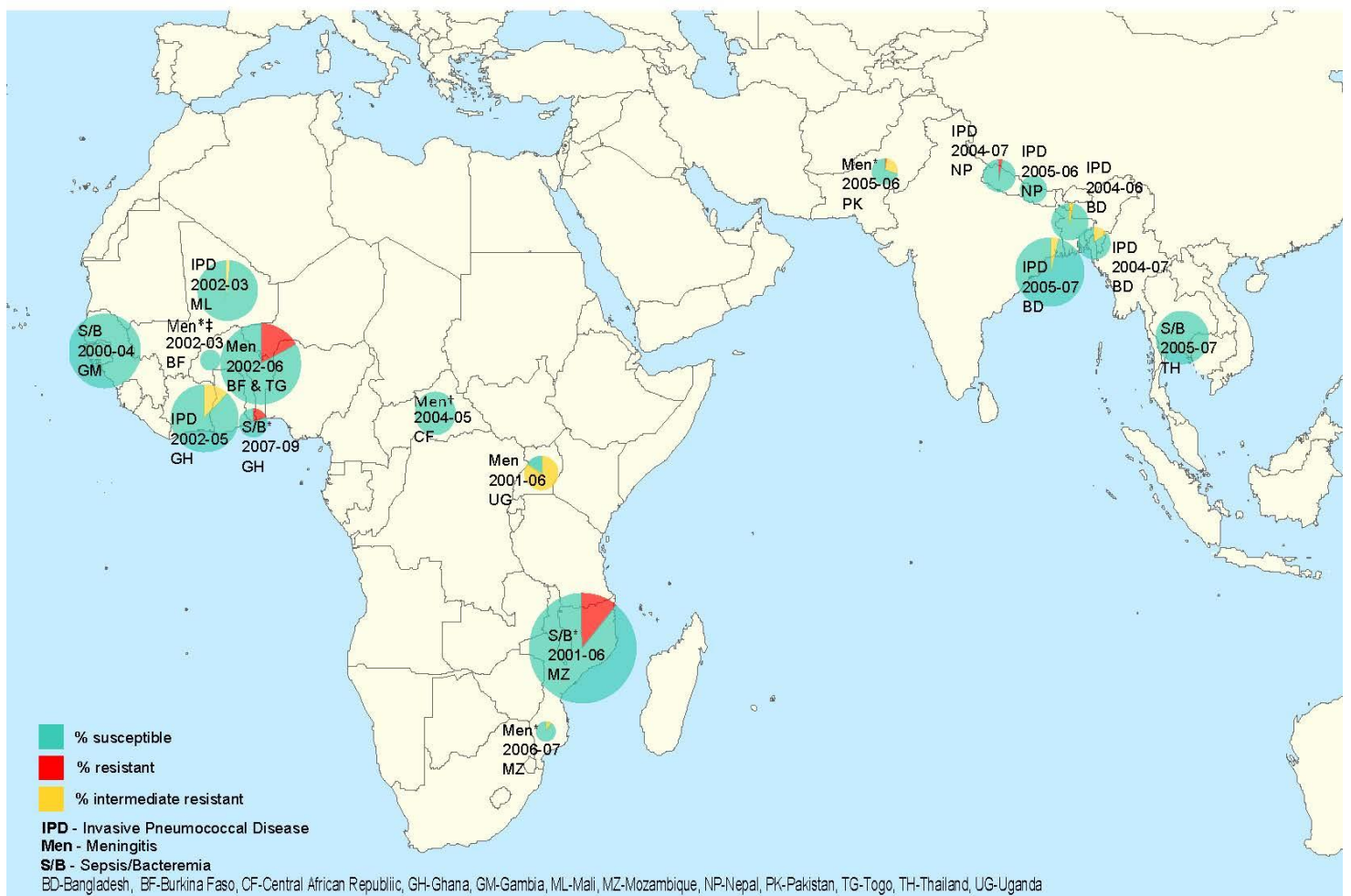
all ages

\* Incidence calculated from information presented in article

**Antibiotic resistance among bacteria from children past the neonatal period (>28 life days)**

*Streptococcus pneumoniae* (Figure 11)

Resistance to penicillin among *S. pneumoniae* was measured for 17 studies among children past the neonatal period.<sup>93, 103, 106, 108, 110, 112, 114, 121-125, 128-132</sup> Six studies relied on resistance guidelines from the CLSI, one study on those from the Antibiogram Committee of the French Microbiology Society and ten studies did not cite specific guidelines. Seven of the studies reported minimum inhibitory concentrations for antibiotics tested. Resistance ranged from 0% to 24% among 10 African studies and from 0% to 4% among six studies in the Indian subcontinent. The single study conducted in South East Asia found 0% resistance.



**Figure 11.** Penicillin resistance among *Streptococcus pneumoniae* isolates along with pathology, study years, and country.

Sources; references<sup>88, 93, 96, 97, 103-105, 109, 112, 113, 119-121, 127, 128, 131, 132</sup>

The size of circles represents the relative number of isolates by study.

Definitions for % susceptible, resistant, and intermediate resistance were those used in each study.

\*Only sensitivity information presented in article, resistance was calculated as 100 minus % sensitive.

†Resistance profile is based on results for amoxicillin.

‡Resistance profile is based on results for oxacillin.

### *Salmonella* spp. (Table 4)

Nine under-two studies reported resistance results among *Salmonella* isolates<sup>82, 93, 106, 110, 115, 120, 124, 133, 135</sup> including non-tyhoid *Salmonella* (NTS) (n=3), *Salmonella* Typhi (n=2), and *Salmonella* spp. (n=4) meaning that no differentiation was made. Resistance to ampicillin across all *Salmonella* types ranged from 33% in Cambodia<sup>135</sup> to 85% in Ghana.<sup>124</sup> Of the six studies testing for resistance to 3<sup>rd</sup> GCs, only two detected resistance: one in India<sup>115</sup> at 11% and one study in Tanzania<sup>82</sup> at 4% for two different 3<sup>rd</sup> GCs. Nine studies reported resistance to co-trimoxazole, ranging from 27% in Cambodia<sup>135</sup> to 100% in Central African Republic.<sup>106</sup>

**Table 4.** Antibiotic resistance of *Salmonella* and *Shigella* isolates from low-income countries (2000-May 2012)

Study, year	Location Setting	Pathogen	Resistance % (95% CI) (N)					
			Ampicillin	Amoxicillin/ clavulanic acid	3rd generation cephalosporins	Co-trimoxazole	Chloramphenicol	Quinolone
Blomberg et al. <sup>82</sup> 2001-2002	Tanzania urban	<i>Salmonella</i> spp. *, †	48 (29-67) (27)	30 (12-47) (27)	4 (0-11) (27) 4 (0-11) (27)	48 (29-67) (27)	15 (2-28) (27)	0‡ (27)
Enwere et al. <sup>110</sup> 2000-2004	Gambia Rural	Non-typhoid <i>Salmonella</i>	65 (55-75) (94)	--	0‡ (94)	60 (50-70) (94)	24 (15-33) (94)	--
Naheed et al. <sup>133</sup> 2003-2004	Bangladesh urban	<i>Salmonella</i> Typhi	40 (25-55) (40)	--	0‡ (40)	43 (28-58) (40)	43 (28-58) (40)	40 (25-55) (40)
Kumar et al. <sup>115</sup> 1999, 2002, 2005	India urban	<i>Salmonella</i> Typhi (2005 isolates only)	--	69 (57-81) (45)	11 (3-19) (45)	80 (69-91) (45)	73 (61-85) (45)	22 (11-33) (45) 22 (11-33) (45) §
Bercion et al. <sup>106</sup> 2004-2005	Central African Republic, urban	<i>Salmonella</i> spp. †	--	--	0‡ (8)	100‡ (8)	100‡ (8)	0‡ (8)
Sigaúque et al. <sup>93</sup> 2001-2006	Mozambique Rural	Non-typhoid <i>Salmonella</i> *	74 (70-78) (395)	38 (32-44) (297)	--	66 (61-71) (390)	55 (49-59) (393)	--
Schwarz et al. <sup>124</sup> 2007-2009	Ghana Rural	Non-typhoid <i>Salmonella</i> *	85 (79-91) (123)	--	0‡ (108)	77 (69-85) (98)	82 (89-75) (127)	0‡ (127)
Meng et al. <sup>135</sup> 2004-2006	Cambodia urban	<i>Salmonella</i> spp. †	33 (26-40) (178)	--	--	27 (20-34) (178)	--	16 (11-21) (178), 1 (0-2) (178) §
		<i>Shigella</i>	78 (65-91) (41)	--	--	98 (94-100) (41)	--	20 (8-32) (41) 0‡ (41) §
Nitiema et al. <sup>120</sup> 2009-2010	Burkina Faso, urban	<i>Salmonella</i> spp. †	43 (6-80) (7)	71 (37-100) (7)	--	57 (20-94) (7)	57 (20-94) (7)	--
		<i>Shigella</i>	50 (27-73) (18)	33 (11-55) (18)	--	72 (51-93) (18)	33 (11-55) (18)	--
Sire et al. <sup>126</sup>	Senegal	<i>Shigella</i>	--	13 (8-18) (165)	0‡ (165)	--	27 (20-34) (165)	1 (0-3) (165),

2004-2006	urban							0‡ (165) §
Nandy et al. <sup>118</sup>	India	<i>Shigella</i>	46 (42-50) (516)	41 (34-48) (174)	0‡ (516)	90 (87-93) (516)	47 (43-51) (516)	80 (77-83) (516),
2001-2007	Urban							26 (22-30) (516) §

\*Results were presented for sensitivity; the resistance was calculated as 100 minus % sensitive.

† Pathogens marked spp. means no further characterization was presented.

‡ Calculation of a CI was impossible.

§ Two different quinolones were tested.



## Discussion

Our results highlight the dramatic lack of data on bacterial resistance patterns in neonatal and young childhood infections in LICs. They also underscore the paucity of reliable and convincing data on the burden of community-acquired invasive bacterial infections among children in these countries. This lack was pointed out by Berkley et al. almost ten years ago and more recently by Lubell et al. in 2009, demonstrating how little progress has been made on this issue.<sup>16, 58</sup> These gaps in knowledge impede the improvement of prevention and treatment strategies of neonatal and young childhood infections in these settings where the risk of death is the highest.

Available data showed a broad range of neonatal and under-two infection incidence estimates. This heterogeneity has been previously noted by other authors confirming this finding.<sup>79, 136</sup>

### *Neonatal bacteria and resistance*

We found that the most common pathogens among neonatal infections were *S. aureus*, *Klebsiella* spp., and *E. coli* which account for almost two thirds of neonatal sepsis cases. This proportion is in line with others reviews conducted in LICs.<sup>57, 79, 137</sup> Care must be taken when interpreting these results, however, as differentiation of infections into community-acquired or hospital-acquired during the neonatal period can be difficult in LICs.<sup>138</sup> As a result, a small number of nosocomial infections may be included in our findings, thus influencing the pathogen distribution. Five studies were included in our analysis which reported coagulase-negative Staphylococci as responsible for a significant proportion of neonatal infection, however positive blood cultures for this pathogen may commonly be due to sample contamination.

The relative importance of the most common neonatal pathogens differs according to disease onset (early vs. late), however this distinction was not detailed in the majority of the studies. Early onset infections are generally attributed to pathogens transmitted from the vaginal or rectal flora of the mother to the child, while late onset infections are attributed to bacteria acquired from the infant's surroundings (hospitals or community) with *S. aureus* and *Klebsiella* species more frequently implicated in hospital infections.<sup>139</sup> Infection control measures designed to prevent the acquisition of bacteria from the environment do not affect pathogens that are acquired at birth. Therefore, distinguishing maternal from environmental infection sources would allow for improved implementation of preventive strategies in these settings.

The number of isolates per study was generally very small among neonatal studies: three-quarters of the 12 neonatal studies reported resistance rates based on fewer than 30 isolates. The WHO recommends ampicillin and gentamicin as first-line treatment of neonatal sepsis unless there is infection of the skin or umbilicus (possible *S. aureus*), when cloxacillin is substituted for ampicillin. Resistance to ampicillin was high among neonatal studies. Data on gentamicin were heterogeneous and no clear conclusion could be drawn. However, the findings of our review are consistent with others studies<sup>57</sup> and confirm a trend of growing resistance to this drug combination.

Data on resistance to third generation cephalosporins among neonatal isolates were heterogeneous except among *Klebsiella* spp. for which notable resistance rates were reported.<sup>97, 98</sup> Moreover, only two studies reported testing for ESBL despite the fact that ESBL have been reported worldwide. Medication required to treat ESBL-producing *Enterobacteriaceae* is expensive and unaffordable for the majority of the population in these settings making these bacteria difficult to treat. It is therefore of the utmost importance to make reliable data available to guide strategies devoted to limiting the spread of ESBL pathogens in LICs.

Importantly, no conclusions can be drawn regarding methicillin resistant *S. aureus* (MRSA) in neonates, despite the fact that this pathogen may be the first cause of neonatal infection. Furthermore, only one of the six neonatal studies describing MRSA infection was conducted in a community setting. Community-associated MRSA (CA-MRSA) has emerged in the developed world and represents a growing problem. Data on CA-MRSA are scarce in LICs despite risk factors associated with drug resistance in the community such as over-the-counter antibiotics use, overcrowding, and poor hygiene.<sup>140</sup>

#### *Under-two bacteria and resistance*

Among infants under two, *S. pneumoniae* was commonly found in cases of meningitis and blood stream infections. Our results suggest that this pathogen has reached an alarming level of resistance to co-trimoxazole (>40% resistant strains in eight of ten studies which tested this antibiotic), one of the most common empirical treatments in LICs. We also highlight that resistance to penicillin overall seems to be low in LICs, with almost one third of the 17 studies reporting that all strains were sensitive. This low level of resistance to penicillin among pneumococci in poor countries, which has already been pointed out by Ashley et al.,<sup>141</sup> is contrary to results from developed countries where penicillin resistance has led to public health campaigns to decrease antibiotic use. We observed regions of increased resistance located in Sub-Saharan Africa with great variation in resistance by areas.

Of note, the majority of studies reporting on *S. pneumoniae* resistance were conducted before 2007 and the susceptibility pattern may have changed since this period. As with neonatal studies, most studies relied on few isolates with two-thirds based on less than 50 isolates. Furthermore, the definitions of resistance were not homogenous across studies making it difficult to draw clear conclusions on *S. pneumoniae* resistance and less than half of the studies reported minimum inhibitory concentrations. Accurate antibiotic resistance data as well as serotype distribution are needed in the context of pneumococcal vaccination implementation in LICs.

Our review shows that non-typhoidal *Salmonella* (NTS) is another important cause of bacteremia in the 28-day to 2-year age group particularly in Africa. A bimodal age distribution of invasive NTS has been shown in which children aged 6-36 months and adults between 20 and 40 years old are at greatest risk.<sup>142</sup> Of note, differentiation in the literature of *Salmonella* spp. into typhoidal and non typhoidal *Salmonella* is often incomplete thus making accurate description of the epidemiology difficult. Third generation cephalosporins still seem to be active against NTS but we confirmed high resistance to first line-drugs

including amoxicillin, chloramphenicol, and cotrimoxazole.<sup>143</sup> Quinolone resistance is also a growing problem in the Indian subcontinent and in Southeast Asia, whereas in Africa quinolone resistance seems to remain quite low.

#### *Incidence rates*

Along with high heterogeneity in incidence rates among both neonates and children under two, the reported infection rates are likely to underestimate the true incidence. Three-quarters of all studies reviewed, including both neonatal and under-two studies, took place in urban settings with recruitment at large or teaching hospitals. In LICs, the majority of families do not seek care in hospitals, particularly in rural areas, because of resource constraints, distances to their homes, or differences in health care seeking behaviours.<sup>112</sup> This is particularly true for early onset neonatal sepsis in the context of home deliveries. Along with underestimating the incidence, these factors undoubtedly play a role in the low detection rates of Group B *Streptococcus* in LICs as these infections generally occur shortly after delivery. These results are contrary to those from developed countries where Group B *Streptococcus* is the major cause of neonatal sepsis.<sup>144, 145</sup>

The observed heterogeneity among incidence rates may also be explained by the difficulty of estimating these rates. Such estimates require accurate population estimations, which can be difficult to obtain in LICs. Confirming diagnosis with blood culture is also difficult in LICs as this requires adequate blood volume drawn in strict aseptic conditions by skilled staff at the right moment along with access to appropriate laboratory equipment. These conditions are often only met in large or teaching hospitals in LICs.<sup>146, 147</sup> A positive blood culture can also be affected by the number of samples taken and antibiotic use prior to blood sampling. Only two studies performed two blood cultures despite an increased chance of pathogen isolation. The proportion of antibiotic usage prior to blood culture performed at the hospital was also high among studies reporting. Thus, a single negative blood culture cannot completely rule out a bacterial infection and a substantial proportion of non-microbiologically confirmed sepsis cases potentially represents false-negatives.<sup>148</sup>

#### *Lack of data*

Of note, almost half of all neonatal and under-two studies reviewed were conducted in Africa. The observed lack of studies in Southeast Asia is alarming as the population in this area is greater than in Africa and studies have shown high levels of antibiotic consumption in these countries.<sup>149, 150</sup>

The relative paucity of reports on antibiotic resistance among neonates and children under two collected after 2008 is of particular concern in a context of rapidly evolving resistance profiles and emerging antibiotic resistance mechanisms. Real-time data are required to provide an accurate understanding of drug sensitivity and resistance patterns.<sup>6</sup> Although a potential explanation may be that recent data collected is less likely to be published, the period of time that has elapsed since 2007 is largely sufficient to reveal a decline in publications.

One limitation of this study may include the restriction of articles to those published in English. Many LICs particularly in Africa may publish articles in French or other languages which may have biased our results.

In its first report on global antimicrobial resistance, with data from 114 countries, the WHO found that resistance to seven common bacteria has reached alarming levels in all regions of the world.<sup>1</sup> It also highlights that many gaps exist in documentation of pathogens of major public health importance. Our analysis is in line with the WHO's conclusion on the need for methodological standards to investigate these issues. The WHO report also draws attention to the fact that resistance may be overestimated in the general population as most reported samples were collected in large hospitals, consistent with our observation that data from the community are lacking. Finally, the WHO calls for actions to strengthen and coordinate collaboration to address these knowledge gaps.

## Conclusion

Despite the recent global awareness of bacterial resistance issues and indications of the growing antibiotic resistance in LICs, epidemiological evidence remains limited and available data are not sufficient to draw a true, recent, and accurate picture of antibiotic resistance in LICs among neonates and young children particularly in the community.

Effective surveillance systems or research programs devoted to anti-infective resistance in infectious diseases such as tuberculosis, malaria, or HIV have been implemented over the past few years. These systems have been able to provide reliable data allowing for the promotion of global action. International alliances to contain antibiotic resistance in LICs exist and have called for several actions including global research and surveillance, public health advocacy, and consumer and practitioner education. However, current research projects are often based in large or teaching hospitals, and drug resistance patterns and trends in antibiotic use are based on data from these hospitals. It is therefore imperative to accurately assess the burden of antibiotic-resistant infections in LICs, particularly among children as they bear the highest burden.

Without data to evaluate the burden of antibiotic resistance in this population, the public health problem will undoubtedly remain underserved. Future research should be able to collect quality, standardized epidemiological data along with a reliable bacteriological diagnosis at the community level in order to allow for adapted public health measures necessary to combat antibiotic resistance.

## Chapter 3 – Measurement of Community Antibiotic Consumption in LICs

### Background

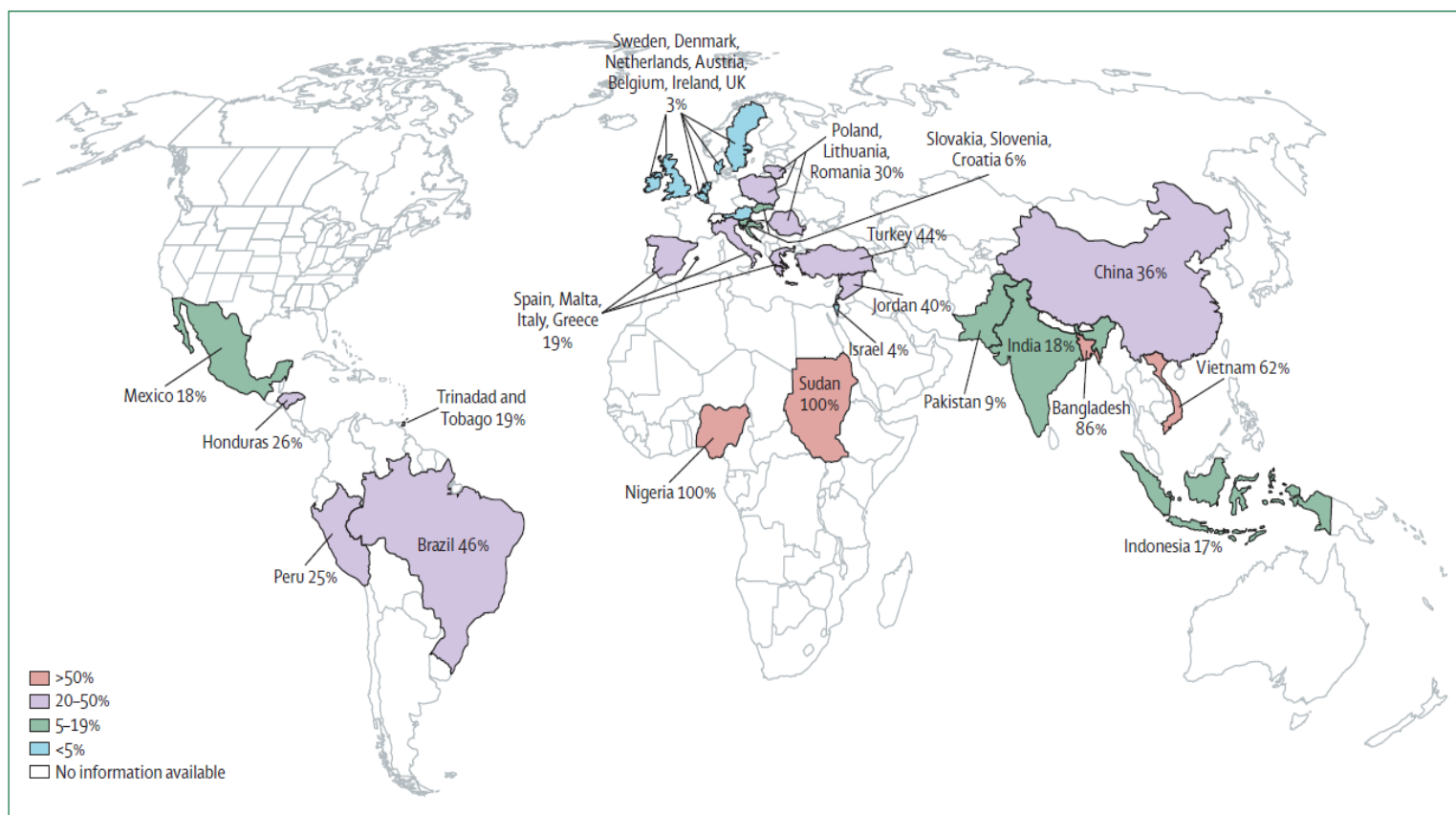
Data on the burden of antibiotic resistance alone is insufficient to respond to antibiotic resistance in LICs. Antibiotic usage is the main driver of antibiotic resistance and studies show that higher levels of consumption are associated with higher levels of resistance in a given community.<sup>45</sup> Responding to resistance therefore means managing antibiotic consumption. This management however is impossible without corresponding antibiotic consumption data.<sup>151</sup> Data on aspects such as antibiotic sources and principal drivers of consumption can help LICs develop resistance management strategies including importantly antibiotic consumption management.

WHO has developed a global strategy to reduce antibiotic resistance and lower consumption and suggests a number of potential intervention targets including: the general population, antibiotic providers, hospitals, and governmental policies.<sup>152</sup> Prioritizing these interventions requires data on issues such as frequency and amount of antibiotic use, patient and provider knowledge, drug source and quality, health care seeking behavior, and reasons for antibiotic use. Reliable consumption information is also needed to monitor trends, evaluate the impact of interventions, and importantly, generate the political will to deal with this issue.<sup>151</sup>

In LICs, these data can be unreliable or non-existent and measurement systems are not often available. While creating international antibiotic surveillance systems has become an international priority, gathering comprehensive data is complicated by the large number of non-prescribed and parallel market sources available in many of these countries.<sup>70, 153</sup> In addition to being frequent in many LICs, this type of consumption presents a particularly high risk for antibiotic resistance development and dissemination and must be taken into account when developing surveillance and measurement systems in LICs.

#### *Non-prescribed antibiotics*

Non-prescribed antibiotics are common in LICs. A review of this practice worldwide found that outside of Europe and North American non-prescribed antibiotics made up from 19 to 100% of total use among the study populations (see Figure 12).<sup>70</sup>



**Figure 12.** Frequency of non-prescription use of antimicrobials in the general population based on published works. Source [70]

A separate review in low and middle-income countries estimated antimicrobial self-medication at 38.8 % (95 % CI: 29.5-48.1). Of studies included in the review 65% found non-prescribed antibiotics from pharmacies, 50% from leftover drugs, and 38% from drug shops.<sup>154</sup> In rural Bangladesh, among all drugs consumed by over 2000 study participants only 8% were prescribed by a physician.<sup>7, 155</sup> In India traditional healers have been found to often prescribe antibiotics.<sup>7</sup>

Unsurprisingly, self-medication with antibiotics has a number of negative consequences. These include unnecessary use, wrong molecule choice, and inadequate treatment durations making it particularly high risk for resistance development and spread. The purchase of small samples for example, is exceedingly common among those who buy antibiotics without a prescription.<sup>7</sup>

Even when obtaining non-prescribed antibiotics from traditional sources including pharmacies, courses dispensed are often unnecessary and the choice of drug is incorrect. Furthermore, pharmacists or pharmacy attendants rarely explain the proper duration and compliance with full courses is poor.<sup>48</sup>

Methods capable of accounting for these non-prescribed antibiotic sources are thus important to accurately measure consumption and prepare necessary interventions in these contexts. Furthermore, measures should be able to provide reliable consumption data on a population level to enhance comparability and relevance including rates and quantities of

consumption. Ideally, this type of measurement would also facilitate intervention by providing easily identifiable intervention targets.

Current reports of consumption in LICs rely on diverse methodologies making comparison difficult. WHO has published guidelines on investigating medicine use by consumers and in health facilities which details numerous methodologies but no clear roadmap for the investigation of community antibiotic consumption is presented and no specific mention of non-prescribed antibiotic use is made.<sup>156, 157</sup>

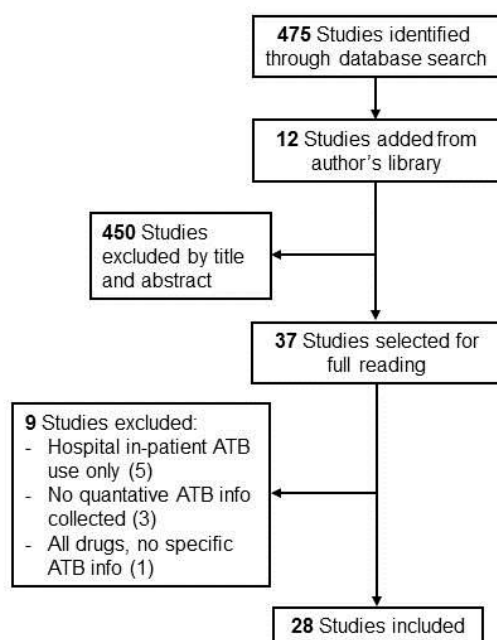
In order to investigate the issue of antibiotic consumption measurement in LICs, we reviewed current methodologies from the published literature including a critical appraisal of each method. Finally, we propose an integrative and adaptive approach to respond to this issue.

## Methods

In order to investigate the methods used for measuring antibiotic consumption in LICs, a literature review was conducted by searching PubMed (last search September 30th, 2015) using the search terms “antibiotic”, “antibiotic consumption”, “developing country”, “low-income country”, “non-prescription antibiotic”, “community”, and “survey”. We excluded search terms “infection” and “tuberculosis” and limited the search to articles published since 1990. Reports on measuring antibiotic or drug use including WHO reports were also examined and references from these reports screened for inclusion as were selected articles from the author’s library. Low-income countries were defined as countries classified by the World Bank as “Low-income economies” or “Lower-middle-income economies”.<sup>158</sup> Inclusion criteria included measures of community and/or outpatient antibiotic consumption. Studies measuring only hospital in-patient use or limited to only one pathology were excluded. Returned articles were first screened by title and abstract followed by full reading of those retained. For the articles included in the analysis, methodologies used, type of data gathered, and methodological appropriateness for desired data as discussed were noted.

## Results and methodology review

Of the 487 studies identified through the search strategy, 37 were selected for full reading. Of these, 27 were retained for final analysis. (Figure 13) Four main investigative methods were identified from literature search results including: pharmacy/hospital document reviews, the simulated client method, observed prescribing encounters/patient exit interviews, and community surveys. (See Table S2- appendix)



**Figure 13.** Flowchart of literature search

*Pharmacy/hospital document reviews*

One of the simplest ways to investigate antibiotic use in a community is to review pharmacy or hospital records or prescription documents.<sup>159-165</sup>

In Vellore India, Chandry and colleagues collected antibiotic sales records from participating pharmacies and rural hospitals.<sup>163</sup> Data allowed for the calculation of defined daily doses (DDDs) dispensed per 100 patients along with proportions of antibiotics dispensed by pharmacy type and location. DDDs are a standardized measure of drug quantity developed by the WHO to allow for easy comparison between drugs and across health care settings. Kotwani and colleagues collected bulk purchase information from participating pharmacies in Delhi, India and calculated consumption as DDDs purchased/per 1000 population. Authors also identified antibiotic proportions and compared proportions between structure types.<sup>165</sup> Outpatient and prescription records were analyzed for participating centers in Brits and Durban South Africa by Holloway and colleagues. The proportion of patients with a prescribed antibiotic and the proportion of prescriptions with an antibiotic were calculated along with DDDs per 100 patients attending the facility. Trends in antibiotics used by facility type were also analyzed.<sup>164</sup> A recent review of global antibiotic use and trends also used pharmacy sales records to estimate country level antibiotic consumption.<sup>64</sup>



The major strength of these methods is that this type of data takes relatively little time to gather making it a potential candidate for surveillance. Antibiotic type, proportion, and DDDs can be easily calculated. A number of weaknesses also exist with these methods. First, the choice of pharmacies or health centers is not random. Only those facilities with appropriate data willing to participate can be included which may bias results.<sup>164</sup> In the case of bulk purchase studies, these data may not correspond directly with purchased or consumed antibiotics. This method also makes it difficult to determine community-level consumption as relating participating pharmacies to a well-defined population is difficult. Importantly, potential sources of non-prescribed antibiotics outside pharmacies are not measured and no information is available on the proportion of antibiotics sold in the pharmacy without a prescription. The limited information gathered on important aspects such as symptoms or patient knowledge, attitudes, and beliefs along with potential biases related to this approach must be taken into account when using this method.

### *Simulated client method*

The simulated client method involves trained field workers posing as clients of pharmacies or health centers. The field worker will present symptoms (either their own or those of another person), ask for medication, and measure the reaction of the medication provider.<sup>28, 150, 162, 166</sup> Measures can include medication delivered, recommendations, or information given.<sup>157</sup>

In Bolivia, Bartoloni and colleagues trained six “actors” to describe various episodes and patient profiles to all pharmacies in a rural town.<sup>162</sup> Actors asked for medication without a prescription and main outcomes included the proportion of visits resulting in the purchase of an antibiotic without a prescription. A similar study in Vietnam trained field workers to pose as the mother of a child suffering from either respiratory symptoms or diarrhea and ask for medication without a prescription.<sup>150</sup> This technique has also been used in developed countries. Llor and colleagues in Spain used this technique both to estimate the proportion of pharmacies providing antibiotics without a prescription and to gather information about dispenser attitudes and beliefs about non-prescribed antibiotics.<sup>167</sup> The study was thus able to assess both distribution patterns of non-prescribed antibiotics as well as the views of the pharmacist without encountering an observation bias.<sup>168</sup>

The simulated client method is one method focused on the medication provider rather than the patient. It is particularly well adapted to non-prescribed antibiotic studies and allows an unbiased collection of information including provider knowledge, attitudes, and beliefs. The unlimited number of possible scenarios (ages, symptoms, etc.) gives this method flexibility and it is relatively quick and cheap to conduct. Interestingly, no evidence was found of this technique being used to investigate non-prescribed antibiotic distribution sources such as markets or other informal providers.

Weaknesses of this approach are related to understanding population-level antibiotic use. Data provided do not allow for determination of average antibiotic consumption or even non-prescribed antibiotic consumption either for a given population or for pharmacy patients. The information gathered responds only to distribution practices related to the scenario or scenarios presented. Like document reviews, not all sources of non-prescribed

antibiotics are taken into account. Lastly, we have no information on real client behavior which may differ from that of the actors and this method is not well adapted to surveillance. This approach is an important one in understanding non-prescribed sales in pharmacies and may be well suited to developing interventions targeting pharmacists but it must be accompanied by other methods in order to determine population level antibiotic consumption patterns.

### *Observed prescribing encounters/patient exit interviews*

Observed prescribing encounters involve trained field workers or pharmacists recording information about pharmacy transactions in real time. Patient exit interviews consist of interviewing patients exiting a pharmacy or health facility about their purchases.<sup>160, 163-165, 169-174</sup>

Chandy and colleagues used the observed encounters method each month for two years in participating pharmacies to investigate antibiotic distribution in Vellore, India.<sup>163</sup> Data allowed for calculation of the proportion of pharmacy visits resulting in antibiotic purchase, the types and proportions of antibiotics distributed, the reasons for antibiotic purchase, and DDDs per 100 pharmacy patients. The repeated measures also allowed for visits to serve as method to monitor the evolution of antibiotic distribution. Esimone in Nigeria collected data using patient exit interviews on a daily basis for a period of 90 days.<sup>169</sup> Results included the percentage of antibiotics sold without a prescription and the percentage of antibiotic DDDs dispensed without a prescription. The exit interview method has also been used in other settings to investigate doctor prescription patterns or evaluate interventions.<sup>174, 175</sup>

This approach has a number of advantages. First, a large number of variables can be gathered. The type and proportion of antibiotics used are easily calculated as are DDDs per patient and the proportion of antibiotics purchased without a prescription. The access to patients in exit interview allows for data on why the antibiotic was purchased, socio-demographic factors associated with antibiotic use along with patient knowledge, beliefs, and attitudes.

However, as with document review studies, pharmacy selection is not random and may be biased. Indeed, a number of studies had difficulties obtaining consent from pharmacies and the interview schedule for those who did agree was often cumbersome which reduced willingness to participate.<sup>163, 164</sup> Like document reviews, this method makes it difficult to determine the total consumption of the local population and potential sources of non-prescribed antibiotics are unmeasured. The presence of researchers may also influence provider behavior specifically in the context of non-prescribed antibiotic distribution resulting in biased results for this variable.<sup>164</sup> While this technique has been tested as a surveillance technique, several studies reported participation fatigue.<sup>164</sup>

Because of the range of data that can be gathered using these techniques, observed encounters and patient exit interviews are flexible and well adapted to the study of antibiotic use in developing countries. However, targeting only pharmacies may bias global estimates.

## *Community surveys*

Unlike strategies focused on drug dispensers and recruiting patients who access health facilities or pharmacies, community surveys use residents in selected geographic areas as the study population. A number of houses are selected randomly using a survey plan and houses are visited by field workers who ask residents about their antibiotic use.<sup>149, 150, 162, 173, 176-185</sup>

Awad and colleagues conducted a multistage cluster survey of 600 household in Sudan. Proportions of the study population consuming antibiotics, antimalarials, or both were calculated and socioeconomic variables associated with high self-prescribing behavior were identified.<sup>177</sup> Saradamma and colleagues in India conducted a survey of 400 households also using a cluster design. Proportions of household members that had used antibiotics in the previous 14 days were calculated along with the proportion of antibiotics purchased without a prescription.<sup>173</sup> The 2-stage cluster design used in both of these studies is common among surveys in LICs. These designs allow for calculation of unbiased population estimates and reduced logistic costs in situations where population lists are not easily obtained.

A number of advantages exist when using community surveys in the investigations of antibiotic consumption. By taking measures on the population level, it is possible to avoid the potential selection bias found in pharmacy exit interviews or pharmacy document reviews. It is also possible to account for all antibiotic sources including non-prescribed sources. With access to patients, this technique is useful for gathering variables on place of purchase, completion of antibiotic courses, and reasons for purchase as well as population characteristics and patient knowledge, attitudes, and beliefs. The type and proportion of specific antibiotics can also be estimated although with less precision than pharmacy-based methods.<sup>173</sup>

Some problems also exist with community surveys. Importantly, they can be time consuming and expensive to organize. This is especially true if large samples are needed in the case of rare events. This could be true in studies of non-prescribed antibiotic consumption in some populations.<sup>173</sup> Participation and recall bias may also be issues with this type of investigation. Finally, calculation of DDDs is difficult using this method and the resources needed makes this approach a poor surveillance method.

