Narrative

1. **Goals:**

To perform a situation analysis and needs assessment on ways to improve the use of antibiotics for treatment of acute respiratory infections and enteric disease in young children in Uganda and Zambia.

Note: all graphs and tables are generated from ARSANA project data unless otherwise noted. *Also note that "objectives" in this report were termed "activities" in the original proposal.*

II. Objectives and results:

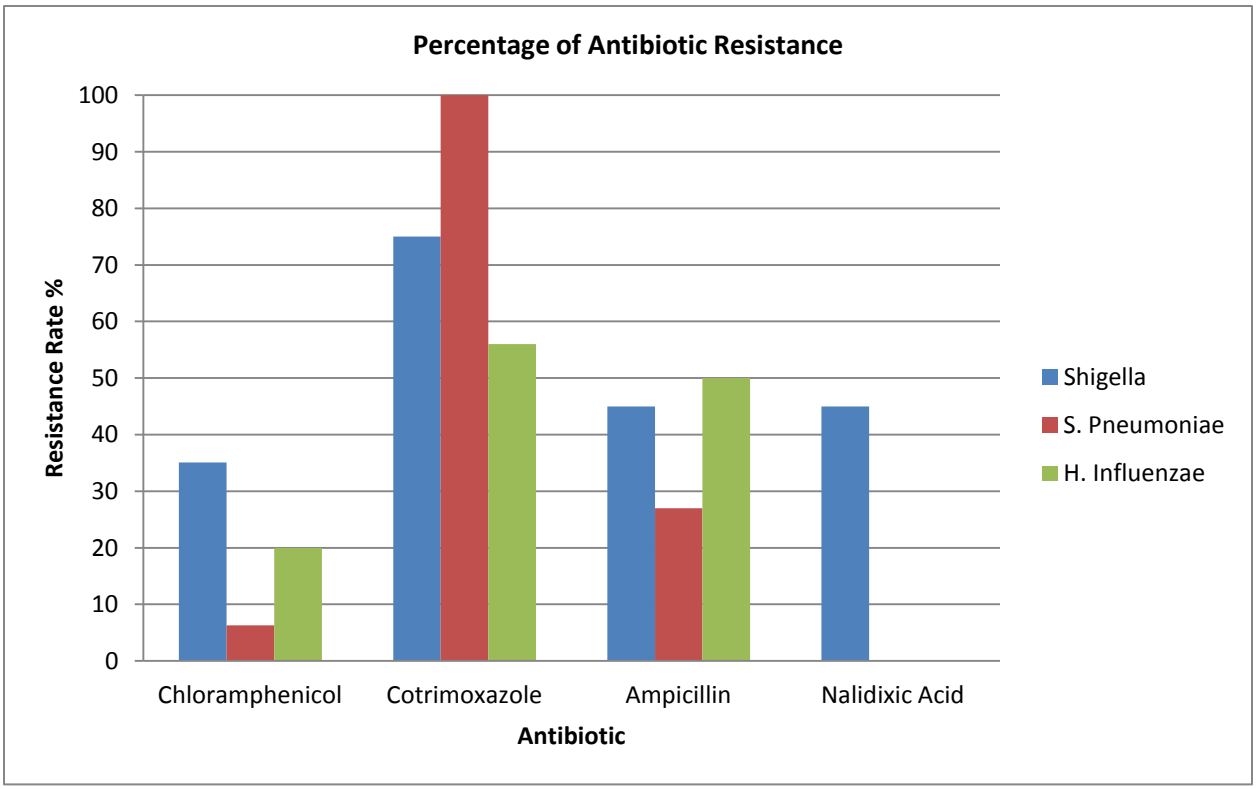
Objective 1: Development of resistance profiles in selected countries

The mortality rate due to acute respiratory infections is high in both Uganda and Zambia; at the University of Zambia Teaching Hospital, approximately 30% of all children under 5 years admitted with severe pneumococcal disease died, and 90% of the children who died were under 1 year of age (too young to have been fully immunized). In Uganda, an average mortality rate of 5.45% was recorded in 4 regions. There is a lack of documentation of the true disease burden due to lack of surveillance and of laboratory diagnosis. These data are only available for urban hospitals, and there is under-representation of the rural population. Some of the major issues identified that could account for such high mortality rates are: lack of cost-effective vaccination programs, lack of minimum essential sustainable diagnostic laboratories, lack of antimicrobial resistance surveillance programs, and lack of effective regulatory policies for the appropriate management of antibiotics. *S.pneumoniae, N. meningitides, and S. aureus* and co-existing non-bacterial respiratory pathogens are common causes of ARI among children under 5 years in both Uganda and Zambia. Among the patients with suspected bacterial meningitis, infants were most likely to have the acute respiratory pathogens identified from their blood or CSF than any other age group.