While community surveys are generally more costly and/or labor intensive than other methods of data collection they are the best way to capture all sources of antibiotics in LICs and can produce the richest results. The ability to gathering peripheral information or risk factors for antibiotic consumption or non-prescribed antibiotic consumption is also important for designing interventions or planning further studies.

## **Discussion and integrating study techniques**

Each of the four methods discussed has specific strengths and weaknesses when responding to the various questions related to antibiotic consumption (see Table 5). The time gains from document reviews are counterbalanced by the relatively limited data gathered while the

time and resource investment of community surveys can provide a great deal of valuable information on consumption and related variables.

Ideally, these studies should be used in concert in order to cover the wide range of data necessary to describe and track antibiotic consumption in LICs and identify areas for intervention. WHO calls the use of multiple strategies “triangulation” and recommends this strategy when investigating medicine use to cross check results from each study type.<sup>157</sup> Because the most appropriate study technique may vary depending on the results of other studies, investigations must be adaptive and capable of reacting to new information by changing or modifying study methods.

In a situation where little to no information exists, it is important to start by gathering as much information as possible as this serves as both a starting point for the development of interventions and the determinant of appropriate follow-up studies or monitoring and surveillance methods.<sup>186</sup> In LICs, community surveys are the only method capable of accounting for all non-prescribed antibiotics and their capacity to gather large amounts of auxiliary data while limiting selection bias makes it an ideal starting point for an integrative and adaptive method. Using this approach, community surveys can be used to answer important questions about the sources and proportion of non-prescribed antibiotics and provide the foundation for additional study and intervention choices.<sup>157</sup> In the absence of non-prescribed antibiotics for example, pharmacy document reviews could be a good option for monitoring antibiotic use and interventions focused on doctors may be most effective in lowering or improving antibiotic usage if necessary.<sup>44</sup> In the case of a high proportion of antibiotics from pharmacies along with pharmacy distribution of antibiotics without a prescription, observed encounters/patient exit interviews may be a suitable choice for monitoring and interventions may be best focused on pharmacists. (Figure 14) During the investigation, qualitative methods may also be added as necessary in order to explore specific topics. These methods could include interviews with doctors or pharmacists for example to better understand patient behavior or the impact of an intervention. They may be particularly valuable after an initial community survey to understand why patients behave as they do in order to develop more effective interventions.

The geographic area of a community survey is also an important aspect of this approach and an additional benefit of starting investigations with this method. A predefined geographic region may benefit subsequent studies by facilitating pharmacy selection, population size calculations, or intervention targets all while avoiding selection bias. Community studies are easily adapted to both urban and rural environments which is important as factors related to consumption may vary significantly with populations size and density and multiple study sites may be necessary to account for this dynamic.<sup>187</sup>

**Table 5.** Capacity of four study types in responding to antibiotic consumption investigation needs in LICs

<b>Antibiotic investigation data</b>	<b>Document review*</b>	<b>Simulated client method</b>	<b>Observed encounters/exit</b>	
			<b>interview*</b>	<b>Community study</b>
Type and proportion of ATB <sup>†</sup> use	+++	-	+++	++
DDDs‡ per patient	+++	+	+++	+
ATB <sup>†</sup> consumption for defined population and time period	+	+	+	+++
ATB <sup>†</sup> source including all n-P sources	-	-	-	+++
Why ATB <sup>†</sup> given	+++§	++	+++	++
Factors associated with ATB <sup>†</sup> use	-	+	++	+++
Non-prescription proportion	-	-	++	+++
Provider knowledge, attitudes, beliefs	-	+++	-	-
Patient knowledge, attitudes, beliefs	-	-	++	+++
<b>Study characteristics</b>				
Adapted to monitoring time trends	+++	+	++	+

+ **Poor**

++ **Moderate**

+++ **Good**

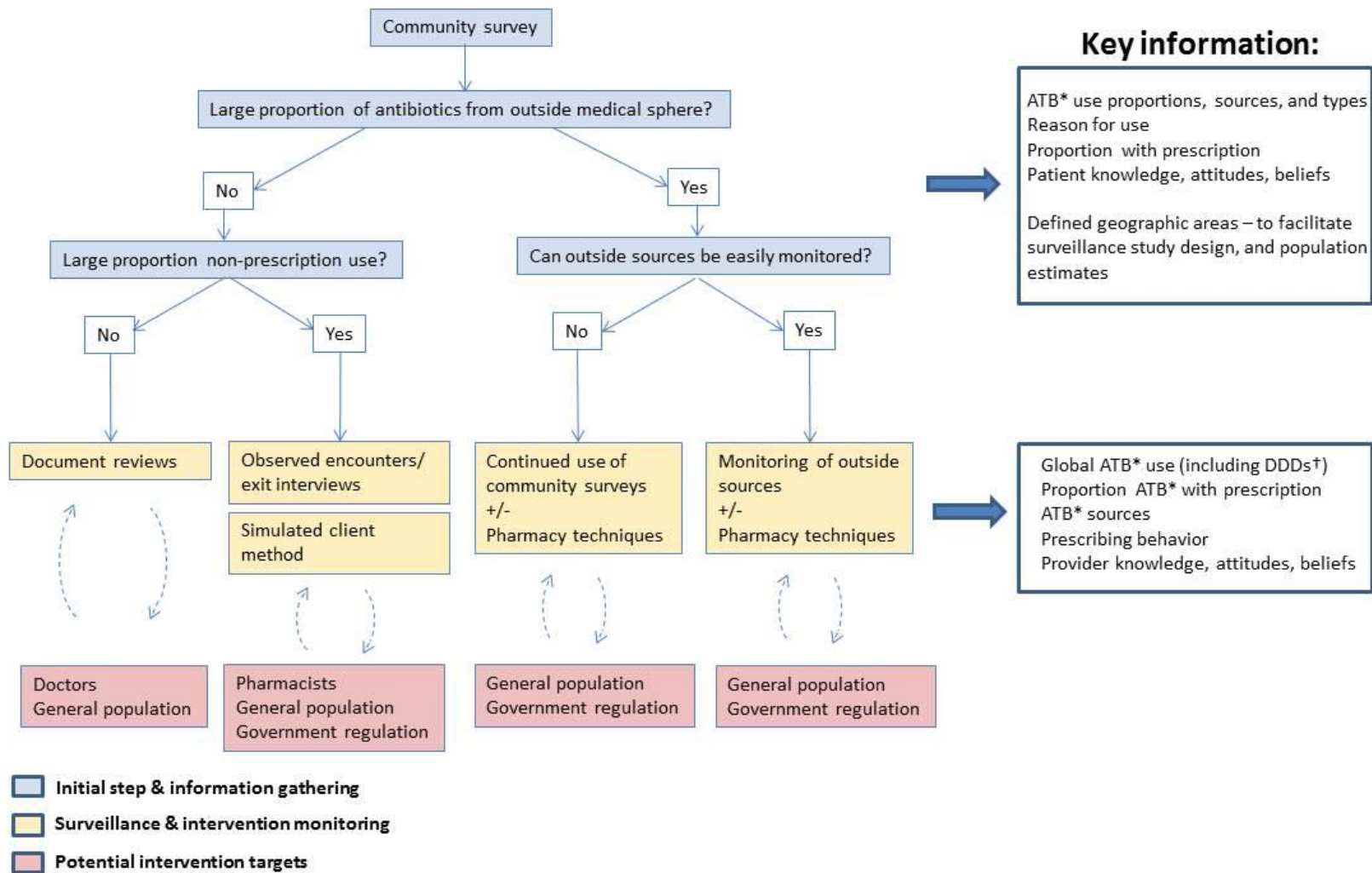
- **Not applicable**

\*Using non-exhaustive sample of centers/pharmacies

† ATB- Antibiotic

‡ DDD- Defined Daily Dose

§ If including patient records



**Figure 14.** Flowchart for integration of study types for antibiotic measurement and surveillance in LICs.

\*ATB – antibiotic

†DDD- defined daily dose

One survey method particularly well-adapted to this integrated approach is compact segment sampling (CSS) method.<sup>188</sup> This two-stage cluster survey technique was developed for use in LICs and responds to some of the methodological and statistical weakness of other widely-used survey techniques such as the WHO EPI method. In a first stage of selection CSS randomly selects larger geographic areas or clusters using probability proportional to size sampling. Each selected cluster is then divided into small geographic regions or “segments” each of which is equal to the desired measure of size. In a second stage, one segment per cluster is selected using simple random sampling and all of the houses in the segments are solicited to participate. The CSS sampling technique can be adapted to any number of research questions and has been used by UNICEF ‘s Multiple Indicator Cluster Surveys, the World Bank as part of their Microenterprise Surveys<sup>189</sup>, and a modified version has been included in methodology of rapid assessment of avoidable blindness (RAAB) surveys created by the London School of Tropical Medicine and Hygiene. This technique provides a number of powerful methodological advantages useful in the investigation of antibiotic consumption. Including all houses in the segment helps facilitate variance estimates and eliminate potential selection biases.<sup>188, 190</sup> Importantly, this technique also allows for revising non-response households thus lowering “at-home” bias which was found to be an important factor in a recent analysis of survey techniques.<sup>191</sup> The defined geographic segments can be easily revisited if necessary or be used to monitor changes.

## Conclusion

Antibiotic resistance is growing in low-income countries and threatens to greatly increase morbidity and mortality among already vulnerable populations. Programs to control antibiotic use are needed to combat the development of resistance particularly in LICs where few controls exist. In order to be effective, these programs need quality data on antibiotic consumption which is made difficult due to the use of antibiotics from non-prescribed sources in some countries. Special techniques are needed to account for these special circumstances and gather the data necessary to control antibiotic use and combat resistance. An integrated and adaptive approach beginning with community surveys responds to the various data needs and difficulties of LIC contexts and may help facilitate the investigation and control of antibiotic consumption in LICs. Use of this type of approach could provide actionable, comparable data across LIC countries.

The LIC context is complicated not only for the study of antibiotic resistance and antibiotic consumption but also for a number of other health issues. Data collection for these issues may face similar difficulties as antibiotic consumption. An integrated approach may therefore also respond to some of the issues in data collection found in other health issues in LICs and it could be easily adapted to other uses.

## Chapter 4 – Madagascar, Senegal Survey

### Introduction

Gathering data on antibiotic consumption must be a priority in LICs to fill knowledge gaps and develop strategies to respond to antibiotic resistance. This data is particularly sparse in countries from Sub-Saharan Africa which is home to 26 of the World Bank's 31 low-income countries.<sup>158</sup> The high infectious disease burden of children in these contexts makes them important drivers of antibiotic consumption in many countries and those most vulnerable to resistance.<sup>16, 57</sup> Africa is home to a high burden of infectious disease which accounts for over 75% of under-5 deaths in the region.<sup>4</sup>

To measure antibiotic consumption and related factors in LICs, we undertook community surveys among children in both Madagascar, a low-income country, and Senegal, a middle-low income country.<sup>158</sup> Along with a need to fill the gap of antibiotic consumption information in these countries, the presence of the BIRDY program allows for valuable antibiotic resistant burden information and a fuller picture of antibiotic resistance.

#### *Madagascar context*

Madagascar is an island nation of over 23 million inhabitants with a GDP per capita of \$440.<sup>192</sup> Over 75% of the population lived below the poverty line in 2014. Health care access and usage is limited in certain regions and as many as 60% of women give birth at home while 40% of the population lives further than 10 kilometers from the closest health center.<sup>193, 194</sup> According to the WHO there are only 1.6 physicians per 10,000 people in Madagascar (vs. over 20 in most high income countries). Basic care is provided for free in state hospitals or lower level government health centers, but families have to pay for supplies such as medication, bed sheets, and food.<sup>21</sup>

Disease risk factors such as malnutrition are widespread and 76% of the population is estimated to consume fewer than the minimum recommended daily caloric intake. These factors are reflected in high infectious disease rates and an under-5 mortality rate of 50 deaths per 1,000 live births.<sup>195</sup>

#### *Senegal context*

Senegal is a West-African nation of over 13 million people and enjoys a slightly higher socioeconomic status than Madagascar. The proportion of Senegalese living under the poverty level as estimated at 47% in 2011 and GDP per capita was \$2,525 in 2013. Access and usage of health care remains heterogeneous with large disparities existing according to socioeconomic status and consultations with traditional healers remains common even in the urban capital of Dakar.<sup>196</sup> Despite better economic conditions, under-5 mortality was roughly equivalent to that of Madagascar, estimated at 47 deaths per 1,000 live births in 2015.<sup>195</sup> The Senegalese health system is organized vertically with a central level, 14 medical regions and 75 health districts. Each district counts one or more hospitals, one health center and several health posts. Like Madagascar there are few doctors at only .6 physicians per



10,000 people. Medical care and many medications are free for children under 5 in public structures since the introduction of Universal Health Coverage in 2013-2014.

## Study Objectives

The main objective of this study was to investigate antibiotic consumption patterns among children under 2 in both Madagascar and Senegal. This included a number of specific objectives including: measuring under-2 consumption of antibiotics in the last three months, estimating the under-2 consumption of non-prescribed antibiotics in the last three months, determining factors associated with antibiotic and non-prescription antibiotic consumption, and studying differences between sites and examining related variables. To our knowledge, no studies have been published on antibiotic consumption among children in these countries. The age range and study sites were selected in an effort to harmonize results with the BIRDY program.

## Methods

### *Survey population*

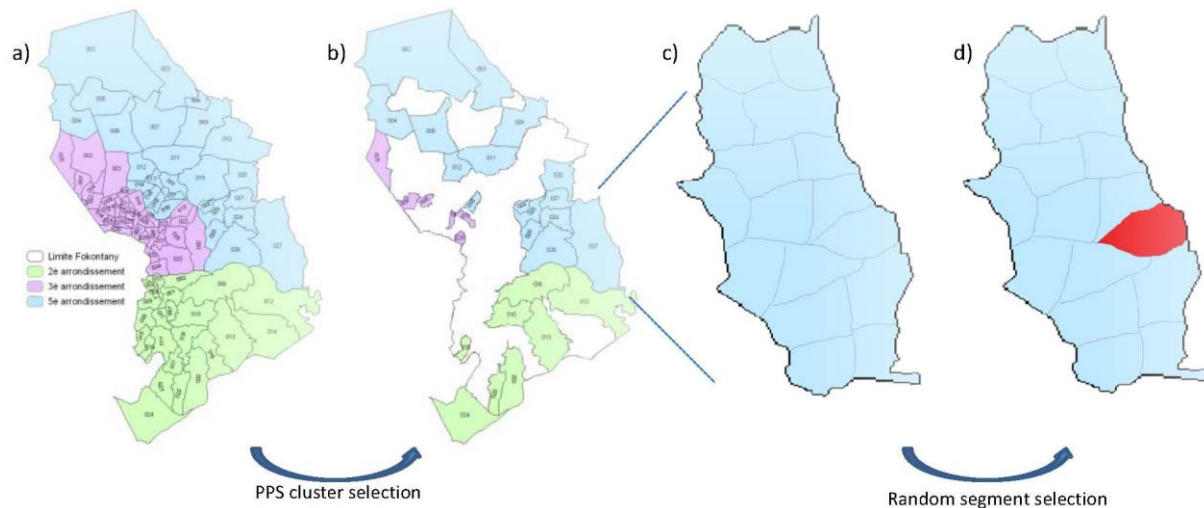
A cross-sectional population-based survey was carried out between November 2014 and February 2015 in Madagascar and from April to July 2015 in Senegal. The study population in Madagascar included children under 2 living in the 2nd, 3rd, and 5th arrondissement of the urban capitol city Antananarivo (total population: 1,168,898) and those living in the semi-rural city of Moramanga (total population: 46,393). In Senegal the study population included children under 2 living in Guediawaye (total population: 329,659), an urban suburb of Dakar. To be included in the study, the household contacted should have been considered the primary residence for the child and consent was required from an adult family member or caregiver who had knowledge of the child's medical history. The study population of children under two in each site was estimated at 23,433, 1,523, and 15,750 for Antananarivo, Moramanga, and Guediawaye respectively.

### *Household selection*

A two-stage cluster survey was undertaken using compact segment sampling (CSS).<sup>188</sup> CSS is a two-stage cluster sampling technique based on the EPI cluster survey method developed by the WHO.<sup>197</sup> First, thirty clusters in each study site were selected from the study zones with probability proportional to size methods (PPS) using national census or demographic survey data. The choice of thirty clusters was made by convention and was considered sufficient to control for anticipated between-cluster variability.<sup>197</sup> A cluster was defined as the smallest administrative district in both Madagascar and Senegal. Average total population for clusters was 7162, 3569, and 4411 for Antananarivo, Moramanga, and Guediawaye respectively. Clusters were divided into smaller equal sized geographic units (segments) each of which contained approximately 14 children. These segments were enumerated and one segment per cluster was selected at random using a random number table. Once a segment was selected all houses/children in the segment were solicited to participate (See Figure 15). In the case of non-response households, one revisit was

scheduled during the week and a second revisit during the weekend if necessary before considering the house unreachable. No attempt was made to replace non-respondent households.

Once selection was completed, field workers were provided with maps and GPS devices to identify segments in the field. The maps and a household tracking sheet were used together to verify that all houses were visited and to facilitate revisits. (Appendix S6, S7)



**Figure 15.** Segment selection steps in Antananarivo using the compact segment sampling method.

- Three study arrondissements in Antananarivo.
- 30 selected clusters/administrative districts using PPS sampling.
- Example of one selected cluster divided into segments.
- Random selection used to select study segment.

### *Study size*

A sample size of 400 children in each site was calculated based on an estimated 40% antibiotic use in the previous 3 months, a desired precision of 10%, and a design effect of 4. The design effect is a measure of the additional variability resulting from cluster sampling techniques.

### *Data gathered*

Before collecting data, village or neighborhood chiefs were consulted and authorization obtained. Data was gathered from the child's parent or other caregiver via face to face interviews by trained field workers. Field workers used pre-tested questionnaires and gathered data on sociodemographic variables, the health history of the child, and the child's antibiotic consumption in the previous three months. (Appendix S5) Sociodemographic variables included information on the profession and education of the mother along with

information about the household. Health history questions included vaccination status, height and weight of the child, and prematurity. Finally, antibiotic consumption questions included reported consumption of antibiotics during the last three months, along with questions about why, where, and how the antibiotic were purchased and consumed if any. Respondents were also asked to show field workers any available prescriptions, antibiotics, or antibiotic packaging remaining from consumption episodes. In Madagascar the questionnaire was translated into Malgash by translation experts from the Institut Pasteur in Madagascar and field tested prior to use. In Senegal the original French version was used with oral translations into Wolof agreed upon between study field workers and supervisors, and field tested prior to use. To reduce memory bias, visuals aids of commonly used pediatric antibiotics as well as a locally adapted calendar were presented. (Appendix S8,S9) Respondents were also asked to show field workers any available prescriptions, antibiotics, or antibiotic packaging remaining from consumption episodes. Adult respondents in Senegal were asked additional questions regarding their own antibiotic use in the previous year as well as health care seeking behavior for themselves and the child.

Up-to-date vaccination was defined by local schedules. Children were considered up to date unless they had exceeded the maximum recommended age for vaccination as defined by the WHO. Newborns under 2.2 kilos were considered underweight and treatment compliance was self-reported based on prescribed duration. Data were double entered into an EpiData database created for the project and checked weekly for errors and missing data.

#### *Health care structures and pharmacies*

A mapping of health care structures and pharmacies located in the study areas was performed for Moramanga and Guediawaye based on the knowledge of local field workers familiar with these areas. For Antananarivo, these data were based on pharmacy lists from the “Agence du Médicament de Madagascar” and data from city records.

#### *Statistical analysis*

Statistical analyses were undertaken with Stata 11.0 (StataCorp. College Station, TX). Population estimates including confidence intervals were calculated for the proportion of children with any medication use, any antibiotic use, or any antibiotic use without a prescription in the last three months.

Pearson’s chi2 test and Wald test were used to compare categorical and continuous variables respectively. An exploratory logistic regression was used to determine variables associated with any consumption of antibiotics in the last three months (consumption in last three months vs none). For multivariate analysis, variables associated with the outcome of interest in the univariate analysis (at the  $p < 0.25$  level) were included and a step-wise descending procedure was used to obtain a final logistic regression model. Pooled multivariate analyses were adjusted for study site. Significance for multivariate analysis was set at  $p=0.05$ .

To take into account within-household correlation among households with multiple children, a multi-level logistic analyses was also performed. The svy command was used where appropriate to take into account the survey design.

### *Ethics*

The study was approved by the Senegalese National Ethics Committee for Health Research (scientific and ethical approval n°55/MSAS/DPRS/CNERS March 31st, 2015) and by the Ethical Committee of the Malgasy Public Health Ministry (n°114/MSANP/CE November 3, 2014). The study was also associated with the BIRDY program.

## Results

### *Sociodemographic characteristics by site*

In total 394 children were recruited in Antananarivo, 502 in Moramanga, and 505 in Guediawaye. Refusals to participate were rare across sites with 23 households (1%) refusing to participate in Moramanga, and 17 (<1%) and 6 (<1%) households refusing in Antananarivo and Guediawaye. No information on the presence of children under two in these houses or the reasons for non-participation was available. Sociodemographic characteristics for the sample populations can be seen in Table 6. Mothers' education differed between sites with lower levels of education in Guediawaye. Unemployment among mothers was also different with 52.9%, 64.6% and 76.9% unemployed at visit in Antananarivo, Moramanga, and Guediawaye respectively. Access to electricity was higher in Guediawaye (98.8%), as compared to Antananarivo (84.7%) and Moramanga (80.2%). Access to flushing toilets also differed between sites ranging from 4.2% in Moramanga, to 6.9% in Antananarivo and 19.6% in Guediawaye. Overall, households in Senegal included more people than in Madagascar but density per room was greater in Antananarivo (2.9 persons per room) than in Moramanga (2.6) and Guediawaye (2.5). No statistical tests were performed comparing these sociodemographic variables across site.

Children's characteristics did not show significant overall differences between sites for baby age, sex, malnutrition, or premature or underweight birth (Table 7). Significant overall differences were found for up-to-date vaccination with proportions of 90.5%, 71.6% and 67.6% in Guediawaye, Moramanga, and Antananarivo respectively.

**Table 6.** Socio-demographic sample characteristics of children under 2 participating in a community survey in Madagascar and Senegal.

	<b>Antananarivo</b> N=392 n (%)	<b>Moramanga</b> N=500 n (%)	<b>Guediawaye</b> N=505 n (%)
<b>Child order (among children under 2 in household)</b>			
1	375 (95.7)	496 (99.2)	418 (82.8)
2	14 (3.6)	4 (0.8)	66 (13.1)
3	3 (0.8)		17 (3.4)
4			4 (0.8)
<b>Mother's age</b>			
Mean (sd)	27.1 (5.7)	25.0 (4.7)	27.9 (5.8)
<b>Respondent</b>			
Mother	335 (85.5)	449 (89.8)	474 (93.9)
Father	23 (5.9)	35 (7.0)	9 (1.8)
Other family member	33 (8.4)	16 (3.2)	22 (4.4)
Other	1 (0.3)	0 (0)	0 (0)
<b>Mother's Occupation</b>			
	n=391	n=479	n=502
Unemployed	207 (52.9)	323 (64.6)	386 (76.9)
Unskilled labor	118 (30.2)	127 (25.4)	84 (16.7)
Skilled labor	66 (16.9)	29 (5.8)	32 (6.4)
other	1 (0.3)	21 (4.2)	3 (0.6)
<b>Mother's Education</b>			
None	4 (1.0)	16 (3.0)	239 (47.3)
Primary	65 (16.6)	91 (18.2)	151 (29.9)
Some high school	158 (40.3)	248 (49.6)	81 (16.0)
High school	119 (30.4)	115 (23.0)	27 (5.4)
University	46 (11.7)	30 (6.0)	7 (1.4)
<b>Housing type</b>			
Individual house	128 (32.7)	255 (51.0)	125 (24.8)
House in compound (lot)	6 (1.5)	214 (42.8)	324 (64.2)
Room in a house	258 (65.8)	31 (6.2)	56 (11.1)
<b>Roof type*</b>			
Low quality	1 (0.3)	4 (0.8)	190 (37.6)
Standard	385 (98.2)	477 (95.4)	0 (0)
High quality	6 (1.5)	19 (3.8)	315 (62.4)
<b>Wall type</b>			
Mud/Wood/Canvas	35 (8.9)	143 (28.6)	2 (0.4)
Brick/Cement/Stone	357 (91.1)	357 (71.4)	503 (99.6)

<b>Floor type</b>				
	Mat/Boards/Dirt/Sand	24 (6.1)	42 (8.4)	31 (6.1)
	Cement	364 (92.9)	457 (91.4)	179 (35.5)
	Tiles/Wood floor	4 (1.0)	1 (0.2)	295 (58.4)
<b>Access to electricity</b>				
	Yes	332 (84.7)	401 (80.2)	499 (98.8)
<b>Toilet type</b>				
	with flush	27 (6.9)	21 (4.2)	99 (19.6)
	without flush	365 (93.1)	478 (95.6)	406 (80.4)
	no toilet		1 (0.2)	
<b>Number of people in home</b>				n=504
	Mean (sd)	4.8 (1.8)	4.4 (1.5)	10.5 (5.2)
<b>People per room</b>				
	Mean (sd)	2.9 (0.5-13)	2.6 (1.3)	2.5 (1.1)

\*Low quality: Madagascar - Canvas, cardboard Senegal - Sheet metal

Standard quality: Madagascar - Sheet metal

High quality: Madagascar - Tile Senegal - Cement

sd: standard deviation of sample distribution, without taking into account added variability from survey methodology.

**Table 7.** Demographic and health history information sample characteristics of children under 2 participating in a community survey in Madagascar and Senegal.

		<b>Antananarivo</b>	<b>Moramanga</b>	<b>Guediawaye</b>	Statistical comparisons		
		<b>N=392</b> <b>n (%)</b>	<b>N=500</b> <b>n (%)</b>	<b>N=505</b> <b>n (%)</b>	P value*		<b>Global</b>
					<b>Antananarivo vs Guediawaye</b>	<b>Antananarivo vs Moramanga</b>	
<b>Baby age (months)</b>							
	Mean (sd)	11.7 (6.5)	9.5 (7.2)	11.5 (6.4)	0.71†	< .01†	0.66
<b>Baby sex</b>	Female	192 (49.0)	266 (53.2)	267 (52.9)	0.31	0.15	0.31
<b>Underweight‡</b>		56 (14.3)	57 (11.4)	69 (13.7)	0.83	0.46	0.78
<b>Premature birth§</b>		n=392	n=499	n=497			
		7 (1.8)	7 (1.4)	14 (2.8)	0.44	0.69	0.45
<b>Underweight birth  </b>		n=387	n=494	n=503			
		14 (3.6)	10 (2.0)	32 (6.4)	0.08	0.21	0.06
<b>Vaccine up to date¶</b>		265 (67.6)	358 (71.6)	457 (90.5)	< .01	0.69	<.01

\*Comparisons take into account added variability from survey methodology

.† Wald test

‡ Based on weight for age definitions from WHO.

§ Prematurity defined as <37 weeks

|| Underweight birth was defined as <2200 grams

¶ Based on local vaccine schedule

sd: standard deviation of sample distribution, without taking into account added variability from survey methodology.

### *Antibiotic consumption*

Levels of antibiotic consumption in the last three months were 37.2% (95% CI 33.4% - 41.2%) in Guediawaye, 29.3% (95% CI 25.0% - 34.1%) in Antananarivo and 24.6% (95% CI 20.6% - 29.1%) in Moramanga (Table 8). These differences were statistically significant overall ( $P < 0.01$ ).

Non-prescription use of antibiotics was not significantly different among the three study sites at 7.8% (95% CI 4.2% - 14.3%) in Antananarivo, 13.0% (95% CI 10.3% - 16.3%) in Moramanga, and 8.0% (95% CI 4.2% - 14.7%) in Guediawaye ( $p=0.66$ ).

While most antibiotics were taken for the full length of the treatment in Moramanga (75.2%) and in Antananarivo (83.7%), only 52.3% of antibiotics were correctly taken in Guediawaye.

Only 6%, 5%, and 2% of the sample had multiple episodes of antibiotic consumption in the previous three months in Antananarivo, Guediawaye, and Moramanga respectively.

The majority of antibiotics were recommended by a doctor or a nurse (regardless of the presence of prescription) in Antananarivo (95.7%), Guediawaye (94.4%), and Moramanga (73.5%) (Table 9). In Guediawaye, a few antibiotics were recommended by the pharmacist directly (5.1%), sometimes followed by purchase without prescription. The person recommending antibiotic use was heterogeneous in Moramanga including 11% of antibiotics advised by a traditional healer and 2.9% by a midwife. Absence of advisor or self-advising was reported in Moramanga (6.6%) and Antananarivo (2.0%) but not Guediawaye.



**Table 8.** Population estimates of antibiotic consumption based on sample of children under 2 participating in a community survey in Madagascar and Senegal.

	<b>Antananarivo</b> <b>N=392</b> <b>% (95% CI)</b>	<b>Moramanga</b> <b>N=500</b> <b>% (95% CI)</b>	<b>Guediawaye</b> <b>N=505</b> <b>% (95% CI)</b>	Statistical comparisons P value*		
				<b>Antananarivo vs Guediawaye</b>	<b>Antananarivo vs Moramanga</b>	<b>Global</b>
<b>Any medication 3 months</b>	61.5 (55.8-66.9)	48.7 (43.7-53.7)	87.5 (82.4-91.3)	< 0.01	< 0.01	< 0.01
<b>Any antibiotic 3 months</b>	29.3 (25.0-34.1)	24.6 (20.6-29.1)	37.2 (33.4-41.2)	0.01	0.14	< 0.01
<b>Non-prescription use†</b>	7.8 (4.2 – 14.3)	13.0 (10.3-16.3)	8.0 (4.2-14.7)	0.97	0.12	0.66
<b>All doses prescribed/bought taken‡</b>	83.7 (76.0.-89.3)	75.2 (66.1-82.5)	52.3 (44.8-59.8)	< 0.01	< 0.01	< 0.01

CI – confidence interval

\*Comparisons take into account added variability from survey methodology.

† Among children with at least 1 antibiotic

‡ Antibiotic consumption episodes used at the denominator for this variable rather than the survey population (Antananarivo=142, Moramanga=134, Guediawaye=214)

**Table 9.** Characteristics of antibiotic consumption episodes in the sample of children under 2 participating in a community survey in Madagascar and Senegal.

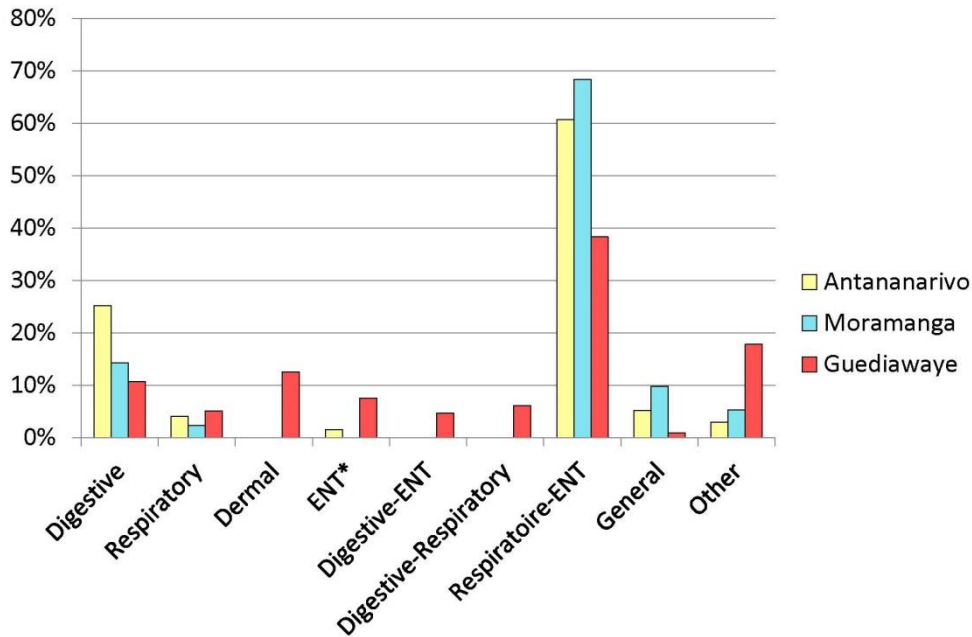
	<b>Antananarivo</b> <b>N=142</b> <b>n (%)</b>	<b>Moramanga</b> <b>N=136</b> <b>n (%)</b>	<b>Guediawaye</b> <b>N=214</b> <b>n (%)</b>
<b>Length of antibiotic (days)</b>			
Mean (sd)	4.1 (2.0)	4.4 (2.0)	5.7 (2.5)
<b>Advisor per episode</b>			
Doctor/Nurse	135 (95.7)	100 (73.5)	202 (94.4)
Matron	0 (0)	1 (0.7)	0 (0)
Healer	0 (0)	15 (11.0)	0 (0)
Shop keeper	3 (2)	1 (0.7)	0 (0)
Midwife	0 (0)	4 (2.9)	0 (0)
Pharmacist	0 (0)	1 (0.7)	11 (5.1)
No one	3 (2)	9 (6.6)	0 (0)
No response	1 (0.7)	5 (3.7)	1 (0.5)
<b>Where bought</b>			
Pharmacy	127 (89.4)	100 (73.5)	168 (78.5)
Doctor	10 (7)	10 (7.4)	0 (0)
Health center	0 (0)	13 (9.6)	46 (21.5)
Depot	0 (0)	1 (0.7)	0 (0)
General store	5 (3.5)	6 (4.4)	0 (0)
Healer	0 (0)	2 (1.5)	0 (0)
No response	0 (0)	4 (2.9)	0 (0)

sd: standard deviation of sample distribution, without taking into account added variability from survey methodology.

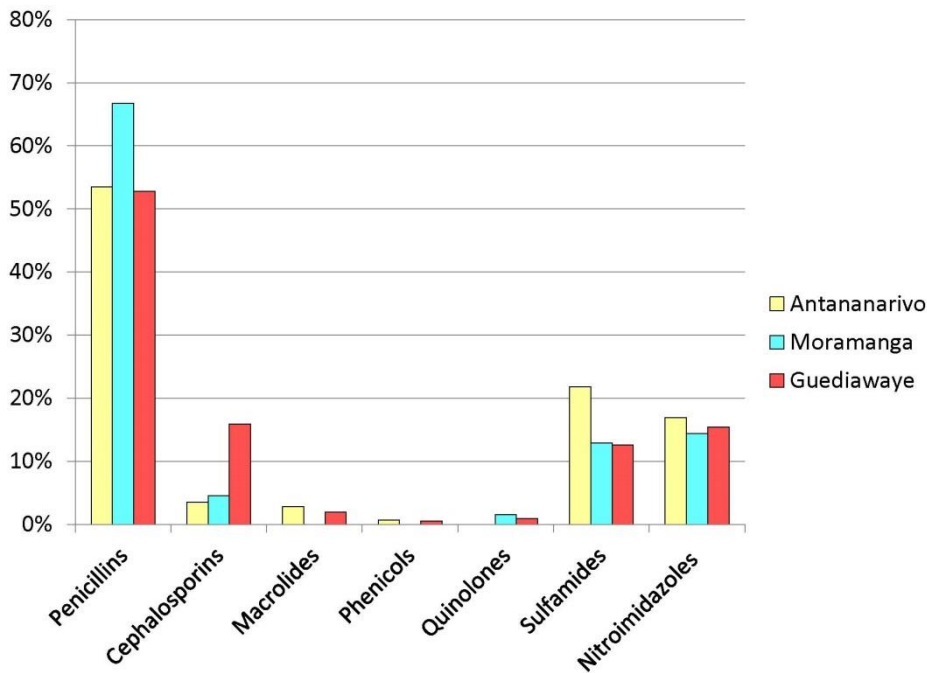
For all sites, the main symptom group leading to antibiotic consumption was respiratory-ENT (ear, nose, throat) symptoms representing 60.7% of consumption episodes in Antananarivo, 68.4% in Moramanga, and 38.3% in Guediawaye (Figure 16). The second most frequent group of symptoms reported in Antananarivo and Moramanga were digestive (25.2% and 14.3% respectively). These symptoms accounted for 10.7% of antibiotics in Guediawaye. Cutaneous symptoms and “other” symptoms not including respiratory, cutaneous, digestive or ENT symptoms represented 12.6% and 17.8% of episodes in Senegal respectively.

The most commonly used antibiotics were penicillins (53.5%, 66.7% and 52.8% for Antananarivo, Moramanga and Guediawaye respectively), including mainly amoxicillin (Figure 17). Other antibiotics commonly used in the three study sites were metronidazole and cotrimoxazole. Cephalosporins represented 15.9% of antibiotics consumed in Guediawaye, 3.5% in Antananarivo, and 4.5% in Moramanga. A small proportion of quinolones was found in Moramanga (1.5%) and in Guediawaye (0.9%).

Most antibiotics were bought in private pharmacies (89.4%, 73.5% and 78.5% in Antananarivo, Moramanga and Guediawaye respectively). In Senegal the remaining antibiotics were obtained in hospitals, health centers, and health posts. In Madagascar, purchase from the doctor directly accounted for 7.0% and 7.4% of antibiotics in Antananarivo and Moramanga respectively. Other sources identified in Moramanga included: depots (0.7%), general stores (4.4%) and traditional healers (1.5%). Non-prescribed antibiotics were purchased in pharmacies 55%, 56% and 80% of the time in Antananarivo, Moramanga, and Guediawaye respectively. In Antananarivo 44% of non-prescribed antibiotics were purchased in general stores, while 38% were purchased in these stores in Moramanga.



**Figure 16.** Distribution of symptoms and antibiotic consumption among children under 2 surveyed  
 \* ENT – Ear, Nose, Throat



**Figure 17.** Types of antibiotic classes used among children under 2 surveyed according to study sites

#### *Factors associated with antibiotic consumption*

Factors associated with antibiotic consumption in univariate analysis using data pooled across sites included housing and baby age (Table 10). Living in a house in a compound (OR 0.9, 95% CI 0.6 - 1.5) and living in a room in a house shared with other households (OR 0.7, 95% CI 0.5 - 0.9) showed lower antibiotic consumption compared to living in an individual house. Living in a family house (OR 1.1, 95% CI .8 - 1.5) showed higher antibiotic consumption compared to living in an individual house. Age above six months was also associated with greater antibiotic consumption compared to the zero to six month group (OR 1.8, 95% CI 1.2 - 2.6 for children 6-12 months, OR 1.7, 95% CI 1.1 - 2.7 for children 12-8 months, OR 1.5, 95% CI 0.9 - 2.2 for children 18-24 months vs children 0-6 months). While overall p-values showed significance for housing, individual level comparisons were not significant. Similar results were obtained when analysis was restricted to babies older than three months old (data not shown).

Following a stepwise selection and adjusting for site, one factor remained significantly associated with higher antibiotic consumption in the last three months, living in houses without flushing toilets (OR 1.4, 95% CI 1.0 - 1.9). Neither vaccination status nor any other child health characteristics were associated with antibiotic consumption.

In site specific analyses, three factors were independently associated with antibiotic consumption in the last three months in Guediawaye: parental antibiotic consumption in the last year (OR 2.5, 95% CI 1.1 - 5.8), systematic use of health structures in case of fever, diarrhea or cough (OR 5.4, 95% CI 2.1 - 13.4) and non-flushing toilets (OR 1.8, 95% CI 1.2 -

2.6). Analyses of combined Madagascar site data found that a child ages of 6-12 months (OR 3.8 95% CI 2.4 - 6.1), 12-18 months (OR 3.4, 95% CI 2.0 - 5.8), and 18-24 months (OR 2.6, 95% CI 1.3 - 5.3) were associated with higher antibiotic consumption as compared to the 0-6 month group. The number of rooms in a household was also significant with higher antibiotic usage among children living in households with two rooms (OR 1.8, 95% CI 1.2 – 2.8) or three or more rooms (OR 1.5, 95% CI 1.0 – 2.3) versus those with one room. Information on parental antibiotic consumption and systematic use of health structures was too sparse for analysis in Antananarivo and Moramanga.

Due to the limited number of households with multiple children, results from multi-level logistic analyses were similar to those obtained from the simple model (results not shown).

#### *Antibiotic consumption and structural factors*

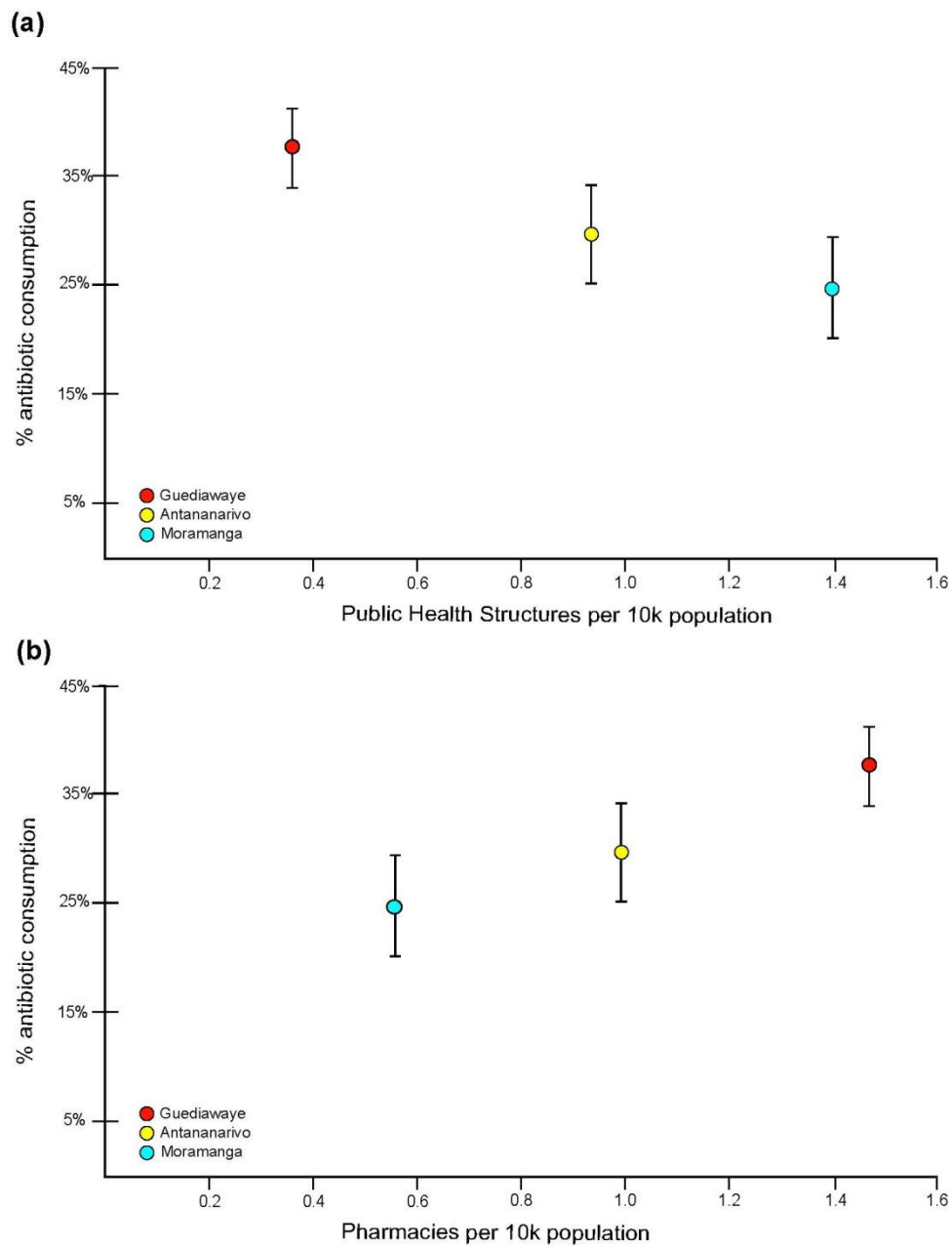
Among our three sites, lower antibiotic consumption levels were observed among sites with a higher density of public health structures. Inversely, higher levels of antibiotic consumption were observed among sites with a higher density of private pharmacies in the study area. (Figure 18).

**Table 10.** Factors associated with antibiotic consumption in the last three months among children under 2 in Madagascar and Senegal.

Variables	OR* (95% CI)	P	ORa† (95% CI)	P
<b>Mother's education</b>		0.09		
No education	1		-	
Primary education or more	0.77 (0.56-1.05)			
<b>Housing</b>		0.02		
Individual house	1		-	
House in compound	0.94 (0.57-1.54)			
Room in a house with other households	0.71 (0.52-0.97)			
Family house	1.08 (0.80-1.48)			
<b>Floor material</b>		0.19		
Mat/Boards/Dirt/Sand	1		-	
Cement	0.97 (0.57-1.66)			
Tiles/Wood floor	1.29 (0.76-2.17)			
<b>Toilet type</b>		0.14		0.03
With flush	1		1	
Without flush	1.26 (0.92-1.72)		1.43 (1.04-1.97)	
<b>Number of people in household</b>		0.14		
2	1		-	
3	3.03 (0.36-25.30)			
4-8	2.51 (0.30-21.32)			
>=9	3.44 (0.41-28.83)			
<b>Statutnut2/underweight</b>		0.07		
No	1		-	
Yes	1.34 (0.98-1.84)			
<b>Suivi2</b>		0.18		
No	1		-	
Yes	0.74 (0.48-1.16)			
<b>Baby age (months)</b>		0.01		
0-6	1		-	
6-12	1.79 (1.21-2.64)			
12-18	1.73 (1.10-2.74)			
18-24	1.47 (0.96-2.24)			

\*Unadjusted Odds ratio (OR)

† The adjusted Odds ratio (ORa) was adjusted for study site. CI – confidence interval



**Figure 18.** Antibiotic consumption estimates centers in study zone in Madagascar and Senegal per (a) number of public health structures and (b) number of pharmacies per 10k population.

## Discussion

The results of our study are the first comprehensive estimates of antibiotic consumption among children in Madagascar and Senegal and add important data to the antibiotic consumption literature in LICs where few quality data exist. The collection of factors related to antibiotic use is also important in order to understand consumption and develop any necessary public health measures or surveillance methods. Substantial levels of consumption in the last three months were found particularly in Senegal.

The observed proportions were lower than those from community surveys in other LICs from South East Asia.<sup>149, 150, 185</sup> In addition to real differences in antibiotic consumption, our methodology and use of various study tools may have reduced selection bias and misclassification of non-antibiotic medication leading to increased consumption measures in other studies. The observed proportions more closely matched those among children in developed countries but remain elevated.<sup>8, 198, 199</sup>

Data from Madagascar and Senegal show no peak in influenza cases during the study recall period (surveillance data from Malagasy Health Ministry).<sup>200</sup> Influenza has been found to be a main driver of antibiotic consumption in other countries and the observed consumption rates may thus reflect a baseline measure.<sup>201</sup>

The majority of antibiotic consumption was prescribed for children with respiratory and ear, nose, and throat symptoms in all sites. These symptoms are related to upper respiratory tract infections which are often caused by viruses and for which antibiotics are not recommended.<sup>202</sup> Use of microbiological results is rare in LICs. However, without proper diagnostic testing, determining the causative agent of an infection is difficult and prescribing an antibiotic may be likely. Development and use of adapted diagnostic tools could help improve prescribing and avoid unnecessary use. In Senegal a number of symptoms classified as “other” included a variety of non-infectious diseases for which antibiotics are inappropriate.

In pooled multivariate exploratory analyses only one variable remained significant after adjusting for site. Non-flush toilets may reflect a lower socioeconomic status or play a role in disease spread through lack of hygiene although no difference was noted in symptoms according to toilet type.

Interestingly, vaccination coverage was not associated with a reduction in antibiotic use in pooled analyses. Increased vaccination has been proposed as a potential means to reduce the use of antibiotics.<sup>3</sup>

Analyses of non-prescription antibiotic use showed lower consumption among children living in houses with access to electricity. This may indicate lower non-prescription use among those with higher socioeconomic status. However, the low number of non-prescription episodes makes these analyses difficult to interpret.

The higher antibiotic consumption in Senegal compared to Madagascar may be due to a higher overall health care use and use of medication which can be seen in the significantly



higher use of any medication in the last three months among Senegalese children. A higher overall socioeconomic status in Senegal might also translate into more health care access and antibiotic consumption.

Recent analyses show that the countries with the highest growth of antibiotic consumption were middle-income countries with growing economies.<sup>64</sup> The difference in consumption between Senegal, a lower-middle income country, and Madagascar, a low-income country, supports this finding.

Respective national health policies in each country may also play a role in consumption differences. In 2013 a Universal Health Coverage law was launched in Senegal under which healthcare for children under-five along with a number of antibiotics became free in public health structures. In Madagascar evaluation and follow-up of children is free in public health centers. However, any medication including antibiotics must be paid for which can create barriers to access for the poorest families.<sup>203</sup> Increases in antibiotic usage, including both appropriate and inappropriate, has been observed in patients provided with free health care compared to controls in randomized and observational studies.<sup>204, 205</sup>

Interestingly, the number of public health care centers per capita was inversely correlated with antibiotic consumption. The Senegalese study population had fewer public health centers per capita. Additionally, 12 of the 13 health care centers in Guediawaye were low level health structures staffed by nurses or other non-doctor health personnel. All public health care structures in Madagascar, on the other hand, were staffed with doctors. The relative scarcity of health structures may translate into shorter consultation times. These shorter consultations combined with under-trained staff and free antibiotics found in Senegal may largely contribute to the higher rates of medication and antibiotics observed in this site.

Antibiotic consumption patterns of children enrolled in the BIRDY cohort study provides insight into the role of prescriber training. This cohort which is active in Madagascar and Senegal enrolls children under 2 in LICs in order to determine the burden of antibiotic resistance infections. Enrolled children benefit from free medical care and medication including medical evaluations by trained pediatricians. BIRDY participants are similar socioeconomically to the children included in our survey and live near survey study zones. Children in the cohort however, showed antibiotic consumption proportions in the last three months of just under 20% in both Antananarivo and Moramanga during the same study period (unpublished data – <http://www.birdyprogram.org/> Huynh BT, Padget M., Herindrainy P., Piola P., Delarocque-Astagneau E., Guillemot D.). In this case, access to free health care and antibiotics did not result in higher consumption highlighting the role of prescriber training.

A higher number of pharmacies per capita was also correlated with increased antibiotic consumption in the three sites. This could be due to a greater availability of drugs overall and greater proximity to the families, resulting in facilitated access to antibiotics. Hypotheses surrounding the access to health care and pharmacy density remain speculative however, and their contribution to antibiotic consumption is unknown.

Non-prescription use in both countries was lower than two other studies in LIC settings.<sup>150, 177</sup> These relatively low proportions may be due to parents and antibiotic distributors being particularly cautious about providing non-prescribed medication to small children. This hypothesis is supported by the much higher proportions of non-prescription parental antibiotic consumption in Antananarivo and Moramanga (50% and 30% respectively) although these data are based on small sample sizes. They may also be due to desirability bias as participants may not want to report non-prescription use.

In Moramanga, slightly higher proportions of non-prescribed antibiotics were observed. A higher heterogeneity of antibiotic advisor and place of purchase, common in rural LIC settings, was also observed although no association with non-prescribed consumption was tested statistically.

The large majority of antibiotics in all sites were obtained in pharmacies and recommended by a doctor. These findings correlate with the relatively low levels of non-prescription use and may reflect a perceived vulnerability of the study population. In Senegal over 90% of respondents suggested they would seek a medical consultation systematically if a child had cough, fever, or diarrhea while only 57% would do the same for themselves. These are positive findings in terms of surveillance and public health interventions. With low use of alternative antibiotic sources and few non-prescribed episodes, antibiotic surveillance for child use focused principally on pharmacies may be appropriate and interventions aimed at doctors might be effective in reducing unnecessary use. The few non-prescription antibiotics observed were purchased mainly in pharmacies and pharmacy interventions might be effective in reducing this practice in children or the general population.

Non-compliance with antibiotic duration may be a risk factor for the development and transmission of resistance and the low compliance seen in Guediawaye is a concern. This may be attributable to the fact that many prescriptions were coming from staff who did not properly explain the importance of finishing the antibiotic course due to lack of training or time constraints.

Some limitations are associated with the cross-sectional nature of this study. Recall bias could have been an issue leading to unreported episodes of antibiotic consumption in the last three months leading to lower observed rates. This may have been a problem specifically when multiple consumption episodes occurred in the study time-frame. Episodes outside the study time-frame may also have been counted. Desirability bias may have played a role in the low-rates of non-prescribed antibiotic consumption as participants may not want to report non-prescription use. We tried to control for these bias with the use of study tools such as the calendar as well as questionnaire design and question placement. Verification of antibiotic packaging and prescriptions consistently corresponded with oral responses confirming our confidence in the data collected.

In addition to important information on a high risk population, results from these surveys are useful for comparing across countries and shaping specific policy measures within countries. While these results may not be generalized to other LICs due to the heterogeneity among these countries, they may be generalized within countries to areas with similar population characteristics.

The presence of the BIRDY study is valuable as consumption data from each site can be compared to local community resistance profiles and add to a larger narrative about antibiotic resistance in LICs. The wide use of third generation cephalosporins in Senegal is of special interest as these drugs are related to the presence of ESBLs. High proportions of ESBL positive bloodstream infections have been recently reported in this country.<sup>206</sup>

## Conclusion

These data are crucial for the implementation of programs aimed at optimizing antibiotic consumption. Our results show elevated levels of antibiotic consumption but often for symptoms suggestive of viral infection. While any unnecessary use must be reduced there is no guarantee that all children needing antibiotics are getting them. LICs must be careful to balance restriction and access in the context of antibiotic resistance.<sup>3</sup>

Country level factors such as density of health care facilities, national antibiotic payment programs, and prescriber training seemed to be important in driving antibiotic consumption and should be taken into account when developing strategies to optimize antibiotic consumption in LICs. Similar investigations could be useful in other LICs where consumption data is lacking and risk factors exist for the development and spread of antibiotic resistance. These investigations could allow for comparison across countries. They may also lay the foundation for permanent surveillance systems, or provide key information to inform and measure public health programs designed to tackle resistance via antibiotic consumption.

## Ch 5 – General Discussion and Conclusions

### Current work and resistance in LICs

#### *Research objectives and results*

The first objective of this work was to quantify the burden of antibiotic resistance in the community among children under two in LICs. This included determining incidence of severe bacterial infections, pathogens involved, and resistance profiles. Due to lack of data on this subject, and a number of limitations and biases in the published data, determining the burden in LICs is currently impossible. The results do however shed light on current measurement weakness and provide a path forward. Future research on this issue should include community-case recruitment, high quality microbiology methods, and the inclusion of both urban and rural communities to account for potentially different disease burden and care access.

The second objective of this work was to review current techniques used to measure antibiotic consumption in LICs from published literature and propose an adapted solution to this issue. Results from the literature review showed that current techniques used in isolation are insufficient to respond to all the data needs in LIC contexts. This is particularly true given the widespread use of non-prescribed antibiotics. Integrating study techniques and starting with community surveys may respond more adequately to this issue in LICs and lead to more actionable results.

The third objective was to investigate patterns of antibiotic consumption and related factors among children under two in two African LICs. This investigation was designed to fill the gap in data on consumption in African LICs and respond to questions necessary to implement techniques to measure and adapt antibiotic consumption. Results fulfilled these objectives and included important information on total consumption, use of non-prescribed antibiotics, sources of antibiotics, and treatment compliance. Results also validated the use of community surveys in achieving study objectives in both urban and rural LIC settings. The use of similar methodology allowed for comparison across countries. These cross-country analyses highlight the importance of local contexts including the availability of health care facilities, availability of pharmacies, national payment schemes, and provider training. Specific recommendations for antibiotic surveillance tailored to the situation as well as interventions are also possible based on these data.

Results from the investigations on both the burden of antibiotic resistance among children in LICs and antibiotic consumption add essential data to the literature where relatively little data exists and reveal lessons about studying these issues in LICs.

#### *Non-prescription antibiotics*

In preparing the work on antibiotic consumption measurement in LICs, the high proportions of non-prescription antibiotic use documented in LICs worldwide<sup>70</sup> played a key role in shaping initial hypotheses and methodological approaches. We expected to see significant

proportions on non-prescription antibiotic use in our investigations as well and the relatively low observed rates were surprising. From the available data, the most probable hypothesis is that parents consider children under two to be fragile and are reluctant to take responsibility for treatment through non-prescription antibiotics. This hypothesis was supported by responses about health care seeking behavior as well as the higher proportions of non-prescription antibiotics among adult respondents. These low observed rates in the current work do not however mean that this type of use should be ignored in LICs particularly in investigations including a wider range of ages.

#### *Strengths and weaknesses of this work*

One major strength of this work is the combination of various perspectives on antibiotic resistance in LICs. Resistance is a multifaceted issue and exploring both burden and risk factor measurement including antibiotic use and misuse is necessary to understand and respond to this issue and provides a more complete picture.<sup>207</sup>

A second major strength of the current work is the combination of theory and practice for antibiotic measurement in LICs. The review of measurement techniques gives the survey work a strong methodological underpinning while the survey work validates the methodology with real world experience across multiple LICs. Using a similar methodology across sites and countries also provided a strong advantage in comparing cross-country similarities and differences and in helping to investigate observed differences.

One weakness of the current work may be limiting our research to children under two in LICs. This age group was chosen due to a higher burden of bacterial disease and to facilitate comparisons with the BIRDY study. However, in our burden study, this limit was sometimes problematic as data is often reported for children under five. In a larger sense, antibiotic resistance burden and determinants including antibiotic consumption are not limited to specific ages.<sup>208</sup> Antibiotic consumption and resistant infections in children under two may have an impact on the resistance burden in a community as a whole. Inversely, resistant bacteria infecting children under two may arise from any number of sources outside this population. Restricting our scope to children under two may limit understanding this global dynamic.

The focus on community infection and antibiotic consumption in the community means that hospital acquired infections are not treated and episodes of hospital antibiotic consumption may be missed. Antibiotic resistance has been noted at high levels in LIC hospitals<sup>56</sup> and a full understanding of resistance in LICs must include these infections.

As part of our investigation of antibiotic use among children in LICs, we planned on using the simulated client method to investigate non-prescription antibiotic use. However, this method proved difficult to apply to children as pharmacists or antibiotic providers in informal markets refused to provide antibiotics without a prescription to children under two. When tested for adults, this method was shown to be effective and could be used in investigations of a wider age range.

Lastly, our two literature searches were limited to articles in English. A number of LICs may not be English-speaking countries and research from these countries may be missed in our review.

## *Challenges*

Treating the topic of resistance or antibiotic consumption in LICs is challenging not only because of the difficulty in gathering data in these countries but also because of country heterogeneity. Treating all low-income countries as a single group and delivering messages applicable to all LICs may not be appropriate in some circumstances. Health care structure, access, and challenges in LICs in South East Asia are not necessarily the same as those in Sub-Saharan Africa and the determinants of infection or antibiotic use may be completely different.<sup>209</sup> Furthermore, high heterogeneity may also exist within countries between urban and rural areas.<sup>187</sup>

Given this heterogeneity, qualitative approaches may be helpful to understand local contexts particularly in the context of non-prescribed antibiotics. Interviews with health care actors including doctors, pharmacists, or government health officials may be useful to understand local contexts and interpret results.<sup>210</sup>

## *Lessons from LIC context*

Much of the work on both antibiotic resistance and antibiotic consumption focused on methodological issues in measurement. Common to both topics is that measurement techniques used in developed countries do not always correspond to LIC contexts.<sup>211</sup> The lack of medical or data infrastructure in LICs is particularly problematic. These limited data may affect not only antibiotic resistance and consumption but other health topics requiring data in LICs. Research based on data from the medical sphere (hospitals, pharmacies, etc.) common in developed countries may exclude data from the community where important medical events may occur including infections, deaths, and antibiotic use in LICs.<sup>212</sup> These lessons must be kept in mind when designing systems to measure antibiotic resistance or consumption in LICs.

## *Interventions in LICs*

Much of the current work revolved around collecting data useful for public health interventions or policy to combat antibiotic resistance. Adapting antibiotic use to curb resistance is often equated with restricting use. In developed countries as much as 50% of antibiotic use is unnecessary<sup>213</sup> and no increased mortality or morbidity have currently been noted with a reduction of their use.<sup>214</sup> Our study shows potentially large proportions of antibiotics used for viral infections among survey children. In LIC contexts reduction of antibiotic use and particularly unregulated non-prescribed use may seem like clear intervention targets. However, non-prescription antibiotic use is often the result of lack of access. For many, non-prescription sources are the only means for accessing life-saving antibiotics. Furthermore, lack of access to antibiotics kills many more people each year worldwide than antibiotic resistance particularly in LICs.<sup>215</sup> Estimates from 2005–2006 in India show that a large proportion of infant and childhood pneumonia deaths would not have occurred if children had been properly treated with antibiotics.<sup>55</sup> Plans to tackle resistance in LICs must therefore be careful not to reduce access to those who need it while trying to reduce unnecessary use. Indeed, expanded health care access may not only save lives by providing more antibiotics to those who need it but may help curb unnecessary and non-prescribed use.<sup>3</sup>

### *One health and animal use*

The current work focused on human resistance burden and consumption. Recent “one health” approaches integrating both human and animal consumption represent an important perspective in the field of resistance research.<sup>216</sup> Indeed, the US food and drug administration estimates that over 70 percent of antibiotics are sold for animal use constituting a significant source of resistance selection pressure leading to high resistance rates in and around animal farms.<sup>217</sup>

The importance of antibiotics use in animals and their effect on humans in LICs was recently highlighted in a study from Ghana. This study showed high levels of antibiotic exposure in urine samples from individuals without an antibiotic consumption episode in the past two weeks but high levels of meat consumption.<sup>218</sup> Environmental selection of antibiotic resistance may also be part of this “one health” approach. Antibiotic contaminated water can be a breeding ground for resistance and has been found to host highly resistant bacterial strains.<sup>219</sup> Taking into account all sources will likely be necessary to plan comprehensive actions to combat the spread of resistance.

## Antibiotic Resistance globally

### *Future of resistance measurement*

A number of calls for resistance surveillance have been made to respond to the lack of data on this issue globally including in LICs. Along with a call for surveillance, the WHO in 2014 noted heterogeneous resistance detection methods and resistance definitions among current data across countries.<sup>1</sup>

Antibiotic resistance measurement in LICs requires a number of elements to provide valuable, reliable, and actionable data. Including both hospital and community infections is necessary to understand the whole burden of resistance. Active population-based surveillance is ideal to capture infections and calculate incidence rates. Given the wide disparities within countries, surveillance must also include both urban and rural areas along with a range of hospital and health center types including community recruitment particularly for early childhood infections.<sup>187</sup>

WHO has recently launched the Global Antimicrobial Resistance Surveillance System (GLASS) in response to this lack of data and to support the global action plan on antimicrobial resistance.<sup>220</sup> This initiative seeks to include countries worldwide including LICs and will include epidemiologic and microbiologic information. To encourage LICs to participate, information technology resources for resistance surveillance and reporting are made available. Countries without the possibility of providing data immediately may still join the initiative and give updates of progress toward program goals rather than data.

Along with high participation, goals include: standardized reporting and detection techniques allowing for cross-country comparability, regular reporting, detection of emerging resistance, and assessment of intervention impacts. Ultimately data is meant to inform decision-making on all levels and provide evidence for interventions.

Initiatives like this are important in gathering standardized data globally and from LICs on antibiotic resistance and moving research and action forward in these countries. However, many of the issues that currently make burden estimation in LICs difficult will remain problematic with this type of initiative. The biases inherent in much of the research on resistance burden such as relying on large or teaching hospitals will likely remain. In addition to these types of initiatives we still need solid investigations which include both hospital and community case recruitment and data from rural areas to truly understand and monitor the burden of resistance in LICs.

#### *Future of antibiotic consumption measurement*

Noticeably absent in much of the discourse surrounding global antibiotic resistance is antibiotic consumption. The GLASS initiative does mention linking with other databases such as those measuring resistance in the environment or the food chain, or measures of antibiotic use. However, these links are secondary aims and no specific information on how to implement them is given. Furthermore, no standard databases or reporting exist for antibiotic consumption in LICs.<sup>64</sup> Without antibiotic consumption data, little action can be taken to reverse global resistance trends in LICs. Resistance monitoring and antibiotic consumption measurement must be undertaken together in order to quantify and respond to the resistance problem in LICs.

The lack of standard measurements and measurement systems of antibiotic consumption in LICs is problematic. The use of Defined Daily Doses (DDDs) in developed countries has helped comparability in these countries but remains difficult to implement in LICs. As part of its Expanded Program on Immunization, the WHO developed a specific survey type to respond to vaccination measurement in LICs leading to wide acceptance and use of this methodology.<sup>197</sup> Developing a similar strategy for antibiotic use in developing countries could have a similar effect.

#### *Global responses to resistance*

One of the most commonly discussed solutions to antibiotic resistance in many developed countries is antibiotic development.<sup>221</sup> Antibiotic research has slowed in recent years due to the increasing difficulty of drug discovery and poor financial incentives for pharmaceutical companies leading to a number of laboratories abandoning antibiotic research and development altogether.<sup>19</sup> Recent proposals have been made to change financial incentives for pharmaceutical laboratories to develop antibiotics.<sup>38</sup> Other proposals have been made to expand access or increase use of little-used antibiotics. These may include previously non-profitable narrow spectrum antibiotics or those that have fallen out of favor due to side-effects.<sup>222</sup>

These initiatives are important in responding to already multi-resistant bacteria. However, public health measures necessary to reduce global selection pressure also need attention in order to address the fundamental driver of resistance. These public health issues include education measures both for the general population and doctors leading to a better understanding of antibiotic uses and misuses and resistance. Without reduced selection pressure, new antibiotics will ultimately lead to increased resistance. Furthermore, any newly discovered drugs may be financially inaccessible for many LICs.<sup>3</sup>



Reducing antibiotic use is necessary to manage resistance but has proven difficult. Certain public health campaigns have shown positive results in reducing overall antibiotic consumption but these reductions are difficult to maintain.<sup>223</sup> The common misconception that antibiotics have no side effects may push patients to ask for them or doctors to prescribe them even in situations where they are not recommended. Regardless of patient or doctor awareness, the risks of resistance may not be a sufficient deterrent to overconsumption given the dynamics of cost benefit from the individual patient perspective.<sup>224</sup> While an individual patient may experience the potential benefit of antibiotics, the cost of antibiotic resistance is shared by the community making questionable consumption a potentially attractive option. At least one part of the cost equation may be experiencing a paradigm shift as the research into the importance of the human microbiome increases. Early research linking high levels of antibiotic use to negative health impacts may shift the cost of antibiotic use from the community to an individual level.<sup>225</sup> Rather than telling a patient that the unnecessary use of antibiotics will, along with millions of other users, lead to higher levels of antibiotic resistance, with additional research doctors may be able to cite individual health risks of over consumption of antibiotics.

A recent report from the Review on Antimicrobial Resistance cites a number of integrated solutions to antibiotic resistance including public health and policy measures to reduce antibiotic consumption in humans and animals, improved measurement of resistance and antibiotic consumption, and financial solutions to encourage new research. This multi-pronged approach is needed to respond to the multi-part problem of resistance and provides a roadmap forward. Implementing these measures in LIC however will remain complicated and interventions must be adapted to the local contexts.

#### *Future of this work*

In addition to answering a number of questions, the current work also raises new ones and opens avenues for future research. Our investigation of antibiotic consumption in particular raised a number of important issues that could be explored through further research. The urban/rural dynamic is an interesting one in LICs due to lifestyles differences and access to health care. In our community survey in Madagascar we attempted to investigate some of these differences. Consumption data from a rural site in Senegal would be valuable not only in providing a greater depth and understanding of local consumption patterns but also in helping to answer questions about the urban/rural differences raised in Madagascar.

Our consumption study also raised many questions and hypotheses about the importance of health structural factors such as payment systems, provider training, and access to care in determining consumption patterns. Conducting consumption studies in other LICs using similar survey techniques would be useful to gather local data in these countries and in testing these hypotheses.

In order to expand our understanding of antibiotics consumption in LICs, future surveys may want to expand the study population to include people of all ages. While children under two represent a vulnerable population, the global selection pressure for resistance development is not limited to this population. Along with a larger proportion of the population, an expanded scope might also take a one health approach including antibiotic use for animals when estimating the global antibiotic selection pressure in these communities.

Different types of investigations could also be useful in understanding antibiotic use in LICs including notably the simulated client method in the presence of non-prescription antibiotic use and anthropological approaches to better understand the drivers of antibiotic use and misuse.

Along with the number of antibiotics consumed in communities, the quality of these antibiotics may play a role in resistance development and dissemination. The quality of medication can be lacking in LICs and can be an important driver of resistance. The ability to test the quality of antibiotics from sources in our study areas could provide valuable information in determining the importance of low-quality antibiotics as a risk factor for resistance development and spread in these areas.

Antibiotic consumption alone is not a health issue. Comparing antibiotic consumption to antibiotic resistant infections for a given population would be valuable to better understand this relationship. The existence of the BIRDY study in both Madagascar and Senegal provides this opportunity. Data from the BIRDY study include community antibiotic resistant infections from children of similar age ranges, geographic area, and socioeconomic status as those in our consumption study. Comparing our consumption results to those of BIRDY could thus provide valuable clues to the complex relationship between consumption and resistant infections.

## Conclusion

Resistance is a growing threat that will continue to cost lives and money if solutions are not found. As international travel grows and the world becomes more interconnected, infectious diseases are no longer local problems. Antibiotic resistance is no exception to this rule. Solution to antibiotic resistance must be global in nature including importantly LICs. These global solutions also need to have local adaptability. Measurement of these issues is the first step toward understanding and action. Adapted measurement of both resistance burden and antibiotic consumption are the first key steps in the global fight against antibiotic resistance.