Antibiotic resistance profiles:

Although existing AMR surveillance information in Uganda and Zambia is unreliable and lacks effective quality assurance measures, there are limited efforts by some individual laboratories to produce data on antibiotic resistance. In Uganda, data were obtained mainly from the NetSPEAR consortium that serves four Ugandan Districts, and from Makerere University Department of Microbiology profiles. Data from Zambia were obtained from the University of Zambia Teaching Hospital microbiology laboratory. Antibiotic resistance rates of pathogens causing acute respiratory infections to most commonly prescribed drugs have increased significantly over the past few years. Cotrimoxazole remained the most commonly prescribed antibiotic for acute respiratory infections due to *S. pneumoniae* despite the high resistance rates recorded. In 2000, the *S. pneumoniae* antibiotic resistance rates were at 11.7% in Kampala, Uganda. This rate increased dramatically to 89.4% in 2007. The situation is similar in other parts of Uganda, for which data were available.

Figure 1. Rates of antibiotic resistance by antibiotic drug, Uganda.



So far, intermediate resistance to amoxicillin has been recorded in parts of Kampala. *S.pneumoniae* resistance rates to ampicillin of up to 34%, oxacillin of up to 49.1%, ceftriaxone of up to 5.7% and gentamycin of up to 5.7% have been recorded. In Zambia, there are still no reliable data on resistance of other frequently isolated respiratory pathogens to commonly used drugs like oxacillin, cefotaxime, ceftriaxone, erythromycin, and gentamicin due to irregular monitoring of resistance. However, the existing data showed that antibiotic resistance of *S. pneumoniae* to cotrimoxazole is still very high, and *S. Pneumoniae* resistance rates to penicillin of up to 53-67% were recorded in 2007.

Enteric Pathogens:
In Uganda, high rates of *Shigella spp, V.cholera* and *Salmonella spp* resistance to the most commonly used antibiotics -- ampicillin, cotrimoxazole, chloramphenicol, and tetracycline -- were also recorded. With the support from WHO, a laboratory network that integrates identification, surveillance of enteric pathogens and their antibiotic resistance patterns of major classes of pathogens responsible for enteric infections has been established at the Central Public Health Laboratory (CPHL) in Uganda. This network has been functional since June 2001, and incorporates approximately 11 districts. There is however no such system in place in Zambia, so much less is known about resistance of enteric pathogens in that country. Enteric infections that affected Zambian children were due to rotavirus and enteric bacteria (*E. coli, V. cholerae*, *Salmonella spp., and Shigella spp)*. Available data showed very high resistance among enteric bacteria to gentamicin, cefotaxime, nalidixic acid, ciprofloxacin, cotrimoxazole and cephalexin, ranging between 70-100%.

Immunization profiles:
Vaccine against *H.influenzae* (Hib) was introduced in both Uganda and Zambia, and coverage has plateaued at 70% in Uganda since 2005; no coverage data were available for Zambia. Both countries are

still awaiting introduction of the *S.pneumoniae* vaccine. No rotavirus vaccines have been introduced in either country.

Objective 2: Analysis of antibiotic drug supply and distribution

In each country a study of the system for importation and sale of antibiotics was undertaken. Samples of three antibiotics were purchased in a variety of outlets in both countries. Data were collected on the generic name, brand name, formulation, type of packaging, country of manufacture, expiry date, and price paid. In addition, quality testing was performed on the samples. The table below shows the most common brands and their market share of the samples found at the outlets surveyed. Four brands dominated the market for all three antibiotics, with market shares ranging from 60-73%. In Uganda, India predominates as the country of manufacture, with 58% of the market, followed by Uganda, 24%; Kenya, 9%; UK, 5%; and others, 4%. All major brands of ciprofloxacin (73% of the market) come from India; the majority of the cotrimoxazole is manufactured in Uganda or Kenya, so the rise in cotrimoxazole resistance has commercial implications for the Ugandan industry. India and Uganda account for two-thirds of the drugs in the sample. Some of the Ugandan manufacturers are in fact subsidiaries of Indian-owned companies, so the actual influence of Indian pharmaceutical industry is very strong on the Ugandan antibiotics market, accounting for over 80% of the total.

Table 1. Most common brands of three antibiotics, source, and market share in Uganda.*

Generic	1st brand (% of total)	2nd brand (% of total)	3rd brand (% of total)	4th brand (% of total)	% of market represented by top 4
Amoxicillin	Asmox (I) (28%)	Hipen (I) (16%)	Moxup (U) (11%)	Spamox (I) (11%)	67%
Ciprofloxacin	Ciprobid (I) (41%)	Ciprowin (I) (12%)	Ciproleb (I) (12%)	Ciprodac (I) (8%)	73%
Cotrimoxazole	Renetrim (U) (20%)	Cotriz (U) (18%)	Unitrim (K) (16%)	Trimago (I) (6%)	60%

* U= Uganda, I= India, K=Kenya.