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## Annex

### Ch2 supplementary materials

**Table S1. Neonatal infections in low-income countries (2000-May 2014)**

Author, country, and study year	Disease type and age	Setting	Neonatal Isolation rate and aetiology*
<b>Sub-Saharan Africa</b>			
Blomberg et al. <sup>82</sup> Tanzania 2001-2002	<i>Bacteremia</i> < 7 yrs	urban, hospital recruitment	<b>54 early onset (EOS) isolates†: 31 late onset (LOS) isolates:</b> <i>Klebsiella</i> spp. EOS 14 (26%), LOS 7 (23%) <i>S. aureus</i> EOS 6 (11%), LOS 5 (16%) <i>E. coli</i> EOS 6 (11%), LOS 3 (10%) Group B <i>Streptococcus</i> EOS 2 (4%), LOS 1 (3%)
Sigaúque et al. <sup>93</sup> Mozambique 2001-2006	<i>Bacteremia</i> < 15 yrs	rural, hospital recruitment	<b>154 isolates: 16% blood cultures positive</b> <i>S. aureus</i> 60 (39%) Group B <i>Streptococcus</i> 31 (20%) <i>E. coli</i> 9 (6%) <i>S. pneumoniae</i> 7 (5%)
Nielsen et al. <sup>89</sup> Ghana 2007-2009	<i>Bacteremia</i> < 5 yrs	rural, hospital recruitment	<b>23 isolates:</b> <i>S. aureus</i> 6 (26%) <i>Klebsiella</i> spp. 6 (26%) <i>Streptococcus</i> spp. 3 (13%) <i>E. coli</i> 3 (13%) Non-tyhoid <i>Salmonella</i> 2 (9%)
Gray et al. <sup>100</sup> Malawi 2004-2005	Group B <i>streptococcus</i> < 90 days	urban, hospital recruitment	<b>290 isolates: 12% blood cultures positive</b> Group B <i>Streptococcus</i> 48 (17%)
Talbert et al. <sup>96</sup>	<i>Neonatal sepsis</i>	rural, hospital recruitment	<b>474 isolates: 9% blood cultures positive</b> (25 infants had 2 bacterial species isolated)

Kenya 2001-2009	< 60 days		<i>Klebsiella</i> spp. 57 (13%) <i>S. aureus</i> 55 (12%) <i>Acinetobacter</i> spp. 48 (11%) <i>E. coli</i> 41 (9%) Group B <i>Streptococcus</i> 32 (7%) <b>86 isolates from CSF samples : 4% CSF cultures positive</b> <i>S. pneumoniae</i> 17 (20%) Group B <i>Streptococcus</i> 16 (19%) <i>Salmonella</i> spp. 10 (12%)
Ojukwu et al. <sup>90</sup> Nigeria 2002-2003	<i>Neonatal sepsis</i> 0-28 days	urban, hospital recruitment	<b>33 isolates: 24% blood cultures positive</b> <i>S. aureus</i> 15 (45%) <i>E. coli</i> 6 (18%) <i>Klebsiella</i> spp. 3 (9%) Group B <i>Streptococcus</i> 1 (3%)
Mugalu et al. <sup>87</sup> Uganda 2002	<i>Neonatal sepsis</i> used WHO guidelines	urban, hospital recruitment	<b>110 isolates: 37% blood or CSF cultures positive</b> <i>S. aureus</i> 69 (63%) <i>E. coli</i> 17 (15%) Group B <i>Streptococcus</i> 7 (6%)
Shitaye et al. <sup>91</sup> Ethiopia 2006-2007	<i>Neonatal sepsis</i> 0-28 days	urban, hospital recruitment	<b>135 isolates: 45% blood cultures positive</b> <i>Klebsiella</i> spp. 53 (39%) <i>S. aureus</i> 30 (22%) Coagulase-negative <i>Staphylococcus</i> 10 (7%)
Mhada et al. Tanzania 2009-2010	<i>Neonatal sepsis</i> 0-28 days	urban, hospital recruitment	<b>52 early onset (EOS) isolates†: 22 late onset (LOS) isolates: 22.4% blood cultures positive</b> <i>S. aureus</i> EOS 15 (29%), LOS 12 (55%) <i>Klebsiella</i> spp. EOS 17 (33%), LOS 5 (23%) <i>E. coli</i> EOS 10 (19%), LOS 4 (18%) <i>Staphylococcus</i> epidermidis EOS 6 (12%), LOS 0 (0%) Group B <i>Streptococcus</i> EOS 1 (2%), LOS 0 (0%)

Kiwanuka et al. <sup>85</sup> Uganda 2010	<i>Neonatal sepsis</i> < 1 month	urban, hospital recruitment	<b>19 early onset (EOS) isolates†: 7 late onset (LOS) isolates: 33% blood cultures</b> <i>S. aureus</i> EOS 13 (68%), LOS 3 (43%) <i>E. coli</i> EOS 3 (16%), LOS 1 (14%) <i>Klebsiella</i> spp. EOS 1 (5%), LOS 1 (14%) Group B <i>Streptococcus</i> EOS 1 (5%), LOS 0 (0%)
<b>SE Asia</b>			
Stoesser et al. <sup>94</sup> Cambodia 2007-2011	<i>Bacteremia</i> < 16 yrs	urban, hospital recruitment	<b>65 isolates :</b> <i>Klebsiella</i> spp. 14 (22%) <i>S. aureus</i> 9 (14%) <i>Enterobacter</i> spp. 4 (6%) <i>E. coli</i> 3 (5%) <i>Streptococcus</i> <i>pyogenes</i> 3 (5%)
Kruse et al. <sup>101</sup> Vietnam 2009-2010	<i>Neonatal sepsis</i> < 28 days	urban, hospital recruitment	<b>399 isolates: 17% blood cultures positive</b> <i>Klebsiella</i> spp. 78 (20%) <i>Acinetobacter</i> spp. 58 (15%) <i>E. coli</i> 21 (5%) <i>Enterobacter</i> spp. 16 (4%) <i>S. aureus</i> 11 (3%) <i>Morganella</i> spp. 8 (2%) <i>Pseudomonas</i> spp. 6 (2%) Coagulase-negative Staphylococcus 175 (44%)
<b>India subcontinent</b>			
Mir et al. <sup>99</sup> Pakistan 2004-2007	<i>Omphalitis with sepsis</i> neonates (< 1 month)	urban, community recruitment	<b>432 isolates: 64% umbilical cord cultures positive</b> <i>S. aureus</i> 225 (52%)‡ <i>Streptococcus</i> <i>pyogenes</i> 78 (18%)‡



			Group B <i>Streptococcus</i> 43 (10%)‡
Jain et al. <sup>98</sup> India 2001-2002	<i>Neonatal sepsis</i> Not defined	urban, hospital recruitment	<b>350 isolates : 48% blood cultures positive for bacteria</b> <i>Klebsiella</i> spp. 86 (25%)‡ <i>Enterobacter</i> spp. 80 (23%)‡ <i>E. coli</i> 49 (14%)‡
Sundaram et al. <sup>95</sup> India 1995-1998, 2001-2006	<i>Neonatal sepsis</i> Not defined	urban, hospital recruitment	<b>527 early onset (EOS) isolates§: 364 late onset (LOS) isolates:</b> <i>S. aureus</i> EOS 108 (20%), LOS 112 (31%) <i>K. pneumoniae</i> EOS 62 (12%), LOS 49 (14%) Non-fermenting gram negative bacilli EOS 161 (30%), LOS 60 (17%) <i>E. coli</i> EOS 48 (9%), LOS 40 (11%)
Zakariya et al. <sup>97</sup> India 2004-2006	<i>Neonatal sepsis</i> <= 30 days	urban, hospital recruitment	<b>50 isolates: 42% blood cultures positive</b> <i>K. pneumoniae</i> 33 (66%) Coagulase-negative Staphylococcus 6 (12%) Group B <i>Streptococcus</i> 1 (2%)
Muhammad et al. <sup>88</sup> Pakistan 2009-2010	<i>Neonatal sepsis</i> < 28 days	urban, hospital recruitment	<b>130 isolates:</b> <i>S. aureus</i> 35 (27%) <i>E. coli</i> 30 (23%) <i>Staphylococcus epidermidis</i> 17 (13%) <i>Acinetobacter</i> spp. 17 (13%) <i>Klebsiella</i> spp. 13 (10%) <i>Streptococcus</i> species only found in early onset sepsis (first week) <i>Klebsiella</i> species only found in late onset sepsis (after first week to 28 days)
Darmstadt et al. <sup>81</sup> Bangladesh 2004-2006	<i>Neonatal sepsis</i> < 28 days	rural, community recruitment	<b>29 isolates: 6% blood cultures positive</b> <i>S. aureus</i> 10 (34%) <i>S. pneumoniae</i> 3 (10%) Group B <i>Streptococcus</i> 1 (3%)

Gyawali et al. <sup>84</sup> Nepal 2009-2010	<i>Neonatal sepsis</i> first 4 weeks of life	urban, hospital recruitment	<b>238 isolates: 15% blood cultures positive</b> <i>S. aureus</i> 94 (40%) <i>Klebsiella</i> spp. 32 (14%) <i>Acinetobacter</i> spp. 30 (13%) <i>Enterobacter</i> spp. 27 (11%) <i>Pseudomonas</i> spp. 21 (9%) <i>E. coli</i> 16 (7%)
Shresta et al. <sup>92</sup> Nepal, 2011-2012	<i>Neonatal sepsis</i> not defined	urban, hospital recruitment	<b>37 isolates: 32% blood cultures positive</b> <i>S. aureus</i> 21 (57%) <i>K. pneumoniae</i> 8 (22%) <i>P. aeruginosa</i> 5 (13%)
<b>Europe</b>			
Macharashvili et al. <sup>86</sup> Georgia 2003-2004	<i>Neonatal sepsis</i> 8 weeks or younger	urban, hospital recruitment	<b>126 isolates: 67% blood cultures positive</b> <i>K. pneumoniae</i> 36 (29%) <i>Enterobacter cloacae</i> 19 (15%) <i>S. aureus</i> 15 (12%) Group B <i>Streptococcus</i> 6 (5%)

\* Percentages calculated when not reported in the article. Pathogens listed in order of relative percentages

† Early onset sepsis (EOS) defined as 0-6 days.

‡ Number of isolates calculated from percentages presented in article.

§ Early onset sepsis (EOS) defined as <72 hours, late onset (LOS) defined as >72 hours.

### Ch3 supplementary material

**Table S2. Studies of antibiotic consumption in the community in low-income countries**

<b>Author, Country, and study year</b>	<b>Method</b>	<b>Main results</b>
Chandy et al. <sup>163</sup> India 2003-2005	Document review - sales records	Selected ATB sales DDD/100 patients Proportions of ATBs sold by health structures
Kotwani et al. <sup>165</sup> India 2003-2004	Document review - sales records	DDDs/1000 population Proportions of ATBs sold
Adebayo et al. <sup>159</sup> Nigeria 2007	Document review - outpatient case notes	Number of ATBs prescribed per patient Proportion of consultations resulting in ATB Number of drugs per prescription
Ahmed et al. <sup>160</sup> Sudan 2008	Document review - outpatient prescriptions	Proportion of prescriptions with ATB ATBs per prescription
Alvarez-Uria et al. <sup>161</sup> India 2011-2012	Document review - outpatient prescriptions	DDDs/100 outpatient visits Proportion outpatients receiving ATB
Bartoloni et al. <sup>162</sup> Bolivia 1992	Document review - sales and budget records	ATBs stocked in pharmacy Proportion of types of ATBs delivered Budget spent on ATBs
Holloway et al. <sup>164</sup> S. Africa (Brits) 2004-2005	Document review - outpatient clinical records	Proportion of prescriptions with ATB. Proportion of ATB types prescribed DDD/100 patients.
Holloway et al. <sup>164</sup> S. Africa (Durban) 2003-2004	Document review - prescription documents	Proportion of prescriptions with ATB Proportion of ATB types prescribed DDDs/100 patients
Bartoloni et al. <sup>162</sup> Bolivia 1992	Simulated client method	Proportion of scenarios with medication delivered Proportion of scenarios with ATBs delivered ATBs dispensed by scenario

		Proportion of pharmacists requiring prescription
Apisarntharak et al. <sup>166</sup> Thailand 2006	Simulated client method	Proportion of scenarios with ATBs delivered Types of ATBs delivered by scenario Appropriateness of ATBs delivered
Quagliarello et al. <sup>150</sup> Vietnam 1999	Simulated client method	Number and Type of ATB distributed Length of medication recommended Proportion of scenarios with ATBs delivered
Wachter et al. <sup>28</sup> Nepal 1996	Simulated client method	Questions asked by drug seller ATB type and duration Proportion of scenarios with ATBs delivered
Chandy et al. <sup>163</sup> India 2003-2005	Patient exit interviews	Type of ATBs prescribed DDDs/100 pharmacy visits Proportion of visits with ATB delivered Proportion and type of ATB delivered by symptom
Ahmed et al. <sup>160</sup> Sudan 2008	Patient exit interviews	Patient knowledge Dispensing time Drugs dispensed vs Drugs prescribed
Holloway, 2011 <sup>164</sup> India 2002-2003	Patient exit interviews	Proportion of visits with ATB - and comparison of facility type Types of ATB delivered DDDs/pharmacy visits
Kotwani et al. <sup>165</sup> India 2003-2004	Patient exit interviews	Proportion of prescriptions with ATB Types of ATB delivered DDDs/pharmacy visits
Saradamma et al. <sup>173</sup> India 1993	Patient exit interviews	Type of ATBs prescribed Proportion of ATB delivered without a prescription Socio-demographic information
Kotwani et al. <sup>174</sup> India 2007-2008	Patient exit interviews	Proportion of respiratory tract infections with ATBs Type of ATBs prescribed DDDs/respiratory tract infection patients with prescription
Nakajima et al. <sup>171</sup> Mongolia	Patient exit interviews	Proportion of pharmacy visits with ATB Proportion of ATB delivered without a prescription

2006		Reasons for use Proportion of patients receiving information about dose and duration
Esimone et al. <sup>169</sup> Nigeria 2003	Observed encounters	Proportion of ATB encounters without a prescription Mean ATB dose delivered DDDs/pharmacy visits Type of ATBs prescribed
Hounsa et al. <sup>170</sup> Ivory Coast 2006-2007	Observed encounters	Proportion of ATBs delivered without a prescription Type of ATB delivered Symptoms leading to automedication
Sabry et al. <sup>172</sup> Egypt 2011	Observed encounters	Total ATBs dispensed Proportion of ATBs with a prescription Types of ATBs Reasons for ATB use
Sturm et al. <sup>184</sup> Pakistan 1995	Community survey	Proportion of population with ATB use in last 4 weeks Type of ATBs used Socio-demographic information Reasons for use Proportion of ATBs used with a prescription
Quagliarello et al. <sup>150</sup> Vietnam 1999	Community survey	Socio-demographic information Proportion of population with ATB use past 2 months Health care seeking behaviors Proportion of ATB used with a prescription Reason for non-prescription use Proportion of patients following treatment duration
Bartoloni et al. <sup>162</sup> Bolivia 1992	Community survey	Socio-demographic information Proportion of population with ATB use past 4 months Reason for ATB use Place of ATB purchase Portion of ATB use with a prescription
Afolabi et al. <sup>176</sup> 2007-2008	Community survey - recruitment at medical facility	Proportion of patients self-medicating with ATBs Reasons for self-medication

Nigeria		Socio-demographic information
Awad et al. <sup>178</sup> Sudan 2005-2006	Community survey	Proportion of population with non-prescription ATB use Reasons for ATB use Reasons for self-medication
Barah et al. <sup>179</sup> Syria year not noted	Community survey	Proportion of population with ATB use last 4 weeks Source of ATBs Proportion of patients following treatment duration Knowledge, attitudes, beliefs Socio-demographic information Proportion of ATB use without a prescription
Belkina et al. <sup>180</sup> Yemen, Saudia Arabia, Uzbekistan 2012	Community survey	Socio-demographic information Poportion of ATB use without a prescription Proportion of population with ATB use in last 3 months Source of ATBs Advisor for ATB Reasons for ATB use Proportion of patients following treatment duration
Bojalil et al. <sup>181</sup> Mexico 1989-1990	Community survey	Proportion of population with ATB use in last two weeks Types of ATBs Reason for ATB use Proportion of ATB use without Prescription Treatment duration
Donkor et al. <sup>182</sup> Ghana 2007-2008	Community survey	Proportion of population ever using non-prescription ATBs Types of ATBs used Symptoms leading to non-prescription ATB use Knowledge, attitudes, beliefs
Shah et al. <sup>183</sup> Pakistan year not noted	Community survey	Socio-demographic information Proportion of population using non-prescription ATBs in last months Frequency of ATB use Types of ATBs used Knowledge, attitudes, beliefs

Awad et al. <sup>177</sup> Sudan year not noted	Community survey	Socio-demographic information Symptoms leading to automedication Types of ATBs Dose and duration of ATBs Source of ATBs Proportion of population with ATB use in last month Proportion of ATB use without prescription
Saradamma et al. <sup>173</sup> India 1993	Community survey	Proportion of population with medication use in last 2 weeks Proportion of population with ATB use in last 2 weeks Socio-demographic information Medication source Proportion of medication acquired without prescription (including ATBs)
Togoobaatar et al. <sup>185</sup> Mongolia 2009	Community survey	Proportion of population with ATB use in last 6 months Proportion of ATB use without prescription Source of ATBs Type of ATBs Advisor for ATB Knowledge, attitudes, beliefs
Larsson et al. <sup>149</sup> Vietnam 1999	Community survey	Proportion of population with ATB use in last month Type of ATBs Treatment duration Reason for ATB use Advisor for ATB

ATB - antibiotic

DDD - Defined Daily Dose

## Ch4 supplementary material

### S3. Results for Madagascar univariate and multivariate analysis. Dependent variable, antibiotic consumption in the last three months (1-Yes, 0-No)

Variables	OR* (95% CI)	P	ORa† (95% CI)	P
<b>Underweight birth</b>		0.21		
No	1		-	
Yes	1.28 (0.60-2.74)			
<b>Premature</b>		0.06		
No	1		-	
Yes	5.06 (0.77-33.06)			
<b>Number of rooms in household</b>		0.01		0.02
1	1		1	
2	1.74 (1.18-2.57)		1.84 (1.22- 2.80)	
>=3	1.47 (0.97-2.23)		1.52 (1.01-2.31)	
<b>underweight</b>		0.07		
No	1		-	
Yes	1.48 (0.96-2.29)			
<b>Baby age (months)</b>		<0.01		0.01
0-6	1		1	
6-12	2.37 (1.34 – 4.20)		2.31 (1.35 - 3.98)	
12-18	2.35 (1.19 - 4.64)		2.43 (1.25 - 4.72)	
18-24	1.40 (0.70 - 2.79)		1.29 (0.68 - 2.46)	
<b>Site</b>		0.14		0.46
Tana	1		1	
Mora	0.79 (0.57-1.09)		0.87 (0.60-1.27)	

### S4. Results for Senegal multivariate analysis. Dependent variable, antibiotic consumption in the last three months (1-Yes, 0-No)

Associated factors	OR (IC95%)	P
Type de toilettes*	1.8 (1.2 - 2.6)	0.008
Parent antibiotic consumption†	2.5 (1.1 - 5.8)	0.030
Systematic health care seeking‡	5.4 (2.1 - 13.4)	0.001

\* gives OR for presence of toilets without flush vs. toilets with flush.

† at least one consumption episode in the last year

‡ Systematic consultation in case of fever, cough, or diarrhea.



**S5. Antibiotic usage questionnaire for Madagascar and Senegal community survey.**

**Identifiant :** |\_|\_|\_|\_|

Arrondissement : |\_|

Fokontany : \_\_\_\_\_ Numéro du Fokontany : |\_|\_|

Numéro du Segment : |\_|\_|

Numéro de la maison : |\_|\_|

Date de visite |\_|\_| / |\_|\_| / |\_|\_|\_|\_|

Site :  Tananarive  Moramanga

**PERSONNE INTERROGEE :**

Lien avec l'enfant :

Mère

Père

Membre de la famille mais avec un autre lien de parenté, préciser : \_\_\_\_\_

Autre, préciser : \_\_\_\_\_

Sexe :  Féminin  Masculin

Age de la mère : |\_|\_|

Etes-vous allé à l'école ?

*Si la personne interrogée n'est pas la mère: La mère est-elle allée à l'école ? Jusqu'à quelle année ?*

Absence

Primaire

Secondaire partielle

Secondaire total

Université

Autre, préciser : \_\_\_\_\_

Quel est votre métier ?

*Si la personne interrogée n'est pas la mère, quel est le métier de la mère ? (un seul choix possible):*

Sans emploi

Emploi manuel sans qualification

Emploi manuel avec qualification

Emploi de bureau

Cadre supérieur

Autre, préciser : \_\_\_\_\_

**HABITAT ET ENVIRONNEMENT**

Type d'habitat (un seul choix possible) :

Maison individuelle

Maison dans un lot avec d'autres ménages

Pièces dans une maison avec d'autres ménages

Autre, préciser : \_\_\_\_\_

Type de logement (un seul choix possible):

Toit :  paille  bâche  tôle  tuile  autre : \_\_\_\_\_

Mur :  boue  bois  tôle  brique/béton/pierre  autre : \_\_\_\_\_

Sol :  planche  natte  terre/sable/bouse  ciment  carrelage/parquet  autre : \_\_\_\_\_

Possédez-vous l'électricité ?

Oui  Non

*Si non* : Quel type d'éclairage utilisez-vous?

Lampe électrique avec piles

Bougies

Pétrole

Rien

Quel type de toilettes utilisez-vous?

Extérieur avec chasse d'eau (communes)

Extérieur sans chasse d'eau (latrines, fosses...)

Intérieur avec chasse d'eau (privées)

Intérieur sans chasse d'eau (seau...)

Aucune / dans la nature

Nombre de pièces dans votre foyer ? \_\_\_\_\_

Nombre de pièces pour dormir ? \_\_\_\_\_

Combien d'enfants de moins de 2 ans vivent avec vous ? \_\_\_\_\_ (y compris le/les bébé(s) d'intérêt)

Combien d'enfants de 2 à 15 ans vivent avec vous ? \_\_\_\_\_

Combien de personnes en tout vivent à votre domicile? \_\_\_\_\_ (y compris le/les bébé(s) d'intérêt)

**Enfant <2 ans (bébé d'intérêt)** Numéro du bébé: |\_|

Date de naissance enfant \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (à vérifier avec carnet de santé ou autre si possible)

Sexe :  Féminin  Masculin

Poids (kg) : |\_|\_|, |\_|  approximative  Ne sait pas

Taille (cm) : |\_|\_|  approximative  Ne sait pas

Est-ce que l'enfant est né prématurément (<37 semaines) ? :  Oui  Non  Ne sait pas

Est-ce l'enfant a eu un faible poids à la naissance (<2200 grammes) ? :  Oui  Non  Ne sait pas

Est-ce que l'enfant a un suivi médical régulier hors maladie (médecin, sage-femme, centre de santé)?  
 Oui  Non  Ne sait pas

**Statut vaccinal** (demander le carnet de santé)

Carnet de santé ?  Oui  Non

BCG  Oui  Non  Ne sait pas Polio  0  1  2  3  4  Ne sait pas

DT coq  0  1  2  3  Ne sait pas Hépatite B  0  1  2  3  Ne sait pas

Haemophilus  0  1  2  3  Ne sait pas PCV10  0  1  2  3  Ne sait pas

Rotarix  0  1  2  Ne sait pas Rougeole  Oui  Non  Ne sait pas

Est-ce que l'enfant a été malade dans les trois mois précédents (référer au calendrier)?  
 Oui  Non  Ne sait pas

Pourriez-vous raconter ce qui s'est passé la dernière fois l'enfant a été malade ?  
(encourager la personne à parler, poser les questions sur ce que l'enfant a eu, ce que la maman(personne) a fait, si l'enfant a pris les médicaments, pourquoi et comment)

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Numéro du bébé: |\_|

Est-ce que l'enfant a pris des médicaments ou des antibiotiques dans les trois mois précédents (*référer au calendrier*)?

Oui

Non

*Si oui*: Combien de médicaments ou antibiotiques différents ? \_\_\_\_\_

**Lister** (*après la première liste, donner des exemples d'antibiotiques /montrer l'aide visuelle et redemander si l'enfant a bien pris un de ces antibiotiques dans les trois mois précédents*)

Medicament 1 \_\_\_\_\_

Medicament 2 \_\_\_\_\_

Medicament 3 \_\_\_\_\_

Medicament 4 \_\_\_\_\_

Medicament 5 \_\_\_\_\_

Medicament 6 \_\_\_\_\_

Medicament 7 \_\_\_\_\_

**Numéro Médicament** |\_|\_| **Numéro du bébé:** |\_|\_|

Date début (*voir calendrier*) |\_|\_| / |\_|\_| / |\_|\_|\_|\_|  Date approximative  Ne se souvient pas  
Date fin |\_|\_| / |\_|\_| / |\_|\_|\_|\_|  Date approximative  Pas terminé  Ne se souvient pas  
Nombre de jours |\_|\_|  Nombre approximative  Pas terminé  
Combien de fois par jour ?  1  2  3  4  5+  Ne se souvient pas

Pourquoi l'enfant a-t-il pris ce médicament ? (*plusieurs réponses possibles*)

Toux  Maux de gorge  Fièvre  Écoulement nasal  mal à une oreille  Respiration difficile ou rapide  Maladie de la peau  Perte d'appétit  Vomissement  Diarrhée  
 Mal au ventre  Autre, précisez : \_\_\_\_\_

Qui vous a conseillé/prescrit ce médicament ?

Médecin  Sage-femme  Pharmacien  Epicier  Guérisseur  Matrone  
 Personne  Ne sait pas  Autre (marché, proche) \_\_\_\_\_

Où avez-vous acheté le médicament ?

Pharmacie  Centre de santé  Médecin  Dépôt de médicament  Marché  
 Guérisseur  Epicerie  Donnés/récupérés  Ne sait pas  Autre \_\_\_\_\_

Avez-vous gardé des comprimés et/ou l'emballage/bouteille?  Oui  Non

**Si oui** : demander à la/les voir

Avez-vous eu une ordonnance ?  Oui  Non  Ne sait pas **Si oui** : demander à la voir

Antibiotique ? :  Oui  Non  Ne sait pas (*Si pas antibiotique arrêter le questionnaire*)

**Molécule** : \_\_\_\_\_

SI Ab :  Ident visuelle du comprimé/sirop  Ident visuelle de la plaquette/emballage en main  
 Ident visuelle de l'ordonnance  Ident de mémoire de la mere/personne interrogée  
 Fournisseur a dit que c'était un antibiotique

**Questions à poser si médicament acheté Avec ordonnance**

Prescription pour quelle durée (en jours) |\_|\_|  Ne se souvient pas

**Questions à poser si médicament acheté Sans ordonnance**

Pourquoi le médicament a-t-il été acheté sans ordonnance ?

Eviter de payer une consultation médicale  Achat sans ordonnance plus pratique  
 pas besoin  Autre \_\_\_\_\_

L'enfant a-t-il pris tous les comprimés/doses prescrits (*avec ordonnance*)/achetés (*sans ordonnance*) ou suit l'ordonnance si toujours en cours?  Oui  Non  Ne sait pas

**Si non** : pourquoi l'enfant n'a pas pris tous les comprimés/doses prescrits (*avec ordonnance*)/achetés (*sans ordonnance*)?

L'enfant se sentait mieux  On ne savait pas qu'il fallait tout finir  Traitement complet trop cher  
 On pensait que c'était dangereux  Autre \_\_\_\_\_

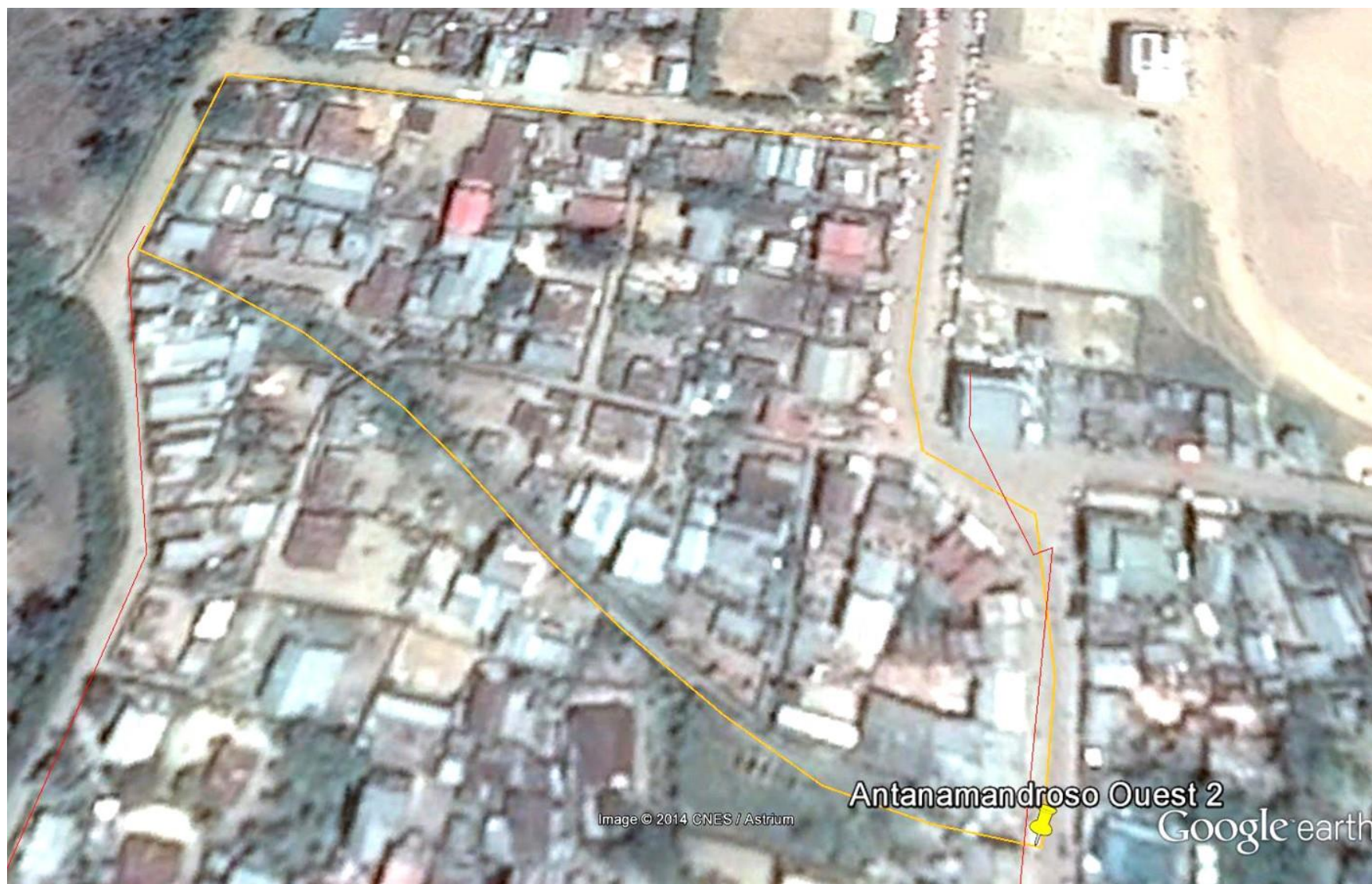
Qu'avez-vous fait avec les comprimés/doses non pris ?

Gardés pour plus tard  Donnés à des proches/à la famille   
Autre \_\_\_\_\_

**S'il reste des comprimés /doses antibiotiques → Demander de les acheter.** Antibiotiques achetés ?

Oui  Non

S6. Sample Fokontany map for Madagascar and Senegal community survey.



S7. Sample Household tracking sheet for Madagascar and Senegal community survey.

Arrondissement 1 Fokontany Antanambonjo Est Code fokontany 05 Segment 03

Maison	Date visite	Resultat	Date 1 er revisite	Resultat	Date 2 eme revisite	Resultat	Commentaire
1	29-12-2014	3					
2	29-12-2014	4	30-12-2014	4			
3	29-12-2014	3					
4	29-12-2014	3					
5	29-12-2014	4	30-12-2014	4			
6	29-12-2014	4	30-12-2014	3			
7	29-12-2014	3					
8	29-12-2014	3					
9	29-12-2014	3					
10	29-12-2014	1					
11	29-12-2014	3					
12	29-12-2014	4					
13	29-12-2014	3					
14	29-12-2014	3					
15	29-12-2014	1					
16	29-12-2014	3					
17	29-12-2014	3					
18	29-12-2014	4	30-12-2014	1			
19	29-12-2014	4	30-12-2014	4			
20	29-12-2014	3					
21	29-12-2014	4	30-12-2014	4			
22	29-12-2014	1					
23	29-12-2014	3					
24	29-12-2014	1					
25	29-12-2014	4	30-12-2014	3			

Code resultat- 1 - reponse - enfant present - entreteint fait  
 2 - reponse - enfant present - entreteint refuse  
 3 - reponse - pas d'enfant  
 4 - pas de reponse  
 5 - autre

S8. Sample antibiotic visuals for Madagascar and Senegal community survey.





**S9. Local calendar for Madagascar and Senegal community survey.**

Mois	Dt	Fêtes nationales	Repères culturels	Repères personnels	
Juin 2012	10		Famadihana Retournement des morts		
	20	26 juin: fête nationale, indépendance			
Juillet 2012	10				
	20				
Aout 2012	10	15 aout: Assomption			
	20				
Septembre 2012	10				
	20				
Octobre 2012	10				
	20				
Novembre 2012	10	1 <sup>er</sup> nov: Toussaint	Fahavaratra Saison des pluies		
	20				
Décembre 2012	10				
	20	25 dec: Noël			
Janvier 2013	10	1 <sup>er</sup> janv: Nouvel an			
	20				
Février 2013	10				
	20				

## Résumé substantiel en langue française

L'OMS (Organisation Mondiale de la Santé) souligne l'importance de la résistance bactérienne à l'échelle mondiale dans les pays développés comme dans les pays en voie de développement (PED).<sup>1</sup> De manière préoccupante, les bactéries résistent à de plus en plus d'antibiotiques et notamment à ceux de dernier recours, les rendant difficiles voire impossibles à traiter.<sup>2</sup>

Ces bactéries multirésistantes ont été détectées à la fois en milieu hospitalier et en dehors de celui-ci. Elles sont associées à des maladies graves impliquant des pathogènes tels que les entérobactéries productrices de carbapenemase et les *Staphylococcus aureus* résistants à la méticilline. Le manque de recherche et de découverte de nouveaux antibiotiques complique ce problème. Contrairement aux décennies passées où nous pouvions compter sur le développement de nouveaux antibiotiques pour combattre les résistances bactériennes, nous devons maintenant centrer nos efforts sur le maintien de l'efficacité des antibiotiques actuels. Si la résistance aux antibiotiques venait à augmenter ce serait non seulement les progrès obtenus en termes de mortalité et de morbidité par maladies infectieuses qui seraient compromis mais également de nombreuses procédures médicales modernes.<sup>3</sup>

Il semblerait que ce problème de résistance aux antibiotiques affecte de manière inégale les PED. En effet, ces pays font face à des fréquences élevées d'infections bactériennes et en parallèle manquent souvent de méthodes de diagnostic et de recours à des antibiotiques de deuxième ligne qui permettraient de lutter contre les effets de la résistance. Dans ces pays, les enfants sont d'autant plus à risque car davantage touchés par les maladies bactériennes. Ainsi en Afrique, les maladies infectieuses sont impliquées dans plus de 75% de la mortalité des enfants moins de 5 ans.<sup>4</sup>

En dépit des risques évoqués, la résistance aux antibiotiques dans les PED a été peu étudiée jusqu'à présent. Cependant, il est important de considérer les PED dans le phénomène mondial de la résistance aux antibiotiques d'autant plus qu'ils représentent une source majeure et en expansion de résistance aux antibiotiques.<sup>5</sup> Les PED sont également le lieu de nouvelles formes de résistance.<sup>6</sup>

Les facteurs de risque de l'émergence et de la propagation de la résistance aux antibiotiques dans les PED sont : une consommation d'antibiotiques en absence de prescription, une consommation d'antibiotiques de mauvaise qualité, contrefaits ou périmés et une surconsommation/consommation inadaptée d'antibiotiques liées à un mauvais diagnostic ou une mauvaise prise en charge.<sup>7</sup> La transmission des bactéries est de plus facilitée, en particulier du fait de conditions d'hygiène défavorables. Dans de nombreux pays les enfants sont acteurs de leur consommation d'antibiotiques et seraient ainsi impliqués dans le développement et la propagation de la résistance aux antibiotiques.<sup>8</sup>

Afin de réduire la résistance aux antibiotiques dans les PED, particulièrement chez les enfants vulnérables, un certain nombre de questions méritent d'être explorées. Quel est le réel problème ? Quelles sont les bactéries impliquées dans les infections chez l'enfant ? Quels sont les types de profils de résistance aux antibiotiques les plus importants ? Il est également important de déterminer si les traitements actuellement recommandés sont adaptés à ces bactéries et à leurs profils de résistance.

En parallèle de la compréhension de ce fléau, nous devons être capables de surveiller l'usage des antibiotiques dans les PED. Les programmes où l'usage des antibiotiques a été surveillé se sont montrés efficaces pour contrôler ou diminuer les taux de résistance aux antibiotiques, à la fois en milieux hospitaliers et en dehors de ceux-ci.<sup>9-11</sup>

Afin de contrôler l'usage des antibiotiques, nous avons besoin de données portant sur les modalités de consommation des antibiotiques. Ces données pourront ainsi nous aider à développer des solutions adaptées au contexte afin de maintenir l'efficacité des antibiotiques administrés et ralentir l'expansion de la résistance aux antibiotiques.

## Problématique et objectifs

La première étape pour faire face à la résistance aux antibiotiques dans les PED est de quantifier le poids de cette résistance. Ces données primordiales sont nécessaires pour atteindre un nombre important d'objectifs et notamment pour permettre aux chercheurs de replacer cette problématique dans un contexte global de problèmes de santé majeurs tels que le VIH, la malaria et la tuberculose. Des moyens financiers internationaux importants ont déjà été mis en place pour faire face à ces problèmes et des progrès considérables ont pu être observés grâce entre autres à l'obtention de données de meilleure qualité. Afin de pouvoir étudier l'évolution des profils de résistance et d'être en capacité d'évaluer l'impact d'interventions réalisées, il est également important de récolter des données répétées dans le temps. Comprendre quels sont les pathogènes impliqués dans les infections bactériennes des PED et quels sont leurs profils de résistance peut permettre la mise à jour des recommandations. A cause des inégalités d'accès aux soins et de traitement dans les PED, la diffusion de l'information à l'échelle des populations est primordiale. Le premier objectif de ce travail a été de quantifier l'ampleur de la résistance aux antibiotiques chez des enfants de moins de 2 ans vivant dans les PED. Cela a consisté dans un premier temps à déterminer l'incidence de nouvelles infections bactériennes invasives chez des enfants de moins de 2 ans vivant dans les PED, puis, dans un second temps, à décrire les pathogènes impliqués dans ces infections, ainsi que leur susceptibilité aux antibiotiques, et ce grâce à la littérature scientifique.

En parallèle de la meilleure compréhension du problème de résistance aux antibiotiques, il est également nécessaire de penser aux moyens pouvant être mis en place pour y faire face. Un certain nombre d'actions cherchant à contrer la résistance aux antibiotiques se sont déjà montrées efficaces. La plupart de ces actions ont consisté à modifier les comportements de prise d'antibiotiques grâce à des campagnes de prévention, grâce à la formation des médecins ou via l'utilisation de nouvelles technologies. Afin de choisir le type d'intervention adaptée et de bien identifier la population cible, il est nécessaire d'établir des profils de consommation d'antibiotiques et de comprendre et caractériser leurs déterminants. Il semble cependant difficile d'obtenir ce type de données dans les PED où les antibiotiques peuvent s'obtenir par des voies très variées et nombreuses et où il existe peu de sources de données est quasi inexistant. Le second objectif de ce travail a donc été de proposer une solution à ce problème en effectuant une revue de la littérature des différentes techniques actuelles utilisées dans les PED, pour mesurer la consommation d'antibiotiques.

En appliquant cette solution, le 3<sup>ème</sup> objectif de ce travail a été d'établir des profils de consommation d'antibiotiques et de caractériser leurs déterminants chez des enfants de

moins de 2 ans vivant dans les PED. Le but de ces travaux de recherche a été de compléter le peu de données disponibles sur la consommation d'antibiotiques dans les PED.

## Poids de la résistance en population chez les enfants dans les pays à faible revenu

### Introduction

Obtenir des données fiables sur le poids de la résistance dans les pays à faible revenu est une étape nécessaire dans le contrôle de la résistance et la réduction de ses effets.<sup>78</sup> En effet, ces données sont nécessaires pour suivre les tendances de la résistance et mettre à jour les recommandations de traitement en prenant en compte l'étiologie locale et les profils de résistance.

Du fait de différences dans le recours et l'accès aux soins, une compréhension du poids de la résistance aux antibiotiques au niveau populationnel dans les pays à faible revenu est particulièrement critique, notamment des taux d'incidence, des pathogènes en cause et des profils de résistance.<sup>79</sup>

Afin d'étudier l'état des connaissances sur l'incidence des infections bactériennes sévères et de la résistance aux antibiotiques en population chez les jeunes enfants dans les pays à faible revenu, nous avons revu la littérature publiée sur ces thématiques chez les enfants de moins de deux ans. Ces résultats ont ensuite été analysés d'un point de vue épidémiologique, notamment les biais potentiels.

### Méthodes

Nous avons recherché sur PubMed les études publiées à partir de 2000 (dernière recherche le 30 avril 2014). Notre recherche a été divisée en deux branches incluant 1) Les infections bactériennes acquises en communauté chez les jeunes enfants dans les pays à faible revenu (IB), et 2) la résistance aux antibiotiques parmi les infections acquises en communauté dans les pays à faible revenu (RA). Les pays à faible revenu étaient identifiés comme « moins avancés », « autre faible revenu », ou « revenu moyen bas » par la Banque Mondiale ou comme « faible indice de développement humain » ou « indice de développement humain moyen » par les Nations Unies.<sup>64, 65</sup> Les résultats ont été divisés en deux périodes : les nouveau-nés, et les enfants de moins de deux ans à l'exception des nouveau-nés.

### Résultats

Des 1543 et 1314 études trouvées par les recherches IB et RA, 84 et 46 respectivement ont été sélectionnées pour lecture complète. Finalement, 46 études IB et 9 études RA ont été retenues pour un total de 55 études incluses dans l'analyse finale. Des 46 études IB, 27 correspondaient également aux critères d'inclusion des études RA et un total de 36 articles a ainsi été inclus dans les analyses de résistance. Vingt-et-une études, dont 20 IB et 1 RA, contenaient des informations concernant les infections néonatales ou la résistance chez les nouveau-nés. Deux études portaient à la fois sur les nouveau-nés et sur les enfants de moins de deux ans.

### **Résultats chez les nouveau-nés**

La majorité des études portant sur les nouveau-nés ont été réalisées en Afrique subsaharienne (n=10) ou du sous-continent indien (n=8). Des 21 articles analysés portant sur les nouveau-nés, 4 études ont été menées dans des contextes ruraux<sup>81, 89, 93, 96</sup> tandis que les 17 restantes ont été conduites dans des contextes urbains. Dix-neuf des 21 études recrutaient leurs participants dans de larges hôpitaux de districts ou dans des hôpitaux universitaires. Seules deux études ont utilisé le recrutement actif en population.<sup>81, 99</sup>

Cinq études IB rapportaient une estimation de l'incidence des infections bactériennes invasives (Figure 10).<sup>81, 90, 95, 99, 100</sup> L'incidence pour 1000 naissances vivantes allait de 2,9 (IC 95% 1,9–4,2) pour les bactériémies chez les nouveau-nés au Bangladesh<sup>81</sup> à 24 (IC 95% 21,8–25,7) pour les septicémies d'apparition précoce (<72 heures) en Inde.<sup>95</sup>

Parmi les 20 études portant sur les nouveau-nés et incluant des données sur les pathogènes impliqués, *S. aureus* était retrouvé dans tous les cas sauf deux, totalisant 3% à 63% (médiane=32,5%) des pathogènes retrouvés. D'autres pathogènes courants étaient rapportés comme *Klebsiella* spp. dans 16 études et représentant de 8% à 66% (médiane=22%) des pathogènes, et *E. coli*, dans 14 études et représentant de 5% à 23% (médiane=12%) des pathogènes isolés.

Sept des 12 études comprenant des données de résistance ont été conduites avant 2008 (Table 3). La résistance à la pénicilline/ampicilline chez les bactéries à Gram négatif (à l'exception de *Klebsiella* spp.) allait de 55% (IC 95% 26%-84%) à 100%. La résistance à la gentamicine chez les bactéries à Gram négatif allait de 0% à 100% tandis que la résistance aux céphalosporines de troisième génération (C3G) allait de 6% à 97%. Seules deux études ont analysé la production de BLSE chez les *Enterobacteriaceae*. L'une a rapporté une production de BLSE de 87% dans des isolats de *Klebsiella* spp., 73% dans des isolats de *Enterobacter* spp., et 65% dans des isolats de *E. coli*.<sup>98</sup> La seconde a rapporté 32% de BLSE parmi des isolats de *K. pneumoniae* de 32%.<sup>97</sup> La résistance d'isolats de *S. aureus* à la méticilline a été rapportée dans cinq études et allait de 0% à 67%.<sup>86, 91, 96, 99, 101</sup>

### **Chez les enfants de moins de deux ans**

Vingt-sept études portant sur les « infections du nourrisson » et 8 études portant sur la « résistance aux antibiotiques » chez les enfants de 1 mois à 2 ans ont été retenues pour un total de 36 études incluses dans l'analyse finale (Figure 9). Des 27 résultats de la branche IB, 18 études correspondaient également aux critères de sélection de la branche RA et un total de 27 articles a ainsi été inclus dans les analyses de résistance. En tout, 33 des 36 études ont été conduites avant 2008.

Seules 11 des 36 études ont été conduites en milieu rural ou incluaient des zones rurales.<sup>93, 103, 104, 107, 110, 114, 121, 122, 124, 128, 132</sup> La majorité des études (22 sur 36) ont été réalisées dans de grands centres hospitaliers hôpitaux de district ou hôpitaux universitaires. Seules 6 études ont mis en œuvre un recrutement actif en communauté, soit comme seul mode de recrutement (n=4)<sup>104, 132-134</sup>, soit en plus d'un recrutement à l'hôpital (n=2).<sup>102, 131</sup>

Vingt articles sur les infections rapportaient des taux d'incidence des infections bactériennes (Table 3). Trois études ont rapporté des estimations d'incidence de bactériémie. Les

estimations s'étendaient de 1108 (IC 95% 953–1282) pour 100 000 enfants-années à 2469 (IC 95% 1,480–3,946) pour 100 000 enfants-années (cf Table 4).<sup>93, 107, 110</sup>

Globalement, *S. pneumoniae* était le pathogène le plus courant, représentant 11% à 50% des pathogènes isolés dans 4 études.<sup>93, 107, 110, 113</sup> Dans deux études, les *Salmonella* non-typhiques étaient retrouvées dans 23% à 26% des isolats<sup>93, 110</sup> tandis que dans une étude, *Salmonella* Typhi représentait 30% de tous les isolats.<sup>113</sup> *S. aureus* a été rapporté dans deux études et correspondait à 6% à 13% des isolats.<sup>82, 113</sup>

Trois études présentaient des taux d'incidence de méningite bactérienne. Les estimations d'incidence pour 100 000 enfants-années s'étendaient de 68 à 1078 (IC 95% 484–2400).<sup>105, 117, 122</sup>

Sept études rapportaient une incidence de la méningite due à *Haemophilus Influenzae* (*H. influenza*) de type B avec des estimations allant de 20,1 pour 100 000 enfants-années à 290 (IC 95% 145–579).<sup>102, 105, 109, 117, 121, 122, 130</sup> Sept études ont également retrouvé des estimations d'incidence de la méningite due à *S. pneumoniae* de 2,7 (IC 95% 0,9–5,9) pour 100 000 enfants-années à 108 (IC 95% 35–337).<sup>108, 114, 117, 121, 122, 128, 130</sup>

Cinq études rapportaient des incidences d'infections invasives au pneumocoque. Les définitions de cas d'infection invasive au pneumocoque étaient hétérogènes (Table 3). Les estimations allaient de 34 à 447.<sup>129, 131</sup> pour 100 000 enfants-années

La résistance à la pénicilline de *S. pneumoniae* chez les enfants après la période néonatale a été mesurée dans 17 études (Figure 11).<sup>93, 103, 106, 108, 110, 112, 114, 121-125, 128-132</sup> La résistance allait de 0% à 24% dans 10 études menées en Afrique sub-saharienne et de 0% à 4% dans 6 études du sous-continent indien. La seule étude conduite en Asie du Sud-Est a évalué cette résistance à 0%.

Neuf études portant sur des enfants de moins de deux ans ont rapporté des résultats de résistance dans des isolats de *Salmonella*<sup>82, 93, 106, 110, 115, 120, 124, 133, 135</sup> répartis entre *Salmonella* non-typhiques (NTS) (n=3), *Salmonella* Typhi (n=2), et *Salmonella* spp. (n=4), sans différenciation entre ces espèces (Table 4). La résistance à l'ampicilline au sein des *Salmonella* allait de 33%<sup>135</sup> à 85%.<sup>124</sup> Des 6 études ayant analysé la résistance aux C3G, seules deux ont détecté de la résistance : 11% en Inde<sup>115</sup> 4% en Tanzanie<sup>82</sup> pour deux C3G différentes. Neuf études rapportaient de la résistance au co-trimoxazole, allant de 27% à 100%.

## Discussion

Nos résultats mettent en évidence le manque de données sur la résistance bactérienne chez les nouveau-nés et chez les jeunes enfants dans les pays à faible revenu. Ils mettent également en exergue le déficit de données fiables et convaincantes sur le poids des infections bactériennes invasives acquises en communauté chez les enfants de ces pays. Ce manque de connaissance entrave l'amélioration des stratégies de prévention et de traitement des infections du nouveau-né et du jeune enfant dans les contextes où la mortalité est la plus élevée.

Les données disponibles montrent une fourchette large d'estimations d'incidence des infections chez les nouveau-nés et les enfants de moins de deux ans.

Nous avons trouvé que les pathogènes les plus courants dans les infections néonatales étaient *S. aureus*, *Klebsiella* spp., et *E. coli* correspondant à presque deux tiers des cas de septicémies néonatales.

Le nombre d'isolats par étude était généralement très limité parmi les études portant sur les nouveau-nés. L'OMS recommande l'ampicilline et la gentamicine comme traitement de première intention en cas de septicémie néonatale. La résistance à l'ampicilline était très élevée dans les études néonatales. Les données sur la gentamicine étaient hétérogènes et aucune conclusion ne pouvait être clairement tirée de ces données.

Les données sur la résistance aux céphalosporines de troisième génération dans des isolats de nouveau-nés étaient hétérogènes à l'exception de *Klebsiella* spp. pour laquelle des taux de résistance importants ont été rapportés.<sup>97,98</sup>

A noter qu'aucune conclusion ne pouvait être faite sur la résistance à la méticilline de *S. aureus* (SARM) chez les nouveau-nés, malgré le fait que ce pathogène pourrait être la première cause d'infection néonatale.

Parmi les enfants de moins de deux ans, *S. pneumoniae* était fréquemment retrouvé dans des cas de méningites et de septicémies. Nos résultats laissent penser que ce pathogène a atteint un niveau alarmant de résistance au co-trimoxazole.

Notre revue montre que la *Salmonella* non typhique (NTS) est une autre cause importante de bactériémie dans la tranche d'âge 28 jours-2 ans, en particulier en Afrique. Nous avons pu confirmer la résistance élevée aux antibiotiques de première ligne, notamment l'amoxicilline, le chloramphénicol et le co-trimoxazole.<sup>143</sup>

En plus de la très grande hétérogénéité des taux d'incidence chez les nouveau-nés et chez les nourrissons, la fréquence d'infection rapportée est probablement également sous-estimée. Les trois quarts des études dans les deux tranches d'âge confondues se sont déroulées dans des contextes urbains avec un recrutement dans des centres hospitaliers universitaires. Dans les pays à faible revenu, la majorité des familles n'a pas recours aux soins à l'hôpital, particulièrement dans les zones rurales, du fait de contraintes financières, de l'éloignement de leur domicile, ou de différences dans les habitudes de recours aux soins.<sup>112</sup> Ceci est particulièrement vrai pour les septicémies néonatales précoces, et dans le contexte des accouchements à domicile.

## Conclusion

Malgré la récente prise de conscience mondiale sur les enjeux de résistance aux antibiotiques et les éléments en faveur de l'augmentation de cette résistance dans les pays à faible revenu, les données épidémiologiques sont limitées et ne permettent pas d'avoir une image exacte et récente de la résistance aux antibiotiques dans les pays à faible revenu chez les nouveau-nés et les jeunes enfants, particulièrement en communauté.

Sans données pour évaluer le poids de la résistance aux antibiotiques dans cette population, ce problème de santé publique restera incontestablement négligé. Les recherches à venir devraient permettre la collecte de données épidémiologiques standardisées de qualité ainsi que des données bactériologiques fiables au niveau communautaire afin de permettre d'adapter les mesures de santé publique nécessaires pour lutter contre la résistance aux antibiotiques.

## Mesure de la consommation d'antibiotiques au niveau communautaire dans les pays à faible revenu

### Contexte

Les données sur le poids de la résistance aux antibiotiques seules sont insuffisantes pour répondre à la question de la résistance aux antibiotiques dans les pays à faible revenu. La consommation d'antibiotique est le principal moteur de la résistance aux antibiotiques et les études montrent que des niveaux de consommations plus élevés sont associés à des niveaux de résistance plus élevés dans une population donnée.<sup>45</sup> Répondre à la résistance implique donc de contrôler la consommation d'antibiotiques. Cependant, ce contrôle est impossible sans les données correspondantes de consommation d'antibiotiques.<sup>151</sup> Des données sur des aspects tels que les sources d'antibiotiques et les principaux moteurs de la consommation peuvent aider les pays à faible revenu à développer des stratégies de contrôle de la consommation d'antibiotiques.

Dans les pays à faible revenu, ces données peuvent être peu fiables voire non-existantes. Rassembler des données pose des problèmes méthodologiques compliqués étant donné le grand nombre de sources d'achat sans prescription ou sur des marchés parallèles dans un certain nombre de ces pays.<sup>70, 153</sup> En plus d'être fréquent dans de nombreux pays à faible revenu, ce type de consommation présente un haut risque de développement de résistance aux antibiotiques et doit être pris en compte.

Afin d'étudier la question de la mesure de la consommation d'antibiotiques dans les pays à faible revenu, nous avons revu les méthodes utilisées actuellement provenant de la littérature publiée incluant une évaluation critique de chacune de ces méthodes. Enfin, nous proposons une approche intégratrice et adaptative afin de répondre à cet enjeu.

### Méthodes

Une revue de littérature a été conduite en recherchant dans PubMed (dernière recherche le 30 Septembre 2015) les mots-clés suivants : "antibiotic", "antibiotic consumption", "developing country", "low-income country", "non-prescription antibiotic", "community", et "survey". Les rapports sur la mesure de l'utilisation d'antibiotiques ou de médicaments, notamment les rapports de l'OMS, ont également été examinés et les références de ces rapports ont été étudiées afin de les inclure ou non. Les critères d'inclusion comprenaient les mesures de consommation d'antibiotique en communauté ou en soins ambulatoires.



## Résultats et revue de la méthodologie

Des 487 études identifiées lors de la recherche, 37 ont été sélectionnées pour lecture complète. De celles-ci, 27 ont été retenues pour l'analyse finale. (Figure 13) Quatre méthodes d'investigation ont été identifiées de cette recherche de la littérature : la revue de documents des hôpitaux et pharmacies, la méthode du client simulé, l'observation de rencontres de prescription/entretien de sortie des patients, et les enquêtes en communauté. (Cf Table S2- appendix)

### *Les revues de documents des hôpitaux et pharmacies*

L'une des manières les plus simples d'étudier la consommation d'antibiotique en communauté est d'examiner les dossiers des hôpitaux et des pharmacies ou les documents prescrits.<sup>159-165</sup>

La force principale de ces méthodes est que ce type de données est relativement rapide à rassembler, en faisant ainsi un candidat potentiel pour la surveillance. Le type d'antibiotique, la proportion, et les doses quotidiennes déterminées (S-DDD), une mesure standardisée de la quantité de médicament développée par l'OMS pour permettre une comparaison facile entre les médicaments et les différents contextes de prise en charge, peuvent être facilement calculés.

En pratique, cette méthode ne permet pas de recueillir des informations limitées recueillies sur les symptômes ou les connaissances, les attitudes et les croyances du patient, de même que les biais potentiels de cette approche, doit être prise en compte lors de l'utilisation de cette méthode.

### *La méthode du client simulé*

La méthode du client simulé nécessite des agents de terrain formés se faisant passer pour des clients auprès des pharmacies, de « points de ventes » sur les marchés, des centres de santé. L'agent de terrain présentera des symptômes (les siens ou ceux d'une autre personne), demandera un traitement, et mesurera la réaction du fournisseur.<sup>28, 150, 162, 166</sup> Les mesures peuvent comprendre le traitement délivré, les recommandations ou l'information donnée.<sup>157</sup>

La méthode du client simulé est une méthode ciblée sur le fournisseur de médicaments plutôt que sur le patient. Elle est particulièrement bien adaptée aux études sur les antibiotiques non prescrits et permet une collecte non biaisée d'informations telles que les connaissances, les attitudes et les croyances du fournisseur. Le nombre illimité de scénarios possibles (âge, symptômes, etc.) donne à cette méthode de la flexibilité et en fait une méthode relativement rapide et peu coûteuse à utiliser.

C'est une approche importante dans la compréhension des ventes de médicaments non prescrits en pharmacie, ou sur les marchés et potentiellement bien adaptée au développement d'interventions ciblant les pharmaciens, mais elle doit être associée à

d'autres méthodes pour déterminer les schémas de consommation d'antibiotiques au niveau de la population.

### *Observation des délivrances de médicaments en Pharmacie/Entretien de sortie des patients*

L'observation des délivrances de médicaments en Pharmacie implique des agents de terrain formés ou des pharmaciens enregistrant en temps réel les transactions réalisées en pharmacie. Les entretiens de sortie des patients consistent à interroger les patients sortant d'une pharmacie ou d'une structure de santé sur leurs achats.<sup>160, 163-165, 169-174</sup>

Cette approche présente un grand nombre d'avantages. Premièrement, un grand nombre de variables peuvent être collectées. Le type et les proportions d'antibiotiques utilisés sont facilement calculables, comme les DDD par patient et la proportion d'antibiotiques achetés sans prescription. L'accès aux patients dans les entretiens de sortie permet l'obtention de données sur les raisons de l'achat d'antibiotiques, les facteurs sociodémographiques associés à l'utilisation d'antibiotique, ainsi que les connaissances, les croyances et les attitudes.

Ces méthodes sont flexibles et adaptées à l'étude de l'utilisation des antibiotiques dans les pays en développement. Cependant, cibler seulement les pharmacies peut biaiser les estimations globales.

### *Les enquêtes en communauté*

Contrairement aux stratégies se focalisant sur les fournisseurs de médicaments ou recrutant les patients ayant accès aux pharmacies et aux structures de santé, les enquêtes en communauté s'intéressent aux résidents d'une aire géographique donnée comme population d'étude. Un nombre de maisons sont sélectionnées aléatoirement par l'utilisation d'un plan d'enquête et les maisons sont visitées par des agents de terrain qui posent des questions aux résidents sur leur consommation d'antibiotiques.<sup>149, 150, 162, 173, 176-185</sup>

Un certain nombre d'avantages existe dans l'utilisation d'enquêtes en communauté dans l'étude de la consommation d'antibiotique. En prenant des mesures au niveau de la population, il est possible d'éviter les biais de sélection potentiels que l'on retrouve dans les entretiens de sortie ou la revue de documents de pharmacie. Il est également possible d'étudier l'ensemble des sources d'obtention d'antibiotiques y compris les sources sans prescription. Avec l'accès aux patients, cette technique est utile pour collecter des variables sur le lieu d'achat, le respect des posologies, les raisons de l'achat ainsi que des caractéristiques de la population et les connaissances, attitudes et croyances du patient. Le type et la proportion d'antibiotiques spécifiques peuvent être estimés bien qu'avec moins de précision que les méthodes mises en œuvre en pharmacie.<sup>173</sup>

Bien que les enquêtes en communauté soient généralement plus coûteuses et nécessitent plus de ressources que d'autres méthodes de collecte de données, elles constituent la meilleure manière de cerner toutes les sources d'antibiotiques dans les pays à faible revenu et génèrent les résultats les plus riches. La capacité à rassembler des informations complémentaires dont celles sur les facteurs associés à la consommation d'antibiotiques

avec ou sans prescription est également importante pour mettre en place des interventions ou planifier de futures études.

## Discussion et intégration des techniques d'étude

Chacune des quatre méthodes discutées possède des avantages et des inconvénients pour répondre aux diverses questions liées à la consommation d'antibiotiques (cf Table 5). Le temps gagné dans la revue de documents est contrebalancé par les données relativement limitées obtenues tandis que l'investissement en temps et en ressources des enquêtes en communauté peut fournir une quantité importante d'informations précieuses sur la consommation d'antibiotiques et les variables liées à celle-ci.

Idéalement, ces méthodes devraient être utilisées en complément afin de couvrir l'ensemble des données nécessaires à la description et au suivi de la consommation d'antibiotiques dans les pays à faible revenu, et d'identifier les champs d'intervention. L'OMS appelle à l'usage de la « triangulation » de plusieurs stratégies et recommande l'utilisation de cette approche pour l'étude de la consommation de médicaments pour croiser les résultats de chacun de ces types d'étude.<sup>157</sup> Puisque la méthode d'étude la plus appropriée peut varier en fonction des résultats d'autres sources de données, les projets de recherche doivent être adaptatifs et capables de réagir à de nouvelles informations en changeant ou modifiant les méthodes d'étude.

Dans les pays à faible revenu, les enquêtes en communauté représentent la seule méthode capable de prendre en compte les antibiotiques non prescrits, et leur capacité à collecter de grandes quantités de données auxiliaires tout en limitant le biais de sélection en fait un point de départ idéal pour une méthode intégratrice et adaptative. En utilisant cette approche, les enquêtes en communauté peuvent être utilisées pour répondre à des questions importantes concernant les sources et la proportion d'antibiotiques non prescrits et pour fournir une base pour des études additionnelles et des interventions de choix.<sup>157</sup> (Figure 14) Pendant l'étude, des méthodes qualitatives peuvent également être ajoutées autant que besoin pour explorer des thématiques spécifiques.

## Conclusion

La résistance aux antibiotiques est en augmentation dans les pays à faible revenu et menace d'augmenter considérablement la morbidité et la mortalité au sein de populations déjà vulnérables. Des programmes de contrôle de l'utilisation des antibiotiques sont nécessaires pour combattre le développement de la résistance, particulièrement dans les pays à faible revenu où peu de contrôles existent. Afin d'être effectifs, ces programmes requièrent des données de qualité sur la consommation d'antibiotiques, ce qui est rendu difficile par l'utilisation d'antibiotiques non prescrits dans certains pays. Des méthodes spécifiques sont nécessaires pour prendre en compte ces circonstances particulières et rassembler les données nécessaires au contrôle de l'utilisation des antibiotiques et à la lutte contre la résistance. Une approche intégrée et adaptative commençant par les enquêtes en communauté répond aux divers besoins de données et aux difficultés liées au contexte des pays à faible revenu, et peut faciliter l'étude et le contrôle de la consommation d'antibiotiques dans ces pays. L'utilisation de ce type d'approche pourrait fournir des données recevables et comparables entre les pays à faible revenu.

## Enquête à Madagascar et au Sénégal

### Introduction

Générer des données sur la consommation d'antibiotiques doit être une priorité dans les pays à faible revenu pour combler les lacunes dans la connaissance de ce sujet et développer des stratégies de lutte contre la résistance aux antibiotiques. Ces données sont particulièrement rares dans les pays d'Afrique sub-saharienne. Le poids important des maladies infectieuses chez les jeunes enfants de ces pays en fait des moteurs importants de la consommation d'antibiotiques dans de nombreux pays et des populations plus vulnérables à la résistance aux antibiotiques.<sup>16, 57</sup>

Pour mesurer la consommation d'antibiotiques et les facteurs liés à celle-ci dans les pays à faible revenu, nous avons entrepris deux enquêtes en communauté chez de jeunes enfants à Madagascar, un pays à faible revenu, et au Sénégal, un pays à revenu moyen bas.<sup>158</sup>

### Méthodes

Une enquête transversale en population a été réalisée entre Novembre 2014 et Février 2015 à Madagascar, et entre Avril et Juillet 2015 au Sénégal. La population d'étude à Madagascar incluait les enfants de moins de deux ans vivant dans les 2<sup>ème</sup>, 3<sup>ème</sup> et 5<sup>ème</sup> arrondissements de la capitale Antananarivo (population totale : 1 168 898) et ceux vivant dans la ville semi-rurale de Moramanga (population totale : 46 393). Au Sénégal, la population d'étude incluait les enfants de moins de deux ans vivant à Guédiawaye (population totale : 329 659), une banlieue urbaine de Dakar.

Une enquête en grappe à deux niveaux a été menée en utilisant un échantillonnage par segments compacts (compact segment sampling or CSS).<sup>188</sup> Une taille d'échantillon de 400 enfants dans chaque site a été calculée.

Les données ont été collectées via des entretiens en face à face avec un des parents de l'enfant ou son gardien par des agents de terrain formés. Les agents de terrain ont utilisé des questionnaires pré-testés et ont collecté des données sur des variables sociodémographiques, les antécédents médicaux de l'enfant, et la consommation d'antibiotiques de l'enfant dans les trois derniers mois.

Une cartographie des structures de santé et pharmacies des zones d'études a été réalisée. Une régression logistique a été réalisée pour déterminer les variables associées à la consommation d'au moins un antibiotique dans les trois derniers mois.

### Résultats

Au total, 394 enfants ont été recrutés à Antananarivo, 502 à Moramanga et 505 à Guédiawaye. Les caractéristiques sociodémographiques de la population échantillonnée sont disponibles dans le tableau 6.

Les caractéristiques des enfants ne présentaient pas de différences selon les trois sites en ce qui concerne l'âge de l'enfant, son sexe, la malnutrition, la prématurité et le poids de naissance (tableau 7). Des différences significatives globalement ont été retrouvées pour le fait d'être à jour de ses vaccins, avec des proportions de 90,5%, 71,6% et 67,6% à Guédiawaye, Moramanga et Antananarivo respectivement.

Les niveaux de consommation d'antibiotiques dans les trois derniers mois étaient de 37,2% (IC 95% 33,4% - 41,2%) à Guédiawaye, 29,3% (IC 95% 25,0% - 34,1%) à Antananarivo et 24,6% (IC 95% 20,6% - 29,1%) à Moramanga (tableau 8). Ces différences étaient statistiquement significatives globalement ( $P < 0.01$ ). L'utilisation d'antibiotiques sans prescription n'était pas significativement différente entre les trois sites d'étude avec 7,8% (IC 95% 4,2% - 14,3%) à Antananarivo, 13,0% (IC 95% 10,3% - 16,3%) à Moramanga, et 8,0% (IC 95% 4,2% - 14,7%) à Guédiawaye ( $p=0.66$ ).

La majorité des antibiotiques ont été recommandés par des médecins ou des infirmiers (indépendamment de la présence ou non d'une prescription) à Antananarivo (95,7%), Guédiawaye (94,4%) et Moramanga (73,5%) (Table 9).

Pour tous les sites, le groupe de symptômes le plus souvent rapporté conduisant à la consommation d'antibiotiques était les symptômes respiratoires et ORL (œil, nez, gorge) représentant 60,7% des épisodes de consommation à Antananarivo, 68,4% à Moramanga et 38,3% à Guédiawaye (Figure 16).

Les antibiotiques les plus couramment utilisés étaient les pénicillines (53,5%, 66,7% et 52,8% pour Antananarivo, Moramanga et Guédiawaye respectivement), dont principalement l'amoxicilline (Figure 17).

La plupart des antibiotiques ont été achetés dans des pharmacies privées (89,4%, 73,5% et 78,5% à Antananarivo, Moramanga et Guédiawaye respectivement).

En analyse multivariée, ajustée sur le site, un facteur restait significativement associé à une consommation d'antibiotiques plus élevée dans les trois derniers mois, le fait d'habiter dans une maison avec des toilettes sans chasse d'eau (OR 1,43, IC 95% 1,04 – 1,97).

Parmi les trois sites, une densité plus grande de structures de santé était observée dans les sites avec des niveaux de consommation plus bas. Inversement, une plus grande densité de pharmacies privées dans la zone d'étude était observée dans les sites ayant un niveau plus élevé de consommation d'antibiotiques (Figure 18).

## Discussion

Les résultats de notre étude sont les premières estimations intégrées de consommation d'antibiotiques chez les enfants à Madagascar et au Sénégal et complètent la littérature sur la consommation d'antibiotiques dans les pays à faible revenu où peu de données de qualité existent. La collecte des facteurs liés à l'utilisation d'antibiotiques est également importante pour comprendre la consommation et développer les mesures de santé publique nécessaires et les méthodes de surveillance. Des niveaux de consommation conséquents dans les trois derniers mois ont été trouvés, particulièrement au Sénégal.

La majorité des antibiotiques ont été prescrits pour des enfants présentant des symptômes respiratoires ou ORL dans tous les sites. Ces symptômes sont liés aux infections des voies respiratoires supérieures, lesquelles sont souvent causées par des virus pour lesquels les antibiotiques ne sont pas recommandés.<sup>202</sup>

Dans les analyses exploratoires multivariées groupées sur les trois sites, seule une variable était significative après ajustement sur le site. Les toilettes non équipées de chasse d'eau peuvent refléter un niveau socioéconomique moindre ou jouer un rôle dans la propagation des maladies du fait du manque d'hygiène, bien qu'aucune différence n'ait été notée dans les symptômes selon le type de toilettes.

De façon intéressante, la couverture vaccinale n'était pas associée à une réduction de l'utilisation d'antibiotiques dans les analyses groupées.

La consommation d'antibiotiques plus élevée au Sénégal pourrait être due à une utilisation plus importante des structures de soins et une plus grande consommation médicamenteuse, ce qui est notamment visible dans l'utilisation de tout type de médicaments dans les trois derniers chez les enfants sénégalais. Un niveau socioéconomique plus élevé au Sénégal pourrait également se traduire par un accès aux soins et une consommation d'antibiotiques plus importante.

Les politiques de santé nationales de chaque pays peuvent également jouer un rôle dans les différences de consommation. En 2013, la Couverture Maladie Universelle a été lancée au Sénégal, sous laquelle la prise en charge des enfants de moins de 5 ans de même qu'un certain nombre d'antibiotiques sont devenus gratuits dans les structures publiques de santé. A Madagascar, l'évaluation et le suivi des enfants est gratuit dans les centres de santé publics. Cependant, tout traitement y compris les antibiotiques doit être payés, ce qui crée une barrière d'accès pour les familles les plus pauvres.<sup>203</sup>

De manière intéressante, le nombre de centres de santé par habitant était inversement corrélé à la consommation d'antibiotiques. La population d'étude Sénégalaise avait moins de centres de santé par habitant.

Un plus grand nombre de pharmacies par habitant était aussi corrélé à une consommation d'antibiotiques plus importante dans les trois sites. Ceci peut être dû à une plus grande disponibilité des médicaments globalement et une plus grande proximité des familles, ayant pour conséquence un accès facilité aux antibiotiques.

L'utilisation sans prescription dans les deux pays était plus faible que dans deux autres études en pays à faible revenu.<sup>150, 177</sup> Ces proportions relativement basses peuvent être dues au fait que les parents et les fournisseurs d'antibiotiques sont plus précautionneux dans l'octroi de médicaments non prescrits aux petits enfants.

La grande majorité des antibiotiques dans tous les sites étaient obtenus dans les pharmacies et recommandés par un médecin. Ces résultats sont concordants avec les niveaux relativement faibles d'utilisation sans prescription et peuvent refléter une perception de vulnérabilité de la population d'étude.

## Conclusion

Ces données sont cruciales pour l'implantation de programmes visant à optimiser la consommation d'antibiotiques. Nos résultats montrent des niveaux élevés de consommation d'antibiotiques mais souvent pour des symptômes suggérant une infection virale. Bien que toute utilisation non nécessaire doive être réduite, il n'y a pas de garantie que tous les enfants ayant besoin d'antibiotiques les reçoivent effectivement. Les pays à faible revenu doivent trouver un équilibre entre la restriction et l'accès dans des contextes de résistance aux antibiotiques.<sup>3</sup>

Les facteurs propres au pays tels que la densité de structures de santé, les programmes de paiement d'antibiotiques nationaux, et la formation des prescripteurs semblent être importants dans la détermination de la consommation d'antibiotiques et devraient être pris en compte lors du développement de stratégies d'optimisation de la consommation d'antibiotiques dans les pays à faible revenu. Des études similaires pourraient être utiles dans d'autres pays à faible revenu où les données de consommation sont insuffisantes et où des facteurs de risque du développement et de la dissémination de la résistance aux antibiotiques existent. Ces études permettraient de réaliser des comparaisons inter-pays. Elles pourraient également constituer la base de systèmes de surveillance permanents, ou des informations clés pour informer et mesurer les programmes de santé publique dont le but est de s'attaquer à la résistance via la consommation d'antibiotiques.

## Travaux actuels et résistance aux antibiotiques dans les PED

Les résultats de nos recherches portant à la fois sur la compréhension de la résistance aux antibiotiques chez des enfants vivant dans des PED et sur la consommation d'antibiotiques, viennent enrichir les données et apporter des éléments de compréhension sur ce sujet.

### *Forces et limites de ce travail*

Le fait d'avoir étudié la résistance aux antibiotiques à travers différentes perspectives représente une des forces majeures de ce travail. La résistance aux antibiotiques est un problème qui implique des retombées diverses et variées. Combiner des études qui permettent d'estimer l'importance de ce fléau avec des recherches portant sur les facteurs de risque associés au développement et à l'expansion de la résistance aux antibiotiques permet de mieux appréhender cette problématique dans les PED.

Une deuxième force majeure de ce travail relève de sa capacité à avoir proposé une solution de mesure de consommation d'antibiotiques qui soit adaptée aux PED et à l'avoir mise en œuvre. La revue de la littérature portant sur la mesure de la consommation d'antibiotiques a permis d'apporter des bases théoriques solides de méthodologie au présent travail. Celles-ci ont ensuite pu être validées sur le terrain dans différents PED. Le fait d'avoir utilisé une méthodologie similaire entre les différents lieux et pays de l'étude est également un avantage non négligeable de notre travail. Cela nous a en effet permis d'étudier les similarités et différences entre pays, et d'essayer de comprendre l'origine des différences observées.

Le fait d'avoir centré nos travaux sur les infections et consommations d'antibiotiques en population générale est une des limites de ce travail. En effet, les infections ayant eu lieu en milieu hospitalier n'ont pas été prises en compte et les consommations d'antibiotiques au

sein des hôpitaux n'ait pas été renseignées de manière spécifique. Or la résistance aux antibiotiques est élevée en milieu hospitalier dans les PED.<sup>56</sup>

Le fait d'avoir limité notre étude à des enfants de moins de 2 ans vivant dans des PED est également une limite de ce travail. La résistance aux antibiotiques et ses déterminants tels que les profils de consommation d'antibiotiques ne sont pas des phénomènes restreints à une catégorie d'âge de la population. En limitant la portée de notre étude à une catégorie de la population, des données importantes relatives aux autres catégories de la population n'ont sans doute pas pu être considérées.

De nouvelles approches intégrant à la fois la consommation d'antibiotiques humaine et animale (souvent citées comme des approches « one health ») ont émergé ces dernières années et amènent de nouvelles perspectives de recherche dans le domaine de la résistance aux antibiotiques.<sup>216</sup> En effet, l'agence américaine des produits alimentaires et médicamenteux (US food and drug administration) estime que plus de 70% des antibiotiques sont vendus dans le cadre de la production animale, constituant ainsi un foyer important d'émergence de résistance aux antibiotiques.

Le phénomène de sélection naturelle associé à la résistance aux antibiotiques peut aussi être considéré dans cette approche dite « one health ». Les eaux polluées par les antibiotiques peuvent constituer un terrain propice à l'émergence de résistances.<sup>219</sup> Il paraît donc nécessaire de prendre en compte l'ensemble des sources menant à la résistance aux antibiotiques afin de mettre en place des actions complètes et ainsi combattre son expansion.

En plus de répondre à un certain nombre de questions, ce travail en apporte de nouvelles et ouvre ainsi la voie pour de futures recherches. En particulier les travaux que nous avons menés en lien avec la consommation d'antibiotiques ont soulevé un nombre important de problématiques qu'il serait pertinent d'étudier lors de futures recherches. Les différences observées entre les milieux urbains et ruraux représentent par exemple une problématique intéressante dans les PED dû aux différences de mode de vie et d'accès aux ressources. Dans notre enquête en population à Madagascar nous avons essayé d'étudier ces différences. Des données de consommation d'antibiotiques concernant une zone rurale au Sénégal seraient précieuses. Elles permettraient non seulement d'approfondir la compréhension de profils de consommation locale mais aideraient également à répondre aux questions liées aux différences existantes entre zones rurales et urbaines à Madagascar.

Notre étude portant sur la consommation d'antibiotiques a également soulevé de nombreuses questions et hypothèses relatives à l'importance d'éléments structuraux de santé (systèmes de paiement, formation du personnel de santé, accès aux soins, etc...) pouvant agir comme déterminants des profils de consommation d'antibiotiques. Le fait d'utiliser des techniques d'enquêtes similaires à celles que nous avons utilisées dans notre étude dans d'autres PED serait utile pour collecter des données propres à ces pays et tester ces hypothèses.

En parallèle de la quantité d'antibiotiques consommés en population générale, la qualité de ces antibiotiques pourrait également jouer un rôle dans le développement et la dissémination du phénomène de résistance aux antibiotiques. Dans les PED, une médication



de qualité n'est pas toujours à disposition. Tester la qualité des antibiotiques distribués dans les zones que nous avons étudiées pourrait contribuer à déterminer le rôle des antibiotiques de mauvaise qualité comme facteurs de risque de développement et de propagation de la résistance aux antibiotiques dans ces régions.