The median prices were the same between the pharmacies, drugshops, and clinics. Table 2 below shows the different prices by type of outlet. Cotrimoxazole is the cheapest at 50 UGX (about US$ 0.03) per tablet/capsule, with amoxicillin two times higher at 100 UGX (US$ 0.05), and ciprofloxacin twice again, at 200 UGX (US$ 0.10). The pharmacies' mean prices were higher by a factor of 1.3 to 2.8, but this was mostly due to the wider range of products they carry, e.g. local brands, Indian, and European brands in blister packaging, whereas the drugshops tend to carry only one or two lower cost local or Indian manufactured brands, often dispensed from large tubs of 100 or 1000 tablets or capsules in paper cones, envelopes, or "Minigrip" plastic zipper bags.

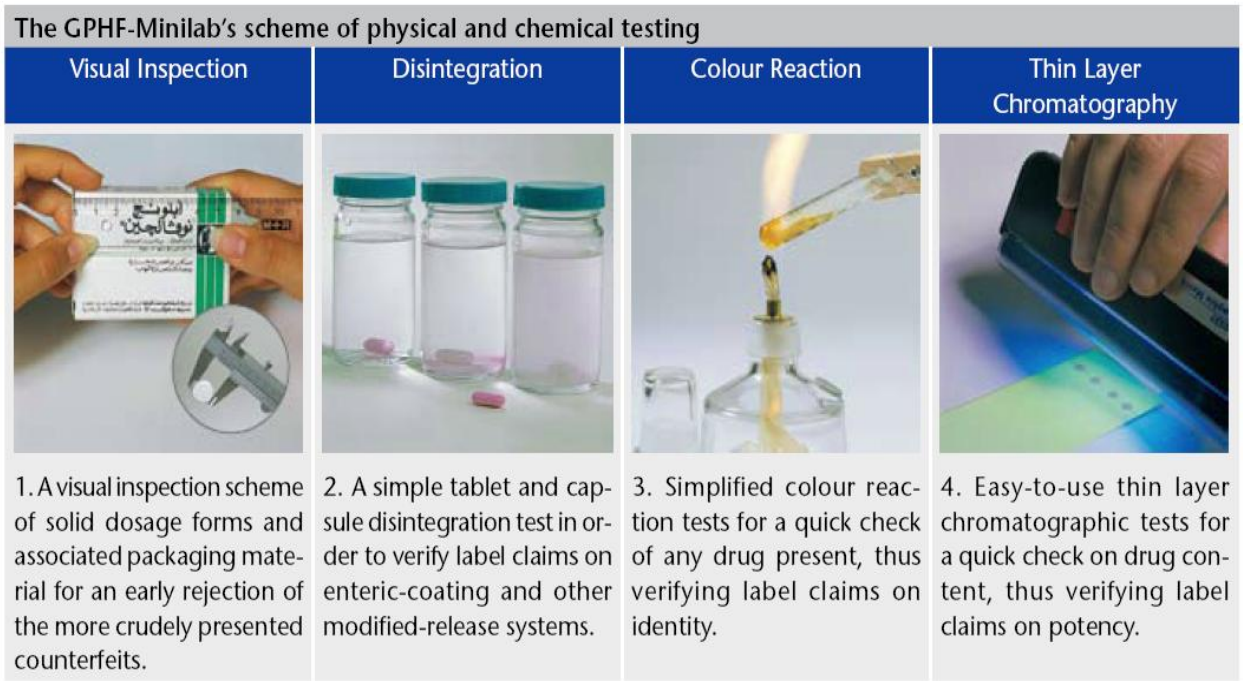
Table 2. Comparison of prices by type of outlet, Uganda (in Uganda shillings, UGX).

	Mean pharmacy price (UGX)	Median pharmacy price (UGX)	Mean drugshop price (UGX)	Median drugshop price (UGX)	Ratio of mean pharmacy price to mean drugshop price
Amoxicillin	189	100	114	300	1.7
Ciprofloxacin	390	200	303	250	1.3
Cotrimoxazole	144	50	51	50	2.8

In Zambia, Indian drugs account for about 58% of those found on the Lusaka market. Locally manufactured drugs account for only a small percentage of available drugs, approximately 4%. The origin could not be determined in 38% of samples, mostly those sold from large tubs of 1000. In Zambia the ranges of prices between type of outlet was wider, although the medians were similar. Median amoxicillin prices were 333-350 Zambian Kwacha per amoxicillin capsule, about US$ 0.07, and median prices of cotrimoxazole were 200-250 ZK (about US$ 0.04-0.05). The reason seems to be as in Uganda, that a wider range of products is stocked in pharmacies, including not only low cost Indian brands distributed in tubs of 100 or 1000, but also "fancier" European brands in blister packaging.