La consommation d'antibiotiques en soi n'est pas un problème de santé. Afin de mieux comprendre les relations entre consommation d'antibiotiques et infections liées à une résistance aux antibiotiques, il serait précieux de pouvoir comparer ces deux phénomènes dans une population donnée. L'étude BIRDY (Bacterial Infections and antibiotic Resistant Diseases among Young children in low-Income countries) qui a lieu à Madagascar et au Sénégal fournit cette opportunité. Les données issues de l'étude BIRDY concernent des infections liées à une résistance aux antibiotiques chez des enfants similaires à ceux inclus dans notre étude de consommation d'antibiotiques, en tenant compte des critères suivants : âge, région géographique et statut socio-économique. De précieuses pistes de recherche sur la relation complexe entre consommation d'antibiotiques et infections liées à la résistance à ceux-ci pourraient être envisagées en comparant les résultats de l'étude BIRDY aux nôtres.

Afin de mieux comprendre encore la consommation d'antibiotiques dans les PED, les futures études pourraient s'intéresser à l'ensemble de la population en incluant des individus de tous âges. Bien que les enfants âgés de moins de deux ans représentent une population vulnérable, les phénomènes de pression de sélection menant au développement de la résistance aux antibiotiques ne sont pas limités à cette population. Une approche « one health » permettrait de prendre en considération l'usage des antibiotiques lié à la production animale, au moment d'estimer la pression de sélection des antibiotiques dans ces populations.

## Conclusion

La résistance aux antibiotiques est un problème coûteux tant d'un point de vue humain qu'économique, qui continuera de s'accroître si des solutions ne sont pas apportées. Comme les échanges à l'international augmentent et que le monde devient de plus en plus interconnecté, les maladies infectieuses ne sont plus des problèmes locaux. La résistance aux antibiotiques n'échappe pas à cette règle. Les solutions à apporter pour faire face à la résistance aux antibiotiques doivent être réfléchies à l'échelle mondiale et inclure les PED. Ces solutions globales ont également besoin de pouvoir être adaptées à l'échelle locale. Prendre conscience de ces enjeux est la première étape vers la compréhension et l'action. Être capables d'évaluer le fléau de la résistance aux antibiotiques ainsi que la consommation de ceux-ci représentent les premières étapes clé nécessaires à la lutte mondiale contre la résistance aux antibiotiques.

## RESEARCH ARTICLE

## Open Access

# Burden of bacterial resistance among neonatal infections in low income countries: how convincing is the epidemiological evidence?

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**Abstract**

**Background:** Antibiotic resistance is a threat in developing countries (DCs) because of the high burden of bacterial disease and the presence of risk factors for its emergence and spread. This threat is of particular concern for neonates in DCs where over one-third of neonatal deaths may be attributable to severe infections and factors such as malnutrition and HIV infection may increase the risk of death. Additional, undocumented deaths due to severe infection may also occur due to the high frequency of at-home births in DCs.

**Methods:** We conducted a systematic review of studies published after 2000 on community-acquired invasive bacterial infections and antibiotic resistance among neonates in DCs. Twenty-one articles met all inclusion criteria and were included in the final analysis.

**Results:** Ninety percent of studies recruited participants at large or university hospitals. The majority of studies were conducted in Sub-Saharan Africa (n = 10) and the Indian subcontinent (n = 8). Neonatal infection incidence ranged from 2.9 (95% CI 1.9–4.2) to 24 (95% CI 21.8–25.7) for 1000 live births. The three most common bacterial isolates in neonatal sepsis were *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella*. Information on antibiotic resistance was sparse and often relied on few isolates. The majority of resistance studies were conducted prior to 2008. No conclusions could be drawn on *Enterobacteriaceae* resistance to third generation cephalosporins or methicillin resistance among *Staphylococcus aureus*.

**Conclusions:** Available data were found insufficient to draw a true, recent, and accurate picture of antibiotic resistance in DCs among severe bacterial infection in neonates, particularly at the community level. Existing neonatal sepsis treatment guidelines may no longer be appropriate, and these data are needed as the basis for updated guidelines. Reliable microbiological and epidemiological data at the community level are needed in DCs to combat the global challenge of antibiotic resistance especially among neonates among whom the burden is greatest.

**Keywords:** Antibiotic resistant bacterial infection, Developing countries, Neonatal, Epidemiology, Community

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## Background

Infectious disease remains the leading cause of death in children under 5 in developing countries (DCs) with neonates bearing the highest burden. In Africa alone, infectious disease accounts for over 76% of under-5 deaths, and an estimated 36% of neonatal deaths worldwide are directly attributable to severe infections [1,2].

Moreover, DCs are also home to a number of risk factors for the emergence and spread of antibiotic resistance. Misuse of antibiotics, over-the-counter and parallel market access, and counterfeit or poor quality drugs, combined with substandard hygiene and living conditions, are the driving forces behind the emergence and spread of antibiotic resistance [3,4]. The potential for the development and rapid spread of new forms of resistance is highlighted by the recent worldwide proliferation of NDM-1-producing *Enterobacteriaceae*. The gene, which confers resistance to carbapenems, originated in India in 2009, and since 2010 NDM-1-producing *Enterobacteriaceae* have been reported in North America, Europe, and Asia [5]. The World Health Organization (WHO) has recently heightened awareness of this pressing issue with calls for action to contain antibiotic resistance on a global scale [6].

A recent report estimates 6.9 million cases of possible severe bacterial infection in neonates in sub-Saharan Africa, south Asia, and Latin America in 2012 [7] underscoring the potential for excess morbidity and mortality due to antibiotic resistance. In this context, antibiotic resistance trends need to be monitored.

We report a systematic review examining studies dealing with invasive bacterial infections and antibiotic resistance among neonates in DCs with a special emphasis placed on community-based studies.

## Methods

An initial search was conducted for articles dealing with infection and antibiotic resistance among children under 2. This search allowed us to identify both neonatal-specific articles as well as articles dealing with young childhood infection that included neonatal-specific information.

We searched PubMed for studies published in 2000 or later (last search April 30th, 2014). To overcome a potential lack of studies dealing with both topics simultaneously, our search was divided into two branches including 1) community-acquired bacterial infections in infants of DCs (BI), and 2) antibiotic resistance among community-acquired infections in DCs (AR). DCs were identified as “least developed”, “other low income”, or “lower middle income” by the World Bank or as “low human development” or “medium human development” by the United Nations [8,9]. We also screened reference lists of relevant articles for further publications.

Before paper selection, duplicates from the BI and AR lists were eliminated. Detailed PubMed search and inclusion criteria are shown Table 1. Abstracts were screened for full text reading by two of the three reviewers (B-T. H., M.P., and E.D.A.) and a third reviewer was called upon as needed. Information was extracted from selected articles including: study year, study location, urban vs. rural location, hospital recruitment vs. other, community or nosocomial infections, study design and microbiology methods (bacterial isolation methods and antibiotic susceptibility testing). Articles were then re-evaluated by two reviewers as before.

Following the selection of articles for children <2, those articles containing information on either bacterial infection or resistance during the neonatal period were retained for analysis. An effort was made to restrict the selection to community-acquired infections, and all articles presenting exclusively nosocomial infections were eliminated.

## Results

Of the 1543 and 1314 studies returned from the BI and AR searches, 84 and 46 were selected for full reading, respectively (Figure 1). Ultimately, 20 BI studies and one AR study were retained for a total of 21 studies included in the final analysis. Of the 20 BI studies selected, 11 also met the selection criteria for inclusion in AR studies and thus a total of 12 articles were included in the resistance analyses.

A majority of studies came from Sub-Saharan Africa (n = 10) or the Indian subcontinent (n = 8) (Table 2).

### Design, recruitment settings, and study topics

Of the 21 articles analyzed, 17 used either a cross-sectional or surveillance study design [10-26]. Four studies were conducted in rural settings [17,21,24,27] while the remaining 17 were conducted in urban settings (Table 2).

Nineteen of 21 studies recruited participants in large district or university hospitals. Only two studies used active community recruitment [27,28]. Sixteen of the 17 urban studies recruited uniquely at large hospitals.

### Bacterial isolation rates

Thirteen of the 20 infant infection articles reported bacteremia rates. Excluding one study from Georgia with an isolation rate of 67% [14], isolation rates ranged from 5.8% to 48% (median = 22.4%). No difference in rates was noted between urban and rural studies [11-15,18-21,23-27,29,30]. Only one study reported bacterial isolation rates from cerebrospinal fluid cultures, with a 4% positivity rate [24]. Of all BI articles, two reported antibiotic use prior to blood culture, with 16% and 67% exposure rates, respectively [10,27] and

**Table 1 Search strategy and selection criteria for neonatal infection and bacterial resistance articles in developing countries (2000-May 2014)**

Search strategy	
<p>For the BI search, each DC was cross-linked with search terms "Bacterial Infections" OR "Sepsis" OR "bacter*" AND "epidemiology". For the AR search, each DC was cross-linked with "Drug resistance, bacterial" OR ("antibiotic resistance" AND "bacter*") AND "epidemiology". Both searches were restricted to English language articles and the BI search was restricted to the PubMed "infant" age category (birth-23 months). Both searches were also limited by excluding the keywords and MeSH terms "travel", "candida", "HIV infection", "leprosy", "tuberculosis", "tetanus", "malaria", "cholera", or "helicobacter". The BI search was further limited by excluding the keywords "immunization", "immunization program", and "vaccination".</p>	
<b>Inclusion criteria</b>	
<b>Infant infection search (BI)</b>	<b>Resistance search (AR)</b>
<ul style="list-style-type: none"> <li>• Information on bacterial infections including either etiology or disease burden/incidence</li> <li>• Community acquired infections</li> <li>• Methodologically sound including clear inclusion criteria</li> <li>• Sound microbiological methods/citation of guidelines used</li> <li>• Neonatal specific information presented</li> </ul>	<ul style="list-style-type: none"> <li>• Bacterial pathogens</li> <li>• Community acquired infections</li> <li>• Information on antibiotic resistance profile of pathogen (proportion resistance/susceptible, etc.)</li> <li>• Sound microbiological methods/citation of guidelines used</li> <li>• Information on pathogen source and/or clinical information</li> <li>• Neonatal specific information presented</li> </ul>
<b>Exclusion criteria</b>	
<b>Both branches</b>	
<ul style="list-style-type: none"> <li>• Review study or expert opinion</li> <li>• Outside of developing country list</li> <li>• Purely nosocomial infections or no possibility to extract only community acquired infections from data</li> <li>• Pathogen not in the restricted list, including <i>Neisseria gonorrhoeae</i>, <i>Campylobacter</i>, <i>Helicobacter</i>, <i>Vibrio</i>, <i>Clostridium tetani</i>, or any Mycobacteria</li> <li>• Obvious methodological weakness including sampling methods</li> <li>• Insufficient number of isolates/insufficient number of isolates for follow-up period (minimum 10 isolates per year)</li> <li>• Data collection done principally before 2000</li> </ul>	
<b>Infant infection search (BI)</b>	<b>Resistance search (AR)</b>
<ul style="list-style-type: none"> <li>• Ages outside of range of interest or ages of interest non-extractable</li> </ul>	<ul style="list-style-type: none"> <li>• Insufficient epidemiological info on sample source/patients/no. of bacteria isolated from neonates</li> </ul>

two studies excluded those with prior antibiotic exposure [15,16].

**Laboratory methods and antibiotic susceptibility testing guidelines**

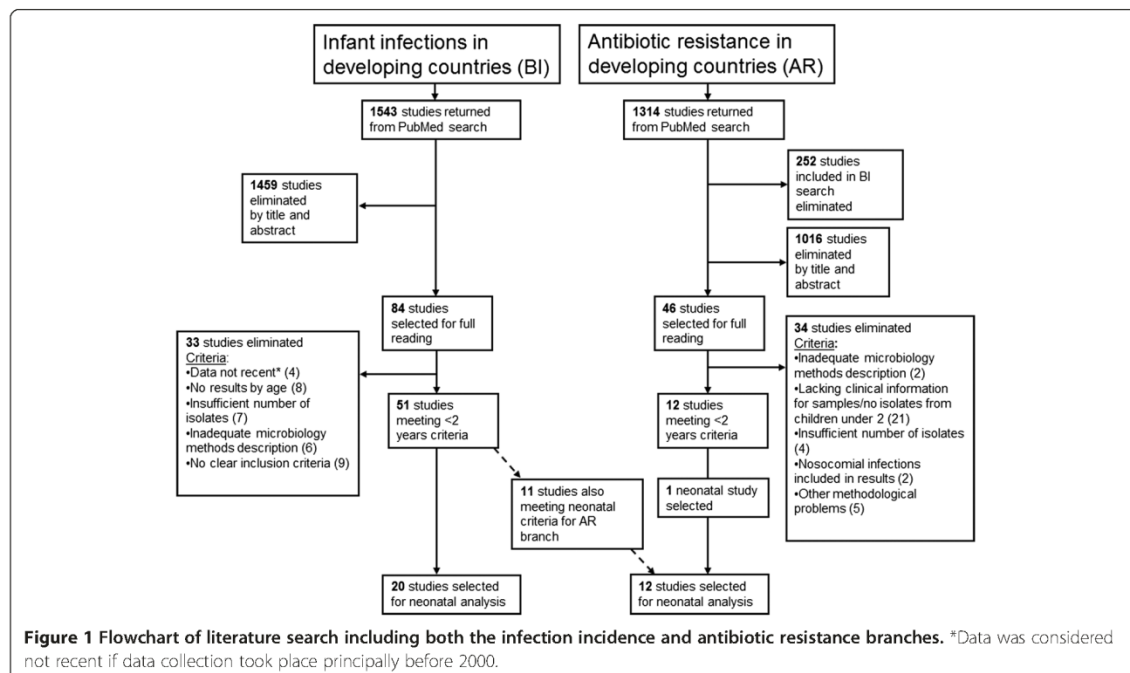
Two of the 19 BI studies with blood cultures reported taking two blood samples from patients [14,15]. Of these 19 studies, 13 reported blood quantity taken [10-13,15-19,21,23,25,27]. Overall, ten of 12 studies retained in the AR analysis (see Figure 1) cited the use of established guidelines for resistance interpretation [11,12,19,20,24-26,28-30] with the majority referring to the Clinical and Laboratory Standards Institute (CLSI) methods. Two studies cited external quality control measures [24,27] and only Darmstadt et al. [27] sent samples to a reference lab for confirmation.

**Bacterial infection incidence estimates and pathogens**

Of 20 studies of BI in neonates, five reported an incidence rate for invasive bacterial infection (Figure 2) [18,23,27-29].

Incidence rates per 1000 live births ranged from 2.9 (95% CI 1.9–4.2) for bacteremia among neonates in Bangladesh [27] to 24 (95% CI 21.8–25.7) for early onset sepsis (<72 hours) in India [23]. Along with Darmstadt et al. [27], Mir et al. [28] used community recruitment and reported an incidence of 20.4 (95% CI 17.3–24.0) in Pakistan for neonatal omphalitis with sepsis [28]. Studies based on hospital recruitment reported sepsis incidence rates of 9.2 (95% CI 8.2–10.3) in Malawi [29] and 7.8 (95% CI 4.4–11.5) in Nigeria [18] per 1000 live births. A third study using hospital recruitment in India reported rates of 24 (95% CI 21.7–25.7) for early onset sepsis (<72 hours), and 16 (95% CI 14.0–18.1) for late onset sepsis (>72 hours) [23].

Among the 20 neonatal studies reporting full bacterial etiology, *Staphylococcus aureus* (*S. aureus*) was reported in all but two, accounting for 3% to 63% (median = 32.5%) of pathogens. Other common pathogens included *Klebsiella* spp., reported in 16 studies and ranging from 8% to 66% (median = 22%) of pathogens, and *Escherichia coli* (*E. coli*), reported in 14 studies and ranging from 5%



to 23% (median = 12%) of isolated pathogens. Sundaram et al. [23] reported that non-fermenting Gram-negative bacteria were the most common isolates in early-onset sepsis (first 72 hrs. of life) representing 30% of isolates, followed by *S. aureus* (20%), *Klebsiella pneumoniae* (*K. pneumoniae*) (12%), and *E. coli* (9%), whereas *S. aureus* predominated in late-onset sepsis (31%), followed by non-fermenting Gram-negative bacteria (17%), *K. pneumoniae* (14%), and *E. coli* (11%) [23]. Blomberg et al. [10] and Mhada et al. [11] reported results for early-onset sepsis defined as 0–7 days. Both studies found early onset sepsis was due primarily to *Klebsiella* spp. (33% and 32% respectively), *S. aureus* (29%, 11%) and *E. coli* (19%, 11%) with late-onset sepsis, defined as 7–28 days and 7–30 days respectively, due mostly to *S. aureus* (55%, 16%), *Klebsiella* spp. (23%, 23%), and *E. coli* (18%, 10%).

Twelve studies reported Group B *streptococcus* isolates. Percentages were low overall, representing between 1% and 20% (median = 4.5) of blood culture isolates in eleven studies [10,11,13-15,18,21,24,25,27-29].

#### Antibiotic resistance

The 12 studies with relevant antibiotic resistance information for selected neonatal pathogens are presented in Table 3. Seven of the 12 studies were conducted before 2008. Resistance to penicillin/ampicillin among Gram-negative bacteria (not including *Klebsiella* spp.) ranged from 55% (95% CI 26%-84%) among *E. coli*

isolates in Georgia [14] to 100% among *E. coli* isolates in Uganda [15]. Resistance to gentamicin among Gram-negative bacteria ranged from 0% for *Pseudomonas* and *E. coli* in Pakistan [28] and for *K. pneumoniae* in Nepal [20] to 100% for *K. pneumoniae* in India [25]. Among Gram-negative bacteria, resistance to third generation cephalosporins (3<sup>rd</sup> GC) ranged from 6% for *E. coli* isolates in Uganda [15] to 97% among *K. pneumoniae* isolates in India [25]. Only two studies tested for extended spectrum beta-lactamase (ESBL) production in *Enterobacteriaceae*. One reported ESBL production in 87% of *Klebsiella* spp. isolates, 73% of *Enterobacter* spp. isolates, and 65% of *E. coli* isolates [26]. The second found 32% ESBL production among *K. pneumoniae* isolates [25]. Resistance of *S. aureus* isolates to methicillin was reported in five studies and ranged from 0% to 67% [14,19,24,28,30].

#### Discussion

Our results highlight the dramatic lack of data on bacterial resistance patterns in neonatal infections in developing countries. They also underscore the paucity of reliable and convincing data on the burden of community-acquired invasive bacterial infections in newborns in these countries. This was pointed out by Berkley et al. almost ten years ago and more recently by Lubell et al. in 2009, demonstrating how little progress has been made on this issue [31,32]. These gaps in knowledge impede the improvement of prevention and

**Table 2 Neonatal infections in developing countries (2000-May 2014)**

Author, country, and study year	Disease type and age	Setting	Neonatal Isolation rate and aetiology*
<b>Sub-Saharan Africa</b>			
Blomberg et al. [10] Tanzania 2001-2002	<i>Bacteremia</i> <7 yrs	urban, hospital recruitment	<b>54 early onset (EOS) isolates<sup>†</sup>: 31 late onset (LOS) isolates:</b> <i>Klebsiella</i> spp. EOS 14 (26%), LOS 7 (23%) <i>S. aureus</i> EOS 6 (11%), LOS 5 (16%) <i>E. coli</i> EOS 6 (11%), LOS 3 (10%) Group B <i>Streptococcus</i> EOS 2 (4%), LOS 1 (3%)
Sigaúque et al. [21] Mozambique 2001-2006	<i>Bacteremia</i> <15 yrs	rural, hospital recruitment	<b>154 isolates: 16% blood cultures positive</b> <i>S. aureus</i> 60 (39%) Group B <i>Streptococcus</i> 31 (20%) <i>E. coli</i> 9 (6%) <i>S. pneumoniae</i> 7 (5%)
Nielsen et al. [17] Ghana 2007-2009	<i>Bacteremia</i> <5 yrs	rural, hospital recruitment	<b>23 isolates:</b> <i>S. aureus</i> 6 (26%) <i>Klebsiella</i> spp. 6 (26%) <i>Streptococcus</i> spp. 3 (13%) <i>E. coli</i> 3 (13%) Non-typhoid <i>Salmonella</i> 2 (9%)
Gray et al. [29] Malawi 2004-2005	Group B <i>streptococcus</i> <90 days	urban, hospital recruitment	<b>290 isolates: 12% blood cultures positive</b> Group B <i>Streptococcus</i> 48 (17%)
Talbert et al. [24] Kenya 2001-2009	<i>Neonatal sepsis</i> <60 days	rural, hospital recruitment	<b>474 isolates: 9% blood cultures positive</b> (25 infants had 2 bacterial species isolated) <i>Klebsiella</i> spp. 57 (13%) <i>S. aureus</i> 55 (12%) <i>Acinetobacter</i> spp. 48 (11%) <i>E. coli</i> 41 (9%) Group B <i>Streptococcus</i> 32 (7%) <b>86 isolates from CSF samples : 4% CSF cultures positive</b> <i>S. pneumoniae</i> 17 (20%) Group B <i>Streptococcus</i> 16 (19%) <i>Salmonella</i> spp. 10 (12%)
Ojukwu et al. [18] Nigeria 2002-2003	<i>Neonatal sepsis</i> 0-28 days	urban, hospital recruitment	<b>33 isolates: 24% blood cultures positive</b> <i>S. aureus</i> 15 (45%) <i>E. coli</i> 6 (18%) <i>Klebsiella</i> spp. 3 (9%) Group B <i>Streptococcus</i> 1 (3%)
Mugalu et al. [15] Uganda 2002	<i>Neonatal sepsis</i> used WHO guidelines	urban, hospital recruitment	<b>110 isolates: 37% blood or CSF cultures positive</b> <i>S. aureus</i> 69 (63%) <i>E. coli</i> 17 (15%) Group B <i>Streptococcus</i> 7 (6%)
Shitaye et al. [19] Ethiopia 2006-2007	<i>Neonatal sepsis</i> 0-28 days	urban, hospital recruitment	<b>135 isolates: 45% blood cultures positive</b> <i>Klebsiella</i> spp. 53 (39%) <i>S. aureus</i> 30 (22%)

**Table 2 Neonatal infections in developing countries (2000-May 2014) (Continued)**

			Coagulase-negative <i>Staphylococcus</i>	10 (7%)
Mhada et al.	<i>Neonatal sepsis</i>	urban, hospital recruitment	<b>52 early onset (EOS) isolates<sup>†</sup>: 22 late onset (LOS) isolates: 22.4% blood cultures positive</b>	
Tanzania 2009-2010	0-28 days		<i>S. aureus</i>	EOS 15 (29%), LOS 12 (55%)
			<i>Klebsiella</i> spp.	EOS 17 (33%), LOS 5 (23%)
			<i>E. coli</i>	EOS 10 (19%), LOS 4 (18%)
			<i>Staphylococcus epidermidis</i>	EOS 6 (12%), LOS 0 (0%)
			Group B <i>Streptococcus</i>	EOS 1 (2%), LOS 0 (0%)
Kiwanuka et al. [13]	<i>Neonatal sepsis</i>	urban, hospital recruitment	<b>19 early onset (EOS) isolates<sup>†</sup>: 7 late onset (LOS) isolates: 33% blood cultures</b>	
Uganda 2010	<1 month		<i>S. aureus</i>	EOS 13 (68%), LOS 3 (43%)
			<i>E. coli</i>	EOS 3 (16%), LOS 1 (14%)
			<i>Klebsiella</i> spp.	EOS 1 (5%), LOS 1 (14%)
			Group B <i>Streptococcus</i>	EOS 1 (5%), LOS 0 (0%)
<b>SE Asia</b>				
Stoesser et al. [22]	<i>Bacteremia</i>	urban, hospital recruitment	<b>65 isolates:</b>	
Cambodia 2007-2011	<16 yrs		<i>Klebsiella</i> spp.	14 (22%)
			<i>S. aureus</i>	9 (14%)
			<i>Enterobacter</i> spp.	4 (6%)
			<i>E. coli</i>	3 (5%)
			<i>Streptococcus pyogenes</i>	3 (5%)
Kruse et al. [30]	<i>Neonatal sepsis</i>	urban, hospital recruitment	<b>399 isolates: 17% blood cultures positive</b>	
Vietnam 2009-2010	<28 days		<i>Klebsiella</i> spp.	78 (20%)
			<i>Acinetobacter</i> spp.	58 (15%)
			<i>E. coli</i>	21 (5%)
			<i>Enterobacter</i> spp.	16 (4%)
			<i>S. aureus</i>	11 (3%)
			<i>Morganella</i> spp.	8 (2%)
			<i>Pseudomonas</i> spp.	6 (2%)
			Coagulase-negative <i>Staphylococcus</i>	175 (44%)
<b>India subcontinent</b>				
Mir et al. [28]	<i>Omphalitis with sepsis</i>	urban, community recruitment	<b>432 isolates: 64% umbilical cord cultures positive</b>	
Pakistan 2004-2007	neonates (<1 month)		<i>S. aureus</i>	225 (52%) <sup>‡</sup>
			<i>Streptococcus pyogenes</i>	78 (18%) <sup>‡</sup>
			Group B <i>Streptococcus</i>	43 (10%) <sup>‡</sup>
Jain et al. [26]	<i>Neonatal sepsis</i>	urban, hospital recruitment	<b>350 isolates: 48% blood cultures positive for bacteria</b>	
India 2001-2002	Not defined		<i>Klebsiella</i> spp.	86 (25%) <sup>‡</sup>
			<i>Enterobacter</i> spp.	80 (23%) <sup>‡</sup>
			<i>E. coli</i>	49 (14%) <sup>‡</sup>
Sundaram et al. [23]	<i>Neonatal sepsis</i>	urban, hospital recruitment	<b>527 early onset (EOS) isolates<sup>§</sup>: 364 late onset (LOS) isolates:</b>	
India 1995-1998, 2001-2006	Not defined		<i>S. aureus</i>	EOS 108 (20%), LOS 112 (31%)
			<i>K. pneumoniae</i>	EOS 62 (12%), LOS 49 (14%)

**Table 2 Neonatal infections in developing countries (2000-May 2014) (Continued)**

			Non-fermenting gram negative bacilli	EOS 161 (30%), LOS 60 (17%)
			<i>E. coli</i>	EOS 48 (9%), LOS 40 (11%)
Zakariya et al. [25]	Neonatal sepsis	urban, hospital recruitment	<b>50 isolates: 42% blood cultures positive</b>	
India 2004-2006	<= 30 days		<i>K. pneumoniae</i>	33 (66%)
			Coagulase-negative Staphylococcus	6 (12%)
			Group B <i>Streptococcus</i>	1 (2%)
Muhammad et al. [16]	Neonatal sepsis	urban, hospital recruitment	<b>130 isolates:</b>	
Pakistan 2009-2010	<28 days		<i>S. aureus</i>	35 (27%)
			<i>E. coli</i>	30 (23%)
			<i>Staphylococcus epidermidis</i>	17 (13%)
			<i>Acinetobacter</i> spp.	17 (13%)
			<i>Klebsiella</i> spp.	13 (10%)
			<i>Streptococcus</i> species only found in early onset sepsis (first week)	
			<i>Klebsiella</i> species only found in late onset sepsis (after first week to 28 days)	
Darmstadt et al. [27]	Neonatal sepsis	rural, community recruitment	<b>29 isolates: 6% blood cultures positive</b>	
Bangladesh 2004-2006	<28 days		<i>S. aureus</i>	10 (34%)
			<i>S. pneumoniae</i>	3 (10%)
			Group B <i>Streptococcus</i>	1 (3%)
Gyawali et al. [12]	Neonatal sepsis	urban, hospital recruitment	<b>238 isolates: 15% blood cultures positive</b>	
Nepal 2009-2010	first 4 weeks of life		<i>S. aureus</i>	94 (40%)
			<i>Klebsiella</i> spp.	32 (14%)
			<i>Acinetobacter</i> spp.	30 (13%)
			<i>Enterobacter</i> spp.	27 (11%)
			<i>Pseudomonas</i> spp.	21 (9%)
			<i>E. coli</i>	16 (7%)
Shrestha et al. [20]	Neonatal sepsis	urban, hospital recruitment	<b>37 isolates: 32% blood cultures positive</b>	
Nepal, 2011-2012	not defined		<i>S. aureus</i>	21 (57%)
			<i>K. pneumoniae</i>	8 (22%)
			<i>P. aeruginosa</i>	5 (13%)
<b>Europe</b>				
Macharashvili et al. [14]	Neonatal sepsis	urban, hospital recruitment	<b>126 isolates: 67% blood cultures positive</b>	
Georgia 2003-2004	8 weeks or younger		<i>K. pneumoniae</i>	36 (29%)
			<i>Enterobacter cloacae</i>	19 (15%)
			<i>S. aureus</i>	15 (12%)
			Group B <i>Streptococcus</i>	6 (5%)

\*Percentages calculated when not reported in the article. Pathogens listed in order of relative percentages.

<sup>†</sup>Early onset sepsis (EOS) defined as 0-6 days.

<sup>‡</sup>Number of isolates calculated from percentages presented in article.

<sup>§</sup>Early onset sepsis (EOS) defined as <72 hours, late onset (LOS) defined as >72 hours.

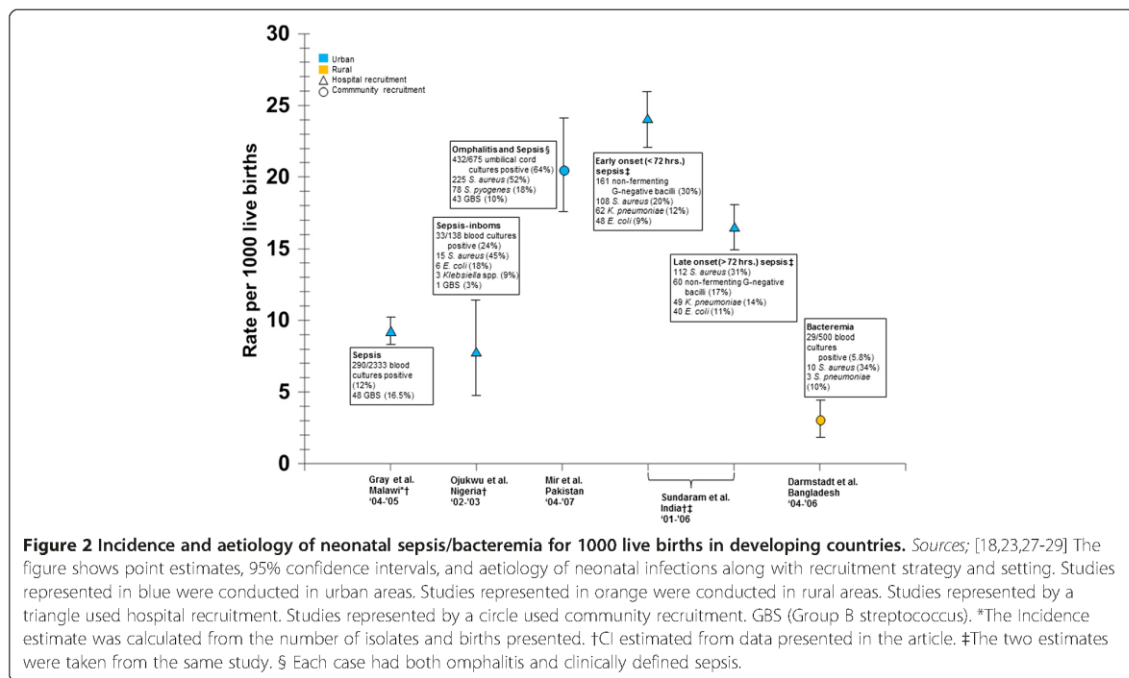
treatment strategies of neonatal infections in these settings where the risk of neonatal death is the highest.

We observed a broad range of neonatal infection incidence estimates. This heterogeneity has been previously noted by other authors [33,34] and emphasizes the need

for routine surveillance across settings to accurately estimate the incidence and monitor trends of neonatal bacterial infections.

We found that the most common pathogens were *S. aureus*, *Klebsiella* spp., and *E. coli* which account for





almost two thirds of neonatal sepsis cases. This proportion is in line with others reviews conducted in DCs [34,35]. Care must be taken when interpreting these results, however, as differentiation of infections into community-acquired or hospital-acquired during the neonatal period can be difficult in DCs [36]. As a result, a small number of nosocomial infections may be included in our findings, thus influencing the pathogen distribution. Five studies were included in our analysis which reported coagulase-negative Staphylococci as responsible for a significant proportion of neonatal infection, however positive blood cultures for this pathogen may commonly be due to sample contamination.

The relative importance of the most common pathogens differs according to disease onset (early vs. late), however this distinction was not detailed in the majority of the studies. Early onset infections are generally attributed to pathogens transmitted from the vaginal or rectal flora of the mother to the child, while late onset infections are attributed to bacteria acquired from the infant's surroundings (hospitals or community) with *S. aureus* and *Klebsiella* species more frequently implicated in hospital infections [37]. Infection control measures designed to prevent the acquisition of bacteria from the environment do not affect pathogens that are acquired at birth. Therefore, distinguishing maternal from environmental infection sources would allow for improved implementation of preventive strategies in these settings.

Our results show that since 2000 few studies with reliable data focused on resistance patterns. In addition, the number of isolates per study was generally very small: three-quarters of the 12 studies reporting resistance rates reported results based on fewer than 30 isolates. The WHO recommends ampicillin and gentamicin as first-line treatment of neonatal sepsis unless there is infection of the skin or umbilicus (possible *S. aureus*), when cloxacillin is substituted for ampicillin. Our review shows that resistance to ampicillin was high. Data on gentamicin were heterogeneous and no clear conclusion could be drawn. However, the findings of our review are consistent with others studies [35] and confirm a trend of growing resistance to this drug combination.

Data on resistance to third generation cephalosporins were heterogeneous except among *Klebsiella* spp. for which notable resistance rates were reported [25,26]. Moreover, only two studies reported testing for extended spectrum beta-lactamase (ESBL) despite the fact that ESBL have been reported worldwide. Medication required to treat ESBL-producing *Enterobacteriaceae* is expensive and unaffordable for the majority of the population in these settings making these bacteria difficult to treat. It is therefore of the utmost importance to make reliable data available to guide strategies devoted to limiting the spread of ESBL pathogens in DCs.

Importantly, no conclusions can be drawn regarding methicillin resistant *S. aureus* (MRSA), despite the fact

**Table 3 Antibiotic resistance of bacteria isolated from invasive neonatal infections in developing countries (2000-May 2014)**

Study, year	Location, setting	Pathogen	Resistant% (95% CI)			
			Penicillin/ampicillin	Gentamicin	3rd generation cephalosporins	% ESBL*
Mugalu et al. [15] 2002	Uganda, urban	17 <i>E. coli</i> <sup>†</sup> , <sup>‡</sup> 7 Group B <i>Streptococcus</i> <sup>†</sup>	100 <sup>§</sup> 14 (0-40)	29 (7-51) 57 (20-94)	6 (0-17) -	- NA
Gray et al. [29] 2004-2005	Malawi, urban	57 Group B <i>Streptococcus</i> <sup>†</sup>	0 <sup>§</sup>	-	0 <sup>§</sup>	NA
Shitaye et al. [19] 2006-2007	Ethiopia, urban	30 <i>S. aureus</i>	67% (50-84) resistance to meticillin			NA
Talbert et al. [24] 2001-2009	Kenya, rural	48 <i>Acinetobacter</i> spp. <sup>†,  </sup> 49 <i>K. pneumoniae</i> <sup>†</sup> 39 <i>S. pyogenes</i> <sup>†</sup> 41 <i>E. coli</i> <sup>†</sup> 55 <i>S. aureus</i> <sup>†</sup>	56 (42-70) 96 (91-100) 0 <sup>§</sup> 78 (65-91) 0% resistance to meticillin <sup>§</sup>	27 (14-39) 49 (35-63) - 10 (1-19) -	35 (22-48) 43 (29-57) - 17 (5-29) -	- - - - NA
Mhada et al. 2009-2010	Tanzania, urban	22 <i>Klebsiella</i> spp. <sup>  </sup> 41 <i>E. coli</i>	100 <sup>§</sup> 93 (69-99)	77 (57-90) 43 (21-67)	18 (7-39) 14 (4-40)	- -
Kruse et al. [30] 2009-2010	Vietnam, urban	78 <i>Klebsiella</i> spp. <sup>†,  </sup> 58 <i>Acinetobacter</i> spp. <sup>†,  </sup> 21 <i>E. coli</i> <sup>†</sup> 16 <i>Enterobacter</i> spp. <sup>†,  </sup> 6 <i>Pseudomonas</i> spp. <sup>†,  </sup> 11 <i>S. Aureus</i> <sup>†</sup>	100 <sup>§</sup> 85 (73-92) 86 (65-95) 93 (72-99) 100 <sup>§</sup> 55% (28-79) resistance to meticillin	85 (75-91) 50 (38-62) 57 (37-76) 62 (39-82) 48 (19-81) -	86 (76-92), 71 (60-79) <sup>¶</sup> 82 (71-80), 71 (58-81) <sup>¶</sup> 58 (37-76), 42 (24-63) <sup>¶</sup> 62 (39-82), 50 (28-72) <sup>¶</sup> 83 (44-97), 33 (10-70) <sup>¶</sup> -	- - - - - -
Jain et al. [26] 2001-2002	India, urban	86 <i>Klebsiella</i> spp. <sup>  </sup> 80 <i>Enterobacter</i> spp. <sup>  </sup> 49 <i>E. coli</i>	100 <sup>§</sup> 100 <sup>§</sup> 96 (91-100)	89 (82-96) 93 (87-99) 90 (72-98)	63 (53-73), 49 (38-60) <sup>¶</sup> 64 (53-75), 54 (43-65) <sup>¶</sup> 65 (52-78), 41 (27-55) <sup>¶</sup>	87 (80-94) 73 (63-83) 65 (52-78)
Zakariya et al. [25] 2004-2006	India, urban	33 <i>K. pneumoniae</i> <sup>†</sup>	-	100 <sup>§</sup>	97(85-99), 97(85-99) <sup>¶</sup>	32 (20-50)
Mir et al. [28] 2004-2007	Pakistan, urban	52 <i>Pseudomonas</i> spp. <sup>†,  </sup> 12 <i>Klebsiella</i> spp. <sup>†,  </sup> 9 <i>E. coli</i> <sup>†</sup> 304 <i>S. aureus</i> <sup>†</sup>	- - - 4% (2-6) resistance to meticillin	0 <sup>§</sup> 8 (0-23) 0 <sup>§</sup> -	- 8 (0-23) 11 (0-31) -	- - - -
Gyawali et al. [12] 2009-2010	Nepal, urban	82 Enterobacteriaceae ? 21 <i>Pseudomonas</i> spp. <sup>  </sup> 30 <i>Acinetobacter</i> spp. <sup>  </sup>	94 (87-97) - -	70 (59-78) 37 (21-59) 56 (39-73)	83 (73-90), 79 (69-87), 87 (78-92) <sup>¶</sup> 47 (28-68), 71 (50-86), 67 (45-82) <sup>¶</sup> 53 (36-70), 65 (46-78), 73 (56-86) <sup>¶</sup>	- - -

**Table 3 Antibiotic resistance of bacteria isolated from invasive neonatal infections in developing countries (2000-May 2014) (Continued)**

Shrestha et al. [20]	Nepal, urban	8 <i>K. pneumoniae</i>	38 (14–69)	0 <sup>§</sup>	–	–
2011–2012						
Macharashvili et al. [14]	Georgia, urban	45 <i>Klebsiella</i> spp. <sup>†,‡,¶</sup>	98 (94–100)	11 (2–20)	16 (5–27), 18 (7–29) <sup>¶</sup>	–
2003–2004		11 <i>E. coli</i> <sup>†,‡</sup>	55 (26–84)	18 (0–41)	9 (0–26), 9 (0–26) <sup>¶</sup>	–
		15 <i>S. aureus</i>	40% (15–65) resistance to meticillin			

<sup>\*</sup>Extended-spectrum beta-lactamase.

<sup>†</sup>Results were presented for sensitivity, resistance calculated as 100 minus% sensitive.

<sup>‡</sup>Pericillin results based on amoxicillin.

<sup>§</sup>Calculation of a CI was impossible.

<sup>¶</sup>Pathogens marked spp. means no further characterization was presented.

<sup>\*\*</sup>Multiple 3GCs were tested.

that this pathogen may be the first cause of neonatal infection. Furthermore, only one of the six studies in our review describing MRSA infection was conducted in a community setting. Community-associated MRSA (CA-MRSA) has emerged in the developed world and represents a growing problem. Data on CA-MRSA are scarce in DCs, despite the existence of risk factors associated with drug resistance in the community, such as over-the-counter antibiotics use, overcrowding, and poor hygiene are highly prevalent [38].

Our review highlights the scarcity and heterogeneity of the available data on both the incidence of invasive bacterial infection and resistance patterns. While these findings may reflect true differences in the burden of neonatal infection and among resistance patterns, they may also be explained by major differences in data-collection methods. The currently available data are thus insufficient to draw a true picture of the burden of invasive bacterial infections and resistance. Furthermore, the reported infection rates are likely to underestimate the true incidence. Three-quarters of the studies reviewed took place in urban settings with recruitment at large or teaching hospitals. In DCs, the majority of families do not seek care in hospitals, particularly in rural areas, because of resource constraints, distances to their homes, or differences in health care seeking behaviours [39]. This is particularly true for early onset neonatal sepsis in the context of home deliveries. Along with underestimating the incidence, these factors undoubtedly play a role in the low detection rates of Group B *Streptococcus* in DCs as these infections generally occur in the few hours after delivery. These results are contrary to those from developed countries where Group B *Streptococcus* is the major cause of neonatal sepsis [40,41].

The observed heterogeneity among incidence rates may also be explained by the difficulty of estimating these rates. Such estimates require population surveillance systems, which are expensive and time-consuming and are often lacking in DCs. Indeed, less than one-fifth of the studies reviewed were based on active surveillance. An additional factor is the difficulty to confirm diagnosis with blood culture. A positive blood culture requires adequate blood volume drawn in strict aseptic conditions by skilled staff at the right moment along with access to appropriate laboratory equipment and techniques accessible almost exclusively in large or teaching hospitals in DCs [42,43]. Furthermore, only two studies performed two blood cultures despite an increased chance of pathogen isolation. The proportion of antibiotic usage prior to blood culture performed at the hospital was also high among studies reporting. Thus, a single negative blood culture cannot completely rule out an infection and a substantial proportion of non-microbiologically confirmed sepsis cases potentially represents false-negatives [44].

Assessment of antibiotic resistance was often based on few isolates collected over several years, which is clearly insufficient to describe trends in bacterial resistance to antibiotics. Almost one-third of the studies reviewed did not refer to any guidelines for interpretation of antibiotic susceptibility, which may call into question the reliability of their results. Given the heterogeneity in antimicrobial susceptibility references, comparisons between studies are difficult. Of note, almost half of the studies reviewed were conducted in Africa. The observed lack of studies in Southeast Asia is alarming as the population in this area is greater than in Africa.

The relative paucity of reports on antibiotic resistance collected after 2008 is of particular concern in a context of rapidly evolving resistance profiles and emerging antibiotic resistance mechanisms. Real-time data are required to provide an accurate understanding of drug sensitivity and resistance patterns [5]. Although a potential explanation may be that recent data collected is less likely to be published, the period of time that has elapsed since 2007 is largely sufficient to reveal a decline in publications.

A recent study published following our last search date deserves to be mentioned. This study included 8889 infants under 2 months brought to health facilities for illness in 6 DCs. Blood culture was performed for more than 10% of these children and antibiotic susceptibility testing was conducted on isolated bacteria. Pathogen distributions and antibiotic sensitivity patterns were similar to our findings [45].

In its first report on global antimicrobial resistance, with data from 114 countries, the WHO found that resistance to seven common bacteria has reached alarming levels in all regions of the world [6]. It also highlights that many gaps exist in documentation of pathogens of major public health importance. Our analysis is in line with the WHO's conclusion on the need for methodological standards to investigate these issues. The WHO report also draws attention to the fact that resistance may be overestimated in the general population as most reported samples were collected in large hospitals, consistent with our observation that data from the community are lacking. Finally, the WHO calls for actions to strengthen and coordinate collaboration to address these knowledge gaps.

Effective surveillance systems or research programs devoted to anti-infective resistance in infectious diseases such as tuberculosis, malaria, or HIV have been implemented over the past few years with the active support of various stakeholders (donors agencies, governments, research institutes). These systems have been able to provide reliable data allowing for the promotion of global action. International alliances to contain antibiotic resistance in DCs exist and have called for several

actions including global research and surveillance, public health advocacy, and consumer and practitioner education. However, current research projects are often based in large or teaching hospitals, and drug resistance patterns and trends in antibiotic use are based on data from these hospitals. It is therefore imperative to accurately assess the burden of antibiotic-resistant infections in DCs, particularly among children as they bear the highest burden.

## Conclusion

Despite the recent global awareness of bacterial resistance issues and indications of the growing antibiotic resistance in DCs, epidemiological evidence remains limited and available data are not sufficient to draw a true, recent, and accurate picture of antibiotic resistance in DCs among neonates and particularly in the community.

Neonatal bacterial diseases are a major cause of death in these countries, and the risk of bacterial resistance emergence and dissemination is exacerbated by poor antibiotic control and precarious living conditions. Without data to evaluate the burden of antibiotic resistance in this population, the public health problem will undoubtedly remain underserved. Future research should be able to collect quality, standardized epidemiological data along with a reliable bacteriological diagnosis at the community level in order to allow for adapted public health measures necessary to combat antibiotic resistance.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

BTH, MP, and EDA designed the search strategy and participated in the data collection and data analysis. BTH and MP performed the literature search. BTH, MP, and EDA screened and selected articles. BTH, MP, BG, PH, EKD, LW, DG, and EDA participated in the writing and review of the article. DG had the original idea for the study. All authors approved the final manuscript.

## Acknowledgements

The authors would like to thank Professor Christian Brun-Buisson for his review of the final manuscript and Karen Berg Brigham for her proofreading help. This work was undertaken as part of the ChARLI project (<http://www.charlproject.org/>) which is supported by the funding of the Department of International Cooperation of the Principality of Monaco. This study has also received funding from the French Government's Investissement d'Avenir program, Laboratoire d'Excellence "Integrative Biology of Emerging Infectious Diseases" (grant n°ANR-10-LABX-62-IBEID).

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Received: 17 October 2014 Accepted: 19 February 2015

Published online: 15 March 2015

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## Review

# Measuring antibiotic consumption in low-income countries: a systematic review and integrative approach



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## ARTICLE INFO

## Article history:

Received 17 November 2015

Accepted 19 April 2016

## Keywords:

Antibiotic resistance  
Antibiotic consumption  
Low-income countries

## ABSTRACT

Antibiotic resistance is a global issue. Risk factors specific to low-income countries (LICs), including non-prescribed antibiotic use, place them at risk for the emergence of resistance and make them important targets for reducing the burden of resistance worldwide. Responding to this threat in LICs means first having access to appropriate antibiotic consumption data. A PubMed search was conducted for studies examining antibiotic consumption in the community in LICs. For the articles included in the analysis, the methodologies used, type of data gathered and methodological appropriateness in responding to specific LIC data needs were noted. Of the 487 articles identified by the search strategy, 27 were retained for final analysis. Four main investigative methods were identified, including pharmacy/hospital document reviews, the simulated client method, observed prescribing encounters/patient exit interviews and community surveys. Observed encounters and exit interviews are well adapted to answering a number of important questions surrounding antibiotic consumption but may include bias and miss some sources of non-prescribed antibiotics. Community surveys are the only approach able to fully account for non-prescribed antibiotics and should be used as the first step in an integrative approach towards antibiotic consumption measurement and monitoring in LICs. Antibiotic consumption data needed for programmes to control use must take into account the LIC context. An integrated and adaptive approach beginning with community surveys responds to the various data needs and difficulties of LIC contexts and may help facilitate the investigation and optimisation of antibiotic consumption in these settings.

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## 1. Introduction

Resistance to antibiotics is a global issue. High levels of resistance have been reported both in high-income countries and low-income countries (LICs), leading the World Health Organization (WHO) to call this issue a 'global health security threat' [1]. A number of specific risk factors exist for the development and spread of resistance in LICs, including substandard hygiene and living conditions, misuse of antibiotics, over-the-counter and parallel market access, and counterfeit or poor quality drugs [2,3]. The role of LICs in the emergence and rapid spread of resistance is highlighted by the worldwide spread of carbapenem-resistant New Delhi metallo- $\beta$ -lactamase 1 (NDM-1)-producing Enterobacteriaceae [4]. The adverse effects of antibiotic resistance are particularly worrisome in LICs where infectious disease rates are significantly higher than devel-

oped countries and where access to second- or third-line antibiotics is often limited [5]. Steps to control rising resistance are urgently needed, including programmes to monitor and control antibiotic consumption in LICs where consumption is growing rapidly [6,7].

The WHO has developed a global strategy to reduce antibiotic resistance and lower consumption and suggests a number of potential intervention targets, including the general population, antibiotic providers, hospitals and government policies [8]. Prioritising these interventions requires reliable data on issues such as frequency and amount of antibiotic use, patient and provider knowledge, drug source and quality, healthcare-seeking behaviour and reasons for antibiotic use. Reliable consumption information is also needed to monitor trends, to evaluate the impact of interventions, and importantly, to generate the political will to deal with this issue [9].

In LICs, these data can be unreliable or non-existent. Furthermore, gathering comprehensive data is complicated by the large number of non-prescribed and parallel market sources available in many of these countries [2,3].

Purchasing antibiotics without a prescription, including from non-medical sources, is common in many LICs and can account for as much as 100% of consumption among certain populations [3,10].

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<http://dx.doi.org/10.1016/j.ijantimicag.2016.04.024>

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Non-prescribed antibiotics are also a driving factor in increasing global antibiotic consumption [11]. Methods capable of accounting for non-prescribed antibiotic sources are thus important to accurately measure consumption in these contexts.

Current reports of consumption in LICs rely on diverse methodologies, making comparison difficult. The WHO has published guidelines on investigating medicine use by consumers and in health facilities. Numerous methodologies are detailed and analysed but no clear roadmap for investigation of community antibiotic consumption is presented [12,13].

Here we review currently used methodologies for antibiotic consumption measurement in LICs and propose an integrative and adaptive approach to respond to this issue.

## 2. Search methods

To investigate the methods used for measuring antibiotic consumption in LICs, a literature review was conducted by searching PubMed (last search 30 September 2015) using the search terms 'antibiotic', 'antibiotic consumption', 'developing country', 'low-income country', 'non-prescription antibiotic', 'community' and 'survey'. The search terms 'infection' and 'tuberculosis' were excluded and the search was limited to articles published since 1990. Reports on measuring antibiotic or drug use, including WHO reports, were also examined and references from these reports were screened for inclusion, as were selected articles from the author's library. LICs were defined as countries classified by the World Bank as 'Low-income economies' or 'Lower-middle-income economies' [14].

Inclusion criteria included measures of community and/or outpatient antibiotic consumption. Studies measuring only hospital inpatient use or limited to only one pathology were excluded. Identified articles were first screened by title and abstract, followed by full reading of the retained articles. For articles included in the analysis, the methodologies used, type of data gathered and methodological appropriateness for desired data as discussed were noted.

## 3. Results and methodology review

Of the 487 studies identified through the search strategy, 37 were selected for full reading. Of these, 27 were retained in the final analysis (Fig. 1). Four main investigative methods were identified from the literature search results, including pharmacy/hospital document reviews, the simulated client method, observed prescribing encounters/patient exit interviews, and community surveys. The articles including methods used and main measures can be seen in Supplementary Table S1.

One of the simplest ways to investigate antibiotic use in a community is to review pharmacy or hospital records or prescription documents [15–21].

In Vellore, India, Chandy et al collected antibiotic sales records from participating pharmacies and rural hospitals [19]. Data allowed for the calculation of defined daily doses (DDDs) dispensed per 100 patients along with the proportion of antibiotics dispensed by pharmacy type and location. DDDs are a standardised measure of drug quantity developed by the WHO to allow for easy comparison between drugs and across healthcare settings. Kotwani et al collected bulk purchase information from participating pharmacies in Delhi, India, and calculated consumption as DDDs purchased per 1000 population. The authors also identified antibiotic proportions and compared proportions between structure types [21].

Outpatient and prescription records were analysed for participating centres in South Africa (Brits and Durban) by Holloway et al [20]. The proportion of patients with a prescribed antibiotic and the proportion of prescriptions with an antibiotic were calculated along with DDDs per 100 patients attending the facility. Trends in antibiotics used by facility type were also analysed [20]. A recent review

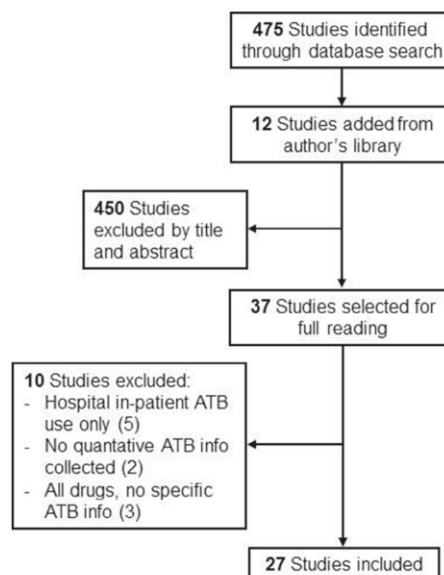


Fig. 1. Flowchart of literature search. ATB, antibiotic.

of global antibiotic use and trends also used pharmacy sales records to estimate country-level antibiotic consumption [7].

The major strength of these methods is that these types of data take relatively little time to gather, making them a potential candidate for surveillance. Antibiotic type, proportion and DDDs can be easily calculated. A number of weaknesses also exist with these methods. First, the choice of pharmacies or health centres is not random. Only those facilities with appropriate data willing to participate can be included, which may bias results [20]. In the case of bulk purchase studies, these data may not correspond directly with purchased or consumed antibiotics. This method also makes it difficult to determine community-level consumption, as relating participating pharmacies to a well-defined population is difficult.

Importantly, potential sources of non-prescribed antibiotics outside pharmacies are not measured and no information is available on the proportion of antibiotics sold in the pharmacy without a prescription. The limited information gathered on important aspects such as symptoms or patient knowledge, attitudes and beliefs along with potential biases related to this approach must be taken into account when using this method.

The simulated client method involves trained field workers posing as clients of pharmacies or health centres. The field worker will present symptoms (either their own or those of another person), ask for medication and measure the reaction of the medication provider [18,22–24]. Measures can include medication delivered, recommendations or information given [13].

In Bolivia, Bartoloni et al trained six 'actors' to describe various episodes and patient profiles to all pharmacies in a rural town [18]. Actors asked for medication without a prescription and the main outcomes included the proportion of visits resulting in the purchase of an antibiotic without a prescription. A similar study in Vietnam trained field workers to pose as the mother of a child suffering from either respiratory symptoms or diarrhoea and to ask for medication without a prescription [23]. This technique has also been used in developed countries. In Spain, Llor and Cots used this technique both to estimate the proportion of pharmacies providing antibiotics without a prescription and to gather information about dispenser attitudes and beliefs about non-prescribed antibiotics [25].



The study was thus able to assess both distribution patterns of non-prescribed antibiotics as well as the views of the pharmacist without encountering an observation bias [26].

The simulated client method is one method focused on the medication provider rather than the patient. It is particularly well adapted to non-prescribed antibiotic studies and allows an unbiased collection of information, including provider knowledge, attitudes and beliefs. The unlimited number of possible scenarios (age, symptoms, etc.) gives this method flexibility and it is relatively quick and cheap to conduct. Interestingly, no evidence was found of this technique being used to investigate non-prescribed antibiotic distribution sources such as markets or other informal providers. Weaknesses of this approach are related to understanding population-level antibiotic use. The data provided do not allow for determination of average antibiotic consumption or even non-prescribed antibiotic consumption either for a given population or for pharmacy patients. The information gathered responds only to distribution practices related to the scenario or scenarios presented. Like document reviews, not all sources of non-prescribed antibiotics are taken into account. Lastly, we have no information on real client behaviour, which may differ from that of the actors, and this method is not well adapted to surveillance. This approach is an important one in understanding non-prescribed sales in pharmacies and may be well suited to developing interventions targeting pharmacists but it must be accompanied by other methods in order to determine population-level antibiotic consumption patterns.

Observed prescribing encounters involve trained field workers or pharmacists recording information about pharmacy transactions in real time. Patient exit interviews consist of interviewing patients exiting a pharmacy or health facility about their purchases [16,19–21,27–32].

Chandy et al used the observed encounters method each month for 2 years in participating pharmacies to investigate antibiotic distribution in Vellore, India [19]. Data allowed for calculation of the proportion of pharmacy visits resulting in antibiotic purchase, the types and proportions of antibiotics distributed, the reasons for antibiotic purchase, and DDDs per 100 pharmacy patients. The repeated measures also allowed for visits to serve as a method to monitor the evolution of antibiotic distribution. In Nigeria, Esimone et al collected data using patient exit interviews on a daily basis for a period of 90 days [27]. The results included the percentage of antibiotics sold without a prescription and the percentage of antibiotic DDDs dispensed without a prescription. The exit interview method has also been used in other settings to investigate doctor prescription patterns or to evaluate interventions [32,33].

This approach has a number of advantages. First, a large number of variables can be gathered. The type and proportion of antibiotics used are easily calculated as DDDs per patient and the proportion of antibiotics purchased without a prescription. The access to patients in exit interview allows for data on why the antibiotic was purchased, sociodemographic factors associated with antibiotic use along with patient knowledge, beliefs and attitudes. However, as with document review studies, pharmacy selection is not random and may be biased. Indeed, a number of studies had difficulties obtaining consent from pharmacies, and the interview schedule for those who did agree was often cumbersome, which reduced willingness to participate [19,20]. Like document reviews, this method makes it difficult to determine the total consumption of the local population, and potential sources of non-prescribed antibiotics are unmeasured. The presence of researchers may also influence provider behaviour specifically in the context of non-prescribed antibiotic distribution, resulting in biased results for this variable [20]. Whilst this technique has been tested as a surveillance technique, several studies reported participation fatigue [20].

Because of the range of data that can be gathered using these techniques, observed encounters and patient exit interviews are flex-

ible and well adapted to the study of antibiotic use in developing countries. However, targeting only pharmacies may bias global estimates.

Unlike strategies focused on drug dispensers and recruiting patients who access health facilities or pharmacies, community surveys use residents in selected geographic areas as the study population. A number of houses are selected randomly using a survey plan and houses are visited by field workers who ask residents about their antibiotic use [18,23,31,34–44].

Awad et al conducted a multistage cluster survey of 600 households in Sudan. Proportions of the study population consuming antibiotics, antimalarials or both were calculated and socioeconomic variables associated with high self-prescribing behaviour were identified [35]. In India, Saradamma et al conducted a survey of 400 households also using a cluster design. Proportions of household members that had used antibiotics in the previous 14 days were calculated along with the proportion of antibiotics purchased without a prescription [31]. The two-stage cluster design used in both of these studies is common among surveys in developing countries. These designs allow for calculation of unbiased population estimates and reduced logistic costs in situations where population lists are not easily obtained.

A number of advantages exist when using community surveys in the investigation of antibiotic consumption. By taking measures on the population level, it is possible to avoid the potential selection bias found in pharmacy exit interviews or pharmacy document reviews. It is also possible to account for all antibiotic sources including non-prescribed sources. With access to patients, this technique is useful for gathering variables on place of purchase, completion of antibiotic courses and reasons for purchase as well as population characteristics and patient knowledge, attitudes and beliefs. The type and proportion of specific antibiotics can also be estimated although with less precision than pharmacy-based methods [31]. Some problems also exist with community surveys. Importantly, they can be time consuming and expensive to organise. This is especially true if large samples are needed because the event is rare. This could be the case in studies of non-prescribed antibiotic consumption in some populations [31]. Participation and recall bias may also be issues with this type of investigation. Finally, calculation of DDDs is difficult using this method, and the resources needed make this approach a poor surveillance method.

Whilst community surveys are generally more costly and/or labour intensive than other methods of data collection, they are the best way to capture all sources of antibiotics in LICs and can produce the richest results. The ability to gather peripheral information or risk factors for antibiotic consumption or non-prescribed antibiotic consumption is also important for designing interventions or planning further studies.

#### 4. Discussion and integrating study techniques

Each of the four methods discussed has specific strengths and weaknesses when responding to the various questions related to antibiotic consumption (Table 1). The time gains from document reviews are counterbalanced by the relatively limited data gathered, whilst the time and resource investment of community surveys can provide a great deal of valuable information on consumption and related variables. Ideally, these studies should be used in concert in order to cover the wide range of data necessary to describe and track antibiotic consumption in LICs and to identify areas for intervention. The WHO calls the use of multiple strategies 'triangulation' and recommends this strategy when investigating medicine use to cross-check results from each study type [13]. Because the most appropriate study technique may vary depending on the results of other studies, investigations must be adaptive and capable of reacting to new information by changing or modifying study

**Table 1**  
Ability of four study types in responding to antibiotic (ATB) consumption investigation needs in low-income countries (LICs).<sup>a</sup>

	Pharmacy/Hospital document review <sup>b</sup>	Simulated client method	Observed prescribing encounters/Patient exit interview <sup>b</sup>	Community survey
<b>Antibiotic investigation data</b>				
Type and proportion of ATB use	+++	-	+++	++
DDDs per patient	+++	+	+++	+
ATB consumption for defined population and time period	+	+	+	+++
ATB source including all non-prescription sources	-	-	-	+++
Why ATB given	+++ <sup>c</sup>	++	+++	++
Factors associated with ATB use	-	+	++	+++
Non-prescription proportion	-	-	++	+++
Provider knowledge, attitudes and beliefs	-	+++	-	-
Patient knowledge, attitudes and beliefs	-	-	++	+++
<b>Study characteristics</b>				
Adapted to monitoring time trends	+++	+	++	+

DDD, defined daily dose.

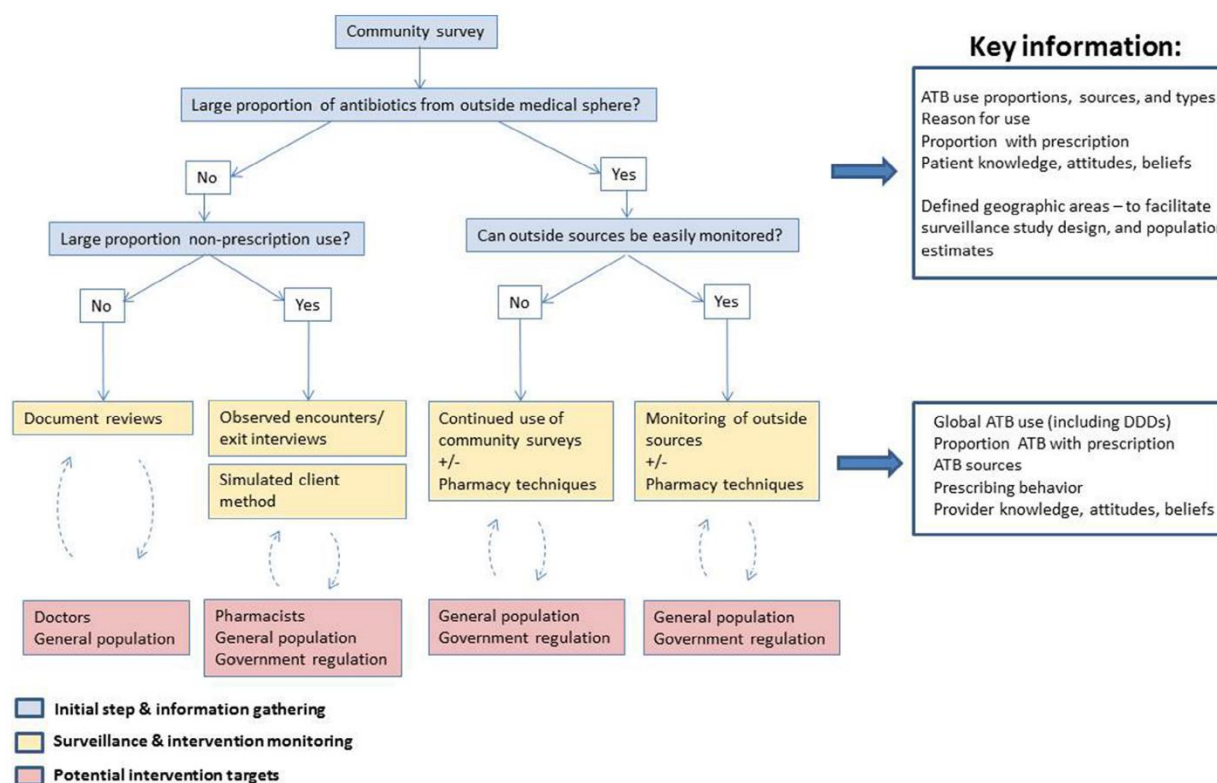
<sup>a</sup> +, poor; ++, moderate; +++, good; -, not applicable.

<sup>b</sup> Using non-exhaustive sample of centres/pharmacies.

<sup>c</sup> If including patient records.

methods. In a situation where little to no information exists, it is important to start by gathering as much information as possible as this serves both as a starting point for the development of interventions and the determinant of appropriate follow-up studies or monitoring and surveillance methods [45]. In LICs, community surveys are the only method capable of accounting for all non-prescribed antibiotics and their capacity to gather large amounts of auxiliary data whilst avoiding selection bias makes it an ideal starting point for an integrative and adaptive method. Using this approach, community surveys can be used to answer questions about the sources and proportion of non-prescribed antibiotics and provide the founda-

tion for additional study and intervention choices [13]. In the absence of non-prescribed antibiotics for example, pharmacy document reviews could be a good option for monitoring antibiotic use, and interventions focused on doctors may be most effective in lowering or improving antibiotic usage [46]. In the case of a high proportion of antibiotics from pharmacies along with pharmacy distribution of antibiotics without a prescription, observed encounters/patient exit interviews may be a suitable choice for monitoring and interventions may be best focused on pharmacists (Fig. 2). During the investigation, qualitative methods may also be added as necessary in order to explore specific topics.



**Fig. 2.** Flowchart for integration of study types for antibiotic (ATB) measurement and surveillance in low-income countries (LICs). DDD, defined daily doses.

The geographic area of a community survey is also an important aspect of this approach and an additional benefit of starting investigations with this method. A pre-defined geographic region may benefit subsequent studies by facilitating pharmacy selection, population size calculations or intervention targets. Community studies are easily adapted both to urban and rural environments, which is important as factors related to consumption may vary significantly with population size and density, and multiple study sites may be necessary to account for this dynamic [47].

One survey method particularly well adapted to this integrated approach is compact segment sampling (CSS) method [48]. This two-stage cluster survey technique was developed for use in LICs and responds to some of the methodological and statistical weakness of other widely used survey techniques such as the WHO Expanded Programme on Immunization (EPI) method. In a first stage of selection, CSS randomly selects larger geographic areas or clusters using probability proportional to size sampling. Each selected cluster is then divided into small geographic regions or 'segments', each of which is equal to the desired measure of size. In a second stage, one segment per cluster is selected using simple random sampling and all of the houses in the segments are solicited to participate. The CSS technique can be adapted to any number of research questions and has been used by UNICEF's Multiple Indicator Cluster Surveys, the World Bank as part of their Microenterprise Surveys [49], and a modified version has been included in methodology of Rapid Assessment of Avoidable Blindness (RAAB) surveys created by the London School of Tropical Medicine and Hygiene (London, UK). This technique provides a number of powerful methodological advantages useful in the investigation of antibiotic consumption. Including all houses in the segment helps facilitate variance estimates and eliminate potential selection biases [48,50]. Importantly, this technique also allows for revising non-response households, thus lowering 'at-home' bias, which was found to be an important factor in a recent analysis of survey techniques [51]. The defined geographic segments can be easily revisited if necessary or to monitor changes.

## 5. Conclusion

Antibiotic resistance is growing in LICs and threatens to greatly increase morbidity and mortality among already vulnerable populations. Programmes to control antibiotic use are needed to combat the development of resistance particularly in LICs where few controls exist. In order to be effective, these programmes need quality data on antibiotic consumption, which is made difficult due to the use of antibiotics from non-prescribed sources in some countries. Special techniques are needed to account for these special circumstances and to gather the data necessary to control antibiotic use and combat resistance. An integrated and adaptive approach beginning with community surveys responds to the various data needs and difficulties of LIC contexts and may help facilitate the investigation and control of antibiotic consumption in LICs.

**Funding:** This work was undertaken as part of the BIRDY project (<http://www.birdyprogram.org/>), which is supported by funding from the Department of International Cooperation of the Principality of Monaco.

**Competing interests:** None declared.

**Ethical approval:** Not required.

## Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.ijantimicag.2016.04.024](https://doi.org/10.1016/j.ijantimicag.2016.04.024).

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## A community survey of antibiotic consumption among children in Madagascar and Senegal: the importance of healthcare access and care quality

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Received 27 April 2016; returned 6 June 2016; revised 21 September 2016; accepted 22 September 2016

**Background:** Antibiotic resistance is growing in low-income countries (LICs). Children in LICs are particularly at risk. Information on antibiotic consumption is needed to control the development and spread of resistant bacteria.

**Methods:** To measure antibiotic consumption and related factors, a community survey was undertaken in two sites in Madagascar (Antananarivo and Moramanga) and in Senegal (Guediawaye) among children under 2. Face-to-face interviews were conducted with parents or caregivers of eligible children. Regression analysis was used to determine variables associated with reported antibiotic consumption. Availability of health structures and health policies were also investigated.

**Results:** Population estimates for antibiotic consumption in the last 3 months were 37.2% (95% CI 33.4%–41.2%) in Guediawaye, 29.3% (95% CI 25.0%–34.1%) in Antananarivo and 24.6% (95% CI 20.6%–29.1%) in Moramanga. In all sites, the large majority of antibiotics were taken with a prescription (92.2%, 87.0% and 92.0% for Antananarivo, Moramanga and Guediawaye, respectively) and purchased in pharmacies (89.4%, 73.5% and 78.5%, respectively). Living in houses without flushing toilets and baby age were significantly associated with any antibiotic consumption after adjusting for site. A higher density of public health structures was associated with lower antibiotic consumption levels, while a higher density of private pharmacies was associated with higher levels across sites.

**Conclusions:** These data are crucial for the implementation of local programmes aimed at optimizing antibiotic consumption. Factors such as density of healthcare facilities, prescriber training and national policy must be taken into account when developing strategies to optimize antibiotic consumption in LICs.

### Introduction

Antibiotic resistance is growing rapidly in both high- and low-income countries (LICs).<sup>1</sup> The WHO has deemed this issue a 'global health security threat' and recently created a global action plan to tackle the problem.<sup>1,2</sup>

LICs are particularly important targets in this global fight as they are home to a number of risk factors for the development and spread of resistance including: substandard hygiene and overcrowding, misuse of antibiotics, over-the-counter and parallel market access, and counterfeit or poor-quality drugs.<sup>3,4</sup> Increasing antibiotic consumption in LICs amplifies these risk factors<sup>5</sup> and the recent worldwide spread of carbapenem resistance NDM-1-producing Enterobacteriaceae highlights the potential for resistance development and spread in LICs.<sup>6</sup>

LICs are also home to a high burden of infectious and bacterial disease particularly among children.<sup>7,8</sup> Bacterial infections, including sepsis, pneumonia, tetanus, meningitis and diarrhoea, are the leading cause of these severe infections.<sup>9,10</sup> Increased childhood morbidity and mortality due to resistance threatens to reverse the gains made in these areas in recent years and jeopardizes the objectives for childhood mortality established by the Sustainable Development Goals.<sup>11</sup> The increased economic burden of resistance also poses a threat to the budgets of overburdened healthcare systems.<sup>12,13</sup>

Misuse and overuse of antibiotics is a major contributor to antibiotic resistance. Several targets exist to reduce inappropriate consumption including: the general population, antibiotic providers, hospitals and governmental policies.<sup>14</sup> Prioritizing these targets requires reliable data on frequency and amount of antibiotic

use, patient and provider knowledge, drug source and quality, healthcare-seeking behaviour, and reasons for antibiotic use. This information is also important for implementation of a broader strategy to maximize the benefits of antibiotics by reducing resistance, while increasing access in LICs.<sup>15,16</sup>

In LICs, these data can be unreliable or non-existent. Furthermore, gathering comprehensive information is complicated by possible non-prescribed and parallel market sources of antibiotics available in many LICs, which can represent up to 100% of consumption among certain populations.<sup>3,4</sup> These data are particularly sparse in countries from sub-Saharan Africa, which is home to 26 of the World Bank's 31 LICs.<sup>17</sup> Methods adapted to these contexts and capable of accounting for all types of non-prescribed consumption must therefore be used in order to explore this issue in LICs.<sup>18</sup>

To measure antibiotic consumption and related factors in LICs, we undertook community surveys among children in both Madagascar, an LIC, and Senegal, a middle–low income country.<sup>17</sup> In 2010, under-5 mortality rates were estimated to be 67 per 1000 live births in Senegal and 63 per 1000 live births in Madagascar. Of these deaths, 15.9% and 18.3% were due to pneumonia and 8.6% and 10.4% to diarrhoea in each country, respectively.<sup>7</sup> While reliable data on the burden of resistance are rare, high rates of bloodstream infections due to ESBL-producing Enterobacteriaceae have been reported in Senegal among children admitted to a paediatric hospital.<sup>19</sup> In Madagascar, high rates of colonization with ESBL-producing bacteria have been found both among children admitted to a paediatric hospital and pregnant women.<sup>20,21</sup>

The objectives of the survey included: estimating the proportion of children under 2 in the study population with at least one episode of consumption in the last 3 months, determining factors associated with antibiotic consumption, and comparing consumption patterns across countries. To our knowledge, no studies have been published on antibiotic consumption among children in these countries. The age range and study sites were selected in an effort to harmonize results with the BIRDY programme, which studies antibiotic resistance among children under 2 in LICs including Madagascar and Senegal.

## Methods

### Ethics

The study was approved by the Senegalese National Ethics Committee for Health Research (scientific and ethics approval no. 55/MSAS/DPRS/CNERS 31 March 2015) and by the Ethics Committee of the Malgasy Public Health Ministry (no. 114/MSANP/CE 3 November 2014).