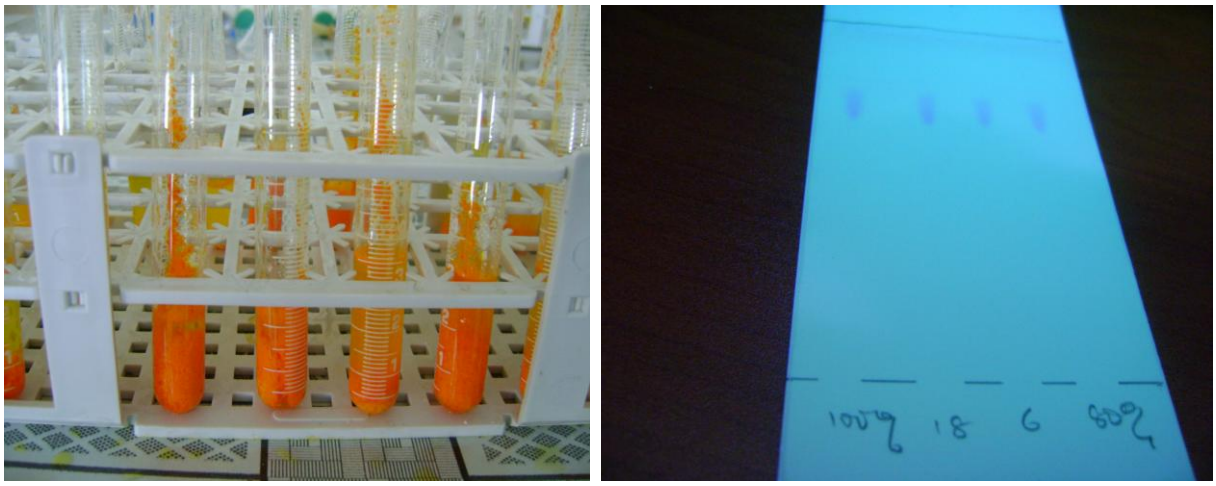
One potential driver of antibiotic resistance could be poor drug quality. Accordingly we carried out an extensive program of quality testing of three key antibiotics - amoxicillin, ciprofloxacin, and cotrimoxazole, in both tablet/capsule form and in liquid form (suspensions and syrups). A total of 813 samples have been or are being tested. 748 samples of solid forms (tablets and capsules) were collected and tested using Minilab ® technology, by the Pharmaceutical Regulatory Authority (PRA) in Zambia and at the APUA office in Kampala. In addition, 65 samples of liquid forms of amoxicillin are being tested at the MEDS Laboratory in Nairobi, Kenya (Minilab ® cannot test liquid formulations); testing results are not yet available. Figure 2 shows the range of tests performed using Minilab ® technology, and Figure 3 shows photos of the testing being performed at the APUA office in Uganda. Table 3 below shows the results of the testing.

Figure 2. Testing scheme with Minilab®.



Source: GPHF Minilab ® Instruction Manual.

Figure 3. Results of color reaction test and thin layer chromatography (TLC) on Ugandan samples*



*In the TLC photo on the right, the reference samples are labeled “100%” and “80%”; samples being tested are nos. 18 and 6.

Table 3. Results of quality testing of three antibiotics, Uganda and Zambia (excludes results of liquid formulations, n=65).

	Uganda (countrywide)	Zambia (countrywide)	Zambia (Lusaka urban)
Amoxicillin cap	12/93, **12.9%**	2/ 25, 8%	9/136, 6.6%
Amoxicillin susp	*Being tested*	*Being tested*	*Being tested*
Ciprofloxacin cap	4/87, 4.6%	1/37, 2.7%	10/110, **9.5%**
Cotrimoxazole tab	1/90, 1.1%	0/36, 0%	2/134, 1.5%
Cotrimoxazole syrup	*Being tested*	*Being tested*	*Being tested*
Overall	**17/270, 6.3%**	**3/98, 3.1%**	**21/380, 5.5%**

* Tablets and capsules only. Total n= 748; overall failure rate = 5.5%

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Overall the results of the testing were better than we expected, with 5.5% of the samples failing thin layer chromatography (TLC) which measures drug potency. No samples failed the color test and therefore all did contain active ingredient, e.g. no frank counterfeit drugs were found. The drug which caused the most concern with regard to quality was amoxicillin, the new recommended therapy for children with pneumonia. Amoxicillin appears to be unstable in tropical settings. Naidoo at all in South Africa(1), (Table 4 below) found that amoxicillin was particularly susceptible to deterioration when dispensed in plastic zipper bags (known locally as “Minigrips”), This is due to the breakage of the fragile beta-lactam ring. Such packaging is the main method of packaging used in both Uganda and Zambia.

Table 4. Comparison of beta-lactam ring breakage of amoxicillin under tropical