### Survey population

A cross-sectional population-based survey was carried out between November 2014 and February 2015 in Madagascar and from April to July 2015 in Senegal. The study population in Madagascar included children under 2 living in the 2nd, 3rd and 5th districts of the urban capital city Antananarivo (total population: 1168 898) and those living in the semi-rural city of Moramanga (total population: 46393). In Senegal the study population included children under 2 living in Guediawaye (total population: 329659), an urban suburb of Dakar. To be included in the study, the household contacted should have been considered the primary residence for the child and consent was required from an adult family member or caregiver who had knowledge of the child's medical history.

The study population of children under 2 in each site was estimated at 23433, 1523 and 15750 for Antananarivo, Moramanga and Guediawaye, respectively.

### Household selection

A two-stage cluster survey was undertaken using compact segment sampling.<sup>22</sup> First, 30 clusters in each study site were selected from the study zones with probability proportional to size (PPS) methods using national census or demographic survey data. The use of 30 clusters was considered sufficient to control for anticipated between-cluster variability.<sup>23</sup> A cluster was defined as the smallest administrative district in both Madagascar and Senegal. The average total populations of the clusters were 7162, 3569 and 4411 for Antananarivo, Moramanga and Guediawaye, respectively. Clusters were divided into smaller equal-sized geographic units (segments), each of which contained ~14 children. These segments were enumerated and one segment per cluster was selected at random using a random number table. Once a segment was selected, all houses/children in the segment were solicited to participate (see Figure 1). In the case of non-respondent households, one revisit was scheduled during the week and a second revisit during the weekend if necessary before considering the house unreachable. No attempt was made to replace non-respondent households.

### Study size

A sample size of 400 children in each site was calculated based on an estimated 40% antibiotic use in the previous 3 months, a desired precision of 10% and a design effect of 4. The design effect is a measure of the additional variability resulting from cluster sampling techniques.

### Data gathering

Data were gathered from the child's parent or other caregiver via face-to-face interviews by trained field workers. Field workers used questionnaires and gathered data including sociodemographic variables, the health history of the child and the child's antibiotic consumption in the previous 3 months. In Madagascar the questionnaire was translated into Malgash by translation experts from the Institut Pasteur, Antananarivo and field tested prior to use (see the Supplementary data available at *JAC* Online). In Senegal the original French version was used with oral translations into Wolof agreed upon between study field workers and supervisors, and field tested prior to use. To reduce memory bias, visual aids of commonly used paediatric antibiotics as well as a locally adapted calendar were presented. Respondents were also asked to show field workers any available prescriptions, antibiotics or antibiotic packaging remaining from consumption episodes. Adult respondents in Senegal were asked additional questions regarding their own antibiotic use in the previous year and healthcare-seeking behaviour for themselves and the child.

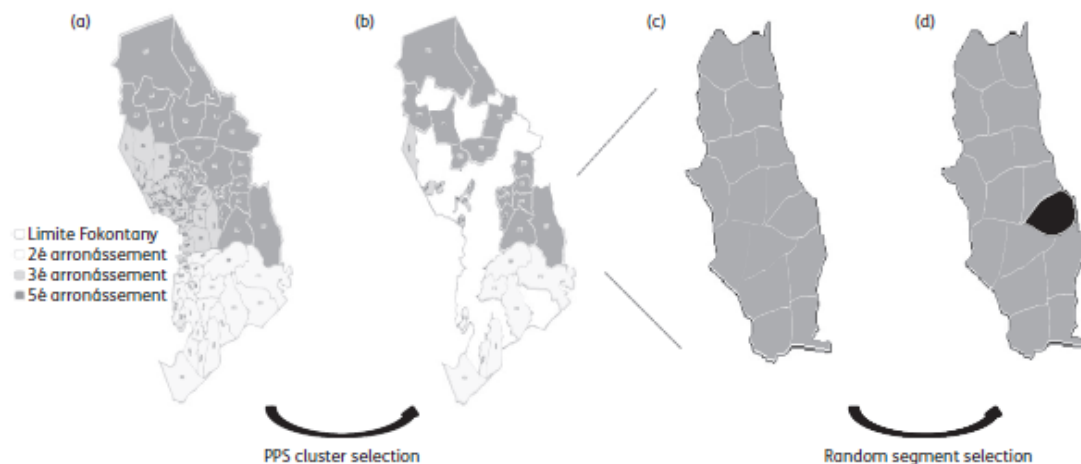
Up-to-date vaccination was defined based on local schedules, and newborns under 2.2 kg were considered underweight.

### Healthcare structures and pharmacies

A mapping of healthcare structures and pharmacies located in the study areas was performed for Moramanga and Guediawaye. For Antananarivo, these data were based on pharmacy lists from the Agence du Médicament de Madagascar and data from city records.

### Statistical analysis

Statistical analyses were undertaken with Stata 11.0 (StataCorp, College Station, TX, USA). Population estimates including CIs were calculated for the proportion of children with any medication use, any antibiotic use or any antibiotic use without a prescription in the last 3 months.



**Figure 1.** Segment selection steps in Antananarivo using the compact segment sampling method. (a) Three study districts in Antananarivo. (b) Thirty selected clusters/administrative districts using PPS sampling. (c) Example of one selected cluster divided into segments. (d) Random selection used to select study segment.

Pearson's  $\chi^2$  test and Wald's test were used to compare categorical and continuous variables, respectively. An exploratory logistic regression was used to determine variables associated with any consumption of antibiotics in the last 3 months (consumption in last 3 months versus none). For multivariate analysis, variables associated with the outcome of interest in the univariate analysis (at the  $P < 0.25$  level) were included and a stepwise descending procedure was used to obtain a final logistic regression model. Pooled multivariate analyses were adjusted for study site. Significance for multivariate analysis was set at  $P = 0.05$ .

To take into account within-household correlation among households with multiple children, a multi-level logistic analysis was also performed. The svy command was used where appropriate to take into account the survey design.

## Results

### Sociodemographic characteristics by site

In total, 394 children were recruited in Antananarivo, 502 in Moramanga and 505 in Guediawaye. Refusals to participate were rare across sites with 23 households (1%) refusing to participate in Moramanga and 17 (<1%) and 6 (<1%) households refusing in Antananarivo and Guediawaye, respectively. No information on the presence of children under 2 in these houses or the reasons for non-participation was available. Sociodemographic characteristics for the sample populations can be seen in Table 1. Mothers' education differed, with lower levels of education in Guediawaye. Unemployment among mothers was also different, with 52.9%, 64.6% and 76.9% unemployed at visit in Antananarivo, Moramanga and Guediawaye, respectively. Access to electricity was higher in Guediawaye (98.8%), as compared with Antananarivo (84.7%) and Moramanga (80.2%). Access to flushing toilets also differed between sites, ranging from 4.2% in Moramanga, to 6.9% in Antananarivo and 19.6% in Guediawaye. Overall, households in Senegal included more

people than in Madagascar, but density per room was greater in Antananarivo (2.9 persons per room) than in Moramanga (2.6) and Guediawaye (2.5).

Children's characteristics did not show significant overall differences between sites for baby age, sex, malnutrition, premature birth or underweight births (Table 2). Significant overall differences were found for up-to-date vaccination at 90.5%, 71.6% and 67.6% in Guediawaye, Moramanga and Antananarivo, respectively.

### Antibiotic consumption

Levels of antibiotic consumption in the last 3 months were 37.2% (95% CI 33.4%–41.2%) in Guediawaye, 29.3% (95% CI 25.0%–34.1%) in Antananarivo and 24.6% (95% CI 20.6%–29.1%) in Moramanga (Table 3). These differences were statistically significant overall ( $P < 0.01$ ).

Non-prescription use of antibiotic was not significantly different among the three study sites at 7.8% (95% CI 4.2%–14.3%) in Antananarivo, 13.0% (95% CI 10.3%–16.3%) in Moramanga and 8.0% (95% CI 4.2%–14.7%) in Guediawaye ( $P = 0.66$ ).

While most antibiotics were taken for the full length of the treatment in Moramanga (75.2%) and in Antananarivo (83.7%), only 52.3% of antibiotics were correctly taken in Guediawaye.

In our sample only 6%, 5% and 2% of the sample had multiple episodes of antibiotic consumption in the previous 3 months in Antananarivo, Guediawaye and Moramanga, respectively.

The majority of antibiotics were recommended by a doctor or a nurse (regardless of the presence of a prescription) in Antananarivo (95.7%) and Guediawaye (94.4%) (Table 4). In Guediawaye, a few antibiotics were recommended by the pharmacist directly (5.1%), sometimes followed by purchase without prescription. The person recommending antibiotic use was heterogeneous in Moramanga, and included 11% of antibiotics advised by a traditional healer and 2.9% by a midwife. Absence of advisor or self-advising was

**Table 1.** Sociodemographic sample characteristics of children under 2 participating in a community survey in Madagascar and Senegal

	Antananarivo (N=392)	Moramanga (N=500)	Guediawaye (N=505)
Child order (among children under 2 in household), n (%)			
1	375 (95.7)	496 (99.2)	418 (82.8)
2	14 (3.6)	4 (0.8)	66 (13.1)
3	3 (0.8)	0 (0)	17 (3.4)
4	0 (0)	0 (0)	4 (0.8)
Mother's age (years), mean (SD)	27.1 (5.7)	25.0 (4.7)	27.9 (5.8)
Respondent, n (%)			
mother	335 (85.5)	449 (89.8)	474 (93.9)
father	23 (5.9)	35 (7.0)	9 (1.8)
other family member	33 (8.4)	16 (3.2)	22 (4.4)
other	1 (0.3)	0 (0)	0 (0)
Mother's occupation, n (%)	n=391	n=479	n=502
unemployed	207 (52.9)	323 (64.6)	386 (76.9)
unskilled labour	118 (30.2)	127 (25.4)	84 (16.7)
skilled labour	66 (16.9)	29 (5.8)	32 (6.4)
other	1 (0.3)	21 (4.2)	3 (0.6)
Mother's education, n (%)			
none	4 (1.0)	16 (3.0)	239 (47.3)
primary	65 (16.6)	91 (18.2)	151 (29.9)
some high school	158 (40.3)	248 (49.6)	81 (16.0)
high school	119 (30.4)	115 (23.0)	27 (5.4)
university	46 (11.7)	30 (6.0)	7 (1.4)
Housing type, n (%)			
individual house	128 (32.7)	255 (51.0)	125 (24.8)
house in compound (lot)	6 (1.5)	214 (42.8)	324 (64.2)
room in a house	258 (65.8)	31 (6.2)	56 (11.1)
Roof type <sup>a</sup> , n (%)			
low quality	1 (0.3)	4 (0.8)	190 (37.6)
standard quality	385 (98.2)	477 (95.4)	0 (0)
high quality	6 (1.5)	19 (3.8)	315 (62.4)
Wall type, n (%)			
mud/wood/canvas	35 (8.9)	143 (28.6)	2 (0.4)
brick/cement/stone	357 (91.1)	357 (71.4)	503 (99.6)
Floor type, n (%)			
mat/boards/dirt/sand	24 (6.1)	42 (8.4)	31 (6.1)
cement	364 (92.9)	457 (91.4)	179 (35.5)
tiles/wood floor	4 (1.0)	1 (0.2)	295 (58.4)
Access to electricity—yes, n (%)	332 (84.7)	401 (80.2)	499 (98.8)
Toilet type, n (%)			
with flush	27 (6.9)	21 (4.2)	99 (19.6)
without flush	365 (93.1)	478 (95.6)	406 (80.4)
no toilet	0 (0)	1 (0.2)	0 (0)
			n=504
Number of people in home, mean (SD)	4.8 (1.8)	4.4 (1.5)	10.5 (5.2)
People per room, mean (SD)	2.9 (0.5–13)	2.6 (1.3)	2.5 (1.1)

SD, standard deviation of sample distribution, without taking into account added variability from survey methodology.

Missing data was due to a small number of unreadable questionnaire forms.

<sup>a</sup>Low quality: Madagascar—canvas, cardboard; Senegal—sheet metal. Standard quality: Madagascar—sheet metal. High quality: Madagascar—tiles; Senegal—cement.



**Table 2.** Demographic and health history information sample characteristics of children under 2 participating in a community survey in Madagascar and Senegal

	Antananarivo (N=392)	Moramanga (N=500)	Guediawaye (N=505)	Statistical comparisons, P value <sup>a</sup>		
				Antananarivo versus Guediawaye	Antananarivo versus Moramanga	global
Baby age (months), mean (SD)	11.7 (6.5)	9.5 (7.2)	11.5 (6.4)	0.71 <sup>b</sup>	<0.01 <sup>b</sup>	0.66
Baby sex female, n (%)	192 (49.0)	266 (53.2)	267 (52.9)	0.31	0.15	0.31
Underweight <sup>c</sup> , n (%)	56 (14.3)	57 (11.4)	69 (13.7)	0.83	0.46	0.78
Premature birth <sup>d</sup> , n (%)	N=392 7 (1.8)	N=499 7 (1.4)	N=497 14 (2.8)	0.44	0.69	0.45
Underweight birth <sup>e</sup> , n (%)	N=387 14 (3.6)	N=494 10 (2.0)	N=503 32 (6.4)	0.08	0.21	0.06
Up-to-date vaccination <sup>f</sup> , n (%)	265 (67.6)	358 (71.6)	457 (90.5)	<0.01	0.69	<0.01

SD, standard deviation of sample distribution, without taking into account added variability from survey methodology.

<sup>a</sup>Comparisons take into account added variability from survey methodology.

<sup>b</sup>Wald test.

<sup>c</sup>Based on WHO weight-for-age definitions.

<sup>d</sup>Prematurity was defined as <37 weeks.

<sup>e</sup>Underweight birth was defined as <2200 g.

<sup>f</sup>Based on local vaccine schedule.

**Table 3.** Population estimates of antibiotic consumption based on sample of children under 2 participating in a community survey in Madagascar and Senegal

	Antananarivo (N=392), % (95% CI)	Moramanga (N=500), % (95% CI)	Guediawaye (N=505), % (95% CI)	Statistical comparisons, P value <sup>a</sup>		
				Antananarivo versus Guediawaye	Antananarivo versus Moramanga	global
Any medication 3 months	61.5 (55.8–66.9)	48.7 (43.7–53.7)	87.5 (82.4–91.3)	<0.01	<0.01	<0.01
Any antibiotic 3 months	29.3 (25.0–34.1)	24.6 (20.6–29.1)	37.2 (33.4–41.2)	0.01	0.14	<0.01
Non-prescription use <sup>b</sup>	7.8 (4.2–14.3)	13.0 (10.3–16.3)	8.0 (4.2–14.7)	0.97	0.12	0.66
All doses prescribed/bought taken <sup>c</sup>	83.7 (76.0–89.3)	75.2 (66.1–82.5)	52.3 (44.8–59.8)	<0.01	<0.01	<0.01

<sup>a</sup>Comparisons take into account added variability from survey methodology.

<sup>b</sup>Among children with at least one antibiotic.

<sup>c</sup>Antibiotic consumption episodes used at the denominator for this variable rather than the survey population (Antananarivo=142, Moramanga=134 and Guediawaye=214).

reported in Moramanga (6.6%) and Antananarivo (2.0%), but not Guediawaye.

For all sites, the main symptom group leading to antibiotic consumption was respiratory–ear/nose/throat symptoms, representing 60.7% of consumption episodes in Antananarivo, 68.4% in Moramanga and 38.3% in Guediawaye. The second most frequent group of symptoms reported in Antananarivo and Moramanga were digestive (25.2% and 14.3%, respectively). These symptoms accounted for 10.7% of antibiotics in Guediawaye. Cutaneous symptoms and ‘other’ symptoms, not including respiratory, cutaneous, digestive or ear/nose/throat symptoms, represented 12.6% and 17.8% of episodes in Senegal, respectively.

The most commonly used antibiotics were penicillins (53.5%, 66.7% and 52.8% for Antananarivo, Moramanga and Guediawaye,

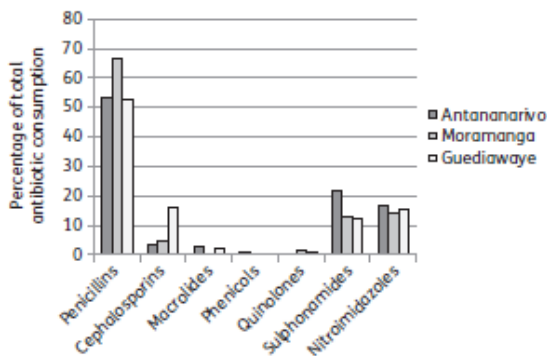
respectively), including mainly amoxicillin (Figure 2). Other antibiotics commonly used in the three study sites were metronidazole and co-trimoxazole. Cephalosporins represented 15.9% of antibiotics consumed in Guediawaye 3.5% in Antananarivo and 4.5% in Moramanga. A small proportion of quinolones was found in Moramanga (1.5%) and in Guediawaye (0.9%).

Most antibiotics were bought from private pharmacies (89.4%, 73.5% and 78.5% in Antananarivo, Moramanga and Guediawaye, respectively). In Senegal the remaining antibiotics were obtained from hospitals and public health facilities. In Madagascar, purchase from the doctor directly accounted for 7.0% and 7.4% of antibiotics in Antananarivo and Moramanga, respectively. Other sources identified in Moramanga included depots (0.7%), general stores (4.4%) and traditional healers (1.5%).

**Table 4.** Characteristics of antibiotic consumption episodes in the sample of children under 2 participating in a community survey in Madagascar and Senegal

	Antananarivo (N=142)	Moramanga (N=136)	Guediawaye (N=214)
Length of antibiotic (days), mean (SD)	4.1 (2.0)	4.4 (2.0)	5.7 (2.5)
Advisor per episode, n (%)			
doctor/nurse	135 (95.7)	100 (73.5)	202 (94.4)
matron	0 (0)	1 (0.7)	0 (0)
healer	0 (0)	15 (11.0)	0 (0)
shopkeeper	3 (2)	1 (0.7)	0 (0)
midwife	0 (0)	4 (2.9)	0 (0)
pharmacist	0 (0)	1 (0.7)	11 (5.1)
no one	3 (2)	9 (6.6)	0 (0)
no response	1 (0.7)	5 (3.7)	1 (0.5)
Where bought, n (%)			
pharmacy	127 (89.4)	100 (73.5)	168 (78.5)
doctor	10 (7)	10 (7.4)	0 (0)
health centre	0 (0)	13 (9.6)	46 (21.5)
depot	0 (0)	1 (0.7)	0 (0)
general store	5 (3.5)	6 (4.4)	0 (0)
healer	0 (0)	2 (1.5)	0 (0)
no response	0 (0)	4 (2.9)	0 (0)

SD, standard deviation of sample distribution, without taking into account added variability from survey methodology.



**Figure 2.** Antibiotic classes used among children under 2 surveyed in Madagascar and Senegal.

**Factors associated with antibiotic consumption**

Factors associated with antibiotic consumption in univariate analysis using data pooled across sites included housing and baby age (Table 5). Living in a house in a compound and living in a room in a house shared with other households was associated with lower antibiotic consumption compared with living in an individual house. Age above 6 months was also associated with greater antibiotic consumption compared with the 0–6 month group.

While overall *P* values showed significance for housing, individual-level comparisons were not significant. Similar results were obtained when analysis was restricted to babies older than 3 months old (data not shown).

Following a stepwise selection and adjusting for site, two factors remained significantly associated with higher antibiotic consumption in the last 3 months: living in houses without flushing toilets (OR 1.4, 95% CI 1.0–1.9) and baby age (OR 1.8, 95% CI 1.2–2.6 for children 6–<12 months; OR 1.8, 95% CI 1.1–2.8 for children 12–<18 months; OR 1.5, 95% CI 0.9–2.2 for children 18–24 months versus children 0–<6 months). Neither vaccination status nor any other child health characteristics were associated with antibiotic consumption.

In site-specific analyses, three factors were independently associated with antibiotic consumption in the last 3 months in Guediawaye: parent antibiotic consumption in the last year (OR 2.5, 95% CI 1.1–5.8), systematic use of health structures in case of fever, diarrhoea or cough (OR 5.4, 95% CI 2.1–13.4) and non-flushing toilets (OR 1.8, 95% CI 1.2–2.6). Analyses of combined Madagascar site data found that child ages of 6–<12 months (OR 3.8, 95% CI 2.4–6.1), 12–<18 months (OR 3.4, 95% CI 2.0–5.8) and 18–24 months (OR 2.6, 95% CI 1.3–5.3) were associated with higher antibiotic consumption as compared with the 0–<6 month group. The number of rooms in a household was also significant with higher antibiotic usage among children living in households with two rooms (OR 1.8, 95% CI 1.2–2.8) or three or more rooms (OR 1.5, 95% CI 1.0–2.3) versus those with one room. Information on parent antibiotic consumption and systematic use of health structures were not available in Antananarivo and Moramanga.

Due to the limited number of households with multiple children, results from multi-level logistic analyses were similar to those obtained from the simple model (results not shown).

**Antibiotic consumption and structural factors**

Among our three sites, a higher density of public health structures was associated with lower consumption levels (Figure 3a). Conversely, a higher density of private pharmacies in the study area was associated with a higher level of antibiotic consumption (Figure 3b).

**Discussion**

To our knowledge, the results of our study are the first comprehensive estimates of antibiotic consumption among children in Madagascar and Senegal and add important data to the antibiotic consumption literature in LICs for which few quality data exist. The collection of factors related to antibiotic use is also important in order to understand consumption and develop any necessary public health or surveillance methods. Substantial levels of consumption in the last 3 months were found, particularly in Senegal.

The observed proportions were lower than results from community surveys in other LICs from South-East Asia.<sup>24–26</sup> In addition to real differences in antibiotic consumption, our methodology and use of various study tools may have reduced selection bias and misclassification of non-antibiotic medication, leading to increased consumption measures in other studies. The observed proportions more closely matched those among children in developed countries, but remain elevated.<sup>27–29</sup>

**Table 5.** Factors associated with antibiotic consumption in the last 3 months among children under 2 in Madagascar and Senegal

Variable	OR <sup>a</sup> (95% CI)	P	aOR <sup>b</sup> (95% CI)	P
Mother's education		0.09		
no education	1			
primary education or more	0.77 (0.56–1.05)		—	
Housing		0.02		
individual house	1			
house in compound	0.94 (0.57–1.54)		—	
room in a house with other households	0.71 (0.52–0.97)			
family house	1.08 (0.80–1.48)			
Wall material		0.44		
mud/wood/metal sheet	1			
bricks/cement/stone	1.28 (0.68–2.42)		—	
Floor material		0.19		
mat/boards/dirt/sand	1			
cement	0.97 (0.57–1.66)		—	
tiles/wood floor	1.29 (0.76–2.17)			
Toilet type		0.14		0.03
with flush	1		1	
without flush	1.26 (0.92–1.72)		1.43 (1.04–1.97)	
Number of people in household		0.14		
2	1			
3	3.03 (0.36–25.30)		—	
4–8	2.51 (0.30–21.32)			
≥9	3.44 (0.41–28.83)			
Number of people per room		0.70		
<1.5	1			
1.5–2.5	1.04 (0.68–1.58)		—	
≥2.5	0.91 (0.62–1.33)			
Baby age (months)		0.01		0.04
0–<6	1		1	
6–<12	1.79 (1.21–2.64)		1.78 (1.21–2.61)	
12–<18	1.73 (1.10–2.74)		1.76 (1.12–2.76)	
18–24	1.47 (0.96–2.24)		1.45 (0.95–2.23)	

<sup>a</sup>Unadjusted OR.<sup>b</sup>The adjusted OR (aOR) was adjusted for study site.

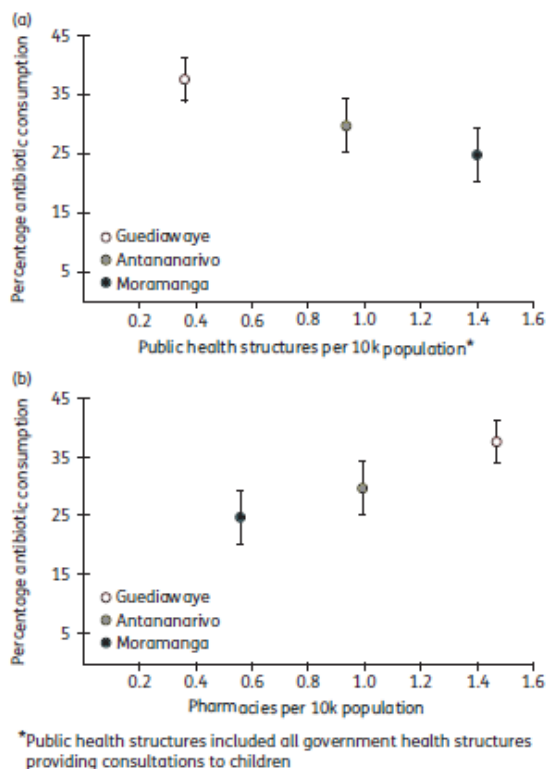
Data from Madagascar and Senegal show no peak in influenza cases during the study recall period (surveillance data from Malagasy Health Ministry).<sup>30</sup> Influenza has been found to be a main driver of antibiotic consumption in other countries and the observed consumption rates may thus reflect a baseline measure.<sup>31</sup>

The majority of antibiotic consumption was prescribed for children with respiratory and ear/nose/throat symptoms in all sites. These symptoms are related to upper respiratory tract infections, which are often caused by viruses and for which antibiotics are not recommended.<sup>32</sup> Use of microbiological test results to guide antibiotic prescribing is rare in LICs. However, without proper diagnostic testing, determining the causative agent of an infection is difficult and prescribing an antibiotic may be more likely. Development and use of a adapted diagnostic tools could help

improve prescribing and avoid unnecessary use. In Senegal a number of symptoms classified as 'other' included a variety of non-infectious diseases for which antibiotics are inappropriate.

In pooled multivariate exploratory analyses adjusted on site only two variables remained significant. Non-flush toilets may reflect a lower socioeconomic status or play a role in disease spread, although no difference was noted in symptoms according to toilet type. Age >6 months was also associated with increased antibiotic consumption. No difference in symptom profiles was found between age groups, suggesting increased infectious episodes rather than changing disease patterns.

Interestingly, vaccination coverage was not associated with a reduction in antibiotic use in pooled analyses. Increased vaccination has been proposed as a potential means to reduce the use of antibiotics.<sup>15</sup>



**Figure 3.** Antibiotic consumption estimates by study site per (a) number of public health facilities and (b) number of pharmacies per 10 000 population.

The higher antibiotic consumption in Senegal compared with Madagascar may be due to a higher overall healthcare use and use of medication, which can be seen in the significantly higher use of any medication in the last 3 months among Senegalese children. A higher overall socioeconomic status in Senegal might also translate into greater healthcare access and antibiotic consumption.

Recent analyses show that the countries with the highest growth of antibiotic consumption were middle-income countries with growing economies.<sup>5</sup> The difference in consumption between Senegal, a lower-middle income country, and Madagascar, an LIC, supports this finding.

Respective national health policies in each country may also play a role in consumption differences. In 2013, a Universal Health Coverage law was launched in Senegal under which healthcare for children under 5, including a number of antibiotics, became free in public health facilities. In Madagascar, evaluation and follow-up of children is free in public health centres. However, any medication, including antibiotics, must be paid for, which can create barriers to access for the poorest families.<sup>33</sup> Increases in antibiotic usage, both appropriate and inappropriate, have been observed in patients provided with free healthcare compared with controls in randomized and observational studies.<sup>34,35</sup>

Interestingly, the number of public healthcare centres per capita was inversely correlated with antibiotic consumption. The Senegalese study population had fewer public health centres per capita. Additionally, 12 of the 13 healthcare centres in Guediawaye were low-level health structures staffed by nurses or other non-doctor health personnel. All public healthcare structures in Madagascar, on the other hand, were staffed with doctors. The relative scarcity of health structures may translate into shorter consultation times. These shorter consultations combined with undertrained staff and free antibiotics found in Senegal may largely contribute to the higher rates of medication and antibiotics observed in that country.

A higher number of pharmacies per capita was also correlated with increased antibiotic consumption in the three sites. This could be due to a greater availability of drugs overall and greater proximity to the families, resulting in facilitated access to antibiotics. Hypotheses surrounding the access to healthcare and pharmacy density remain speculative, however, and their contribution to antibiotic consumption is unknown.

Antibiotic consumption patterns of children enrolled in the BIRDY cohort study provide insight into the role of prescriber training. Enrolled children benefit from free medical care and medication, including medical evaluations by trained paediatricians. They are similar socioeconomically to the children included in our survey and live near survey study zones. Children in the cohort, however, showed antibiotic consumption proportions in the last 3 months of just under 20% in both Antananarivo and Moramanga during the same study period (B. T. Huynh, M. Padget, P. Herindrainy, P. Piola, E. Delarocque-Astagneau and D. Guillemat, unpublished data; <http://www.birdyprogram.org/>). In this case, access to free healthcare and antibiotics did not result in higher consumption, highlighting the role of prescriber training.

Non-prescription use in both countries was lower than two other studies in LIC settings.<sup>26,36</sup> These relatively low proportions may be due to parents and antibiotic distributors being particularly cautious about providing non-prescribed medication to small children.

In Moramanga, slightly higher proportions of non-prescribed antibiotics were observed. A higher heterogeneity of antibiotic advisor and place of purchase, common in rural LIC settings, was also observed although no association with non-prescribed consumption was tested statistically.

The large majority of antibiotics in all sites were obtained in pharmacies and recommended by a doctor. These findings correlate with the relatively low levels of non-prescription use. In Senegal over 90% of respondents suggested they would always seek a medical consultation if a child had cough, fever or diarrhoea, while only 57% would do the same for themselves. These are positive findings in terms of surveillance and public health interventions. With low use of alternative antibiotic sources and few non-prescribed episodes, antibiotic surveillance for child use focused principally on pharmacies may be appropriate and interventions aimed at doctors might be effective in reducing unnecessary use.

Non-compliance with antibiotic duration may be a risk factor for the development and transmission of resistance and the low compliance seen in Guediawaye is a concern. This may be attributable to the fact that many prescriptions were coming from staff who did not properly explain the importance of finishing the antibiotic course due to lack of training or time constraints.

Some limitations are associated with the cross-sectional nature of this study. Recall biases could have been an issue leading to unreported episodes of antibiotic consumption in the last 3 months, leading to lower observed rates. This may have been a problem specifically when multiple consumption episodes occurred in the study time-frame. Episodes outside the study time-frame may also have been counted. Desirability bias may have played a role in the low rates of non-prescribed antibiotic consumption as participants may not want to report non-prescription use. We tried to control for these biases with the use of study tools such as the calendar as well as questionnaire design and question placement. Verification of antibiotic packaging and prescriptions consistently corresponded with verbal responses, confirming our confidence in the data collected.

In addition to important information on a high-risk population, the results from these surveys are useful for comparing across countries and shaping specific policy measures. While these results may not be generalized to other LICs due to the heterogeneity among these countries, they may be generalized within countries to areas with similar population characteristics.

The presence of the BIRDY study is valuable as consumption data from each site can be compared with local community resistance profiles and inform a larger narrative on antibiotic resistance in LICs. The widespread use of third-generation cephalosporins in Senegal is of special interest as these drugs are related to the presence of ESBLs and high proportions of ESBL-positive bloodstream infections have recently been reported in this country.<sup>19</sup>

### Conclusions

These data are crucial for the implementation of programmes aimed at optimizing antibiotic consumption. Our results show elevated levels of antibiotic consumption, but often for symptoms suggestive of viral infection. While any unnecessary use must be reduced, there is no guarantee that all children needing antibiotics are getting them. LICs must be careful to balance restriction and access in the context of antibiotic resistance.<sup>15</sup>

Country-level factors such as density of healthcare facilities, national antibiotic payment programmes and prescriber training were important in driving antibiotic consumption and must be taken into account when developing strategies to optimize antibiotic consumption in LICs. Similar investigations could be useful in other LICs where consumption data are lacking and risk factors exist for the development and spread of antibiotic resistance.

### Acknowledgements

We would like to thank all the families who participated in this study. We would also like to thank the members of the BIRDY Study Group.

### BIRDY Study Group

Members from the Institut Pasteur include Maud Seguy, Fanny Cherblanc, Laurence Watier, Maya Nadimpalli, Lenaig Le Fouler, Benoit Garin and Bich-Tram Huynh. Members from the Institut Pasteur in Madagascar include Jean-Marc Collard, Bodonirina Tanjona Raheliharivo, Feno Manitra Jacob Rakotoarimanana and Frédérique Randrianirina. Members from the Institut Pasteur in Dakar include Muriel Vray, Abdoulaye Seck, Raymond Bercion, Amy Gassama Sow, Jean Baptiste Diouf, Pape Samba

Dieye, Balla Sy and Bouya Ndao. Members from the Institut Pasteur in Cambodia include Laurence Borand, Thida Chon, Agathe de Lauzanne, Sophie Goyet, Alexandra Kerleguer, Siyin Lach, Veronique Ngo, Arnaud Tarantola and Sok Touch. Members from Necker Hospital Paris include Elsa Kermorvant-Duchemin.

### Funding

This work was undertaken as part of the Bacterial Infections and antibiotic Resistant Diseases among Young children (BIRDY) project (<http://www.birdyprogram.org/>), which is made possible by the funding of the Department of International Cooperation of the Principality of Monaco. This work has also received funding from the French Government's Investissement d'Avenir programme, Laboratoire d'Excellence 'Integrative Biology of Emerging Infectious Diseases' (grant no. ANR-10-LABX-62-IBEID), the Epidemiology and Infectious Disease Unit of the Institute Pasteur of Dakar, and the Foundation Pierre Ledoux - Jeunesse Internationale.

### Transparency declarations

None to declare.

### Supplementary data

Supplementary data are available at *JAC* Online (<http://jac.oxfordjournals.org/>).

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**Title:** Antibiotic resistance among children in low-income countries - Investigating community antibiotic consumption.

**Keywords:** antibiotic resistance, bacterial infections, antibiotic consumption, low-income countries, children

**Abstract :** Antimicrobial resistance is a growing threat across the world and is likely to disproportionately affect children in low-income countries (LICs).

To estimate the burden of antibiotic resistance in the community among children under two in LICs we undertook a review of published literature. Common isolates in neonatal sepsis cases included *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella*. Among children 1 mo. to 2 yrs., *Streptococcus pneumoniae* and *Salmonella* were most often reported. Information on antibiotic resistance was sparse and often relied on few isolates.

We reviewed methods to measure antibiotic consumption in LICs from published literature and showed that current techniques used in isolation are insufficient to respond to all the data needs in LICs. Integrating study techniques and starting with community surveys may respond more adequately to this issue in LICs and lead to more actionable results.

To investigate patterns of antibiotic consumption and related factors among children under two in Madagascar and Senegal we undertook community surveys in two sites in Madagascar (Antananarvo and Moramanga) and one site in Senegal. Results showed relatively high levels of antibiotic use among children. The majority of antibiotics were purchased in pharmacies with a prescription in both countries. Data suggest a high proportion of use for likely viral infections. Local contexts including the availability of health care facilities, availability of pharmacies, national payment schemes, and provider training seemed to play a role in country usage rates.

Results from this work add essential data to the literature where relatively little data exists and reveal important lessons about studying and combating antibiotic resistance in LICs.

**Titre :** La résistance aux antibiotiques chez les enfants dans les pays à faible revenu - Enquête sur la consommation d'antibiotiques.

**Mot clés;** résistance aux antibiotiques, infections bactériennes, consommation d'antibiotiques, pays en développements, enfant

**Résumé :** La résistance bactérienne aux antibiotiques est un problème de santé publique majeur, touchant plus particulièrement les enfants dans les pays en développement (PED).

Nous avons effectué une revue systématique de la littérature pour quantifier le niveau de résistance aux antibiotiques chez les enfants âgés de moins de 2 ans dans les PED. De manière générale, les données sur la résistance aux antibiotiques dans la population étudiées sont rares. Selon les publications identifiées, *Staphylococcus aureus*, *Escherichia coli*, et *Klebsiella* spp. apparaissent comme les causes les plus fréquentes d'infections néonatales sévères. Chez les enfants âgés de 1 à 24 mois, *Streptococcus pneumoniae* et *Salmonella* spp. apparaissent comme les causes les plus fréquentes d'infections bactériennes invasives.

Dans une seconde revue systématique, nous avons examiné les méthodologies actuelles utilisées pour mesurer la consommation d'antibiotiques dans les PED. Nos résultats montrent qu'aucunes des méthodologies

ne permet, à elle seule, de répondre aux besoins de ces pays en terme de données.

Nous avons conduit une enquête en population à Madagascar et au Sénégal afin d'examiner les modalités de consommation d'antibiotiques chez des enfants de moins de 2 ans. Dans les 2 pays, la plupart des antibiotiques étaient achetés en pharmacie sur présentation d'une ordonnance. Une proportion élevée des antibiotiques était utilisée pour le traitement d'infections probablement d'origine virale. Des facteurs tels que la disponibilité de centres de santé, de pharmacies, l'existence de programmes de remboursement ou encore la formation du personnel pourraient influencer la fréquence de consommations d'antibiotiques au niveau national.

Les résultats issus de ces travaux de recherche ajoutent des données essentielles à la littérature existante et mettent en évidence des leçons importantes pour la lutte contre la résistance aux antibiotiques dans les PEDs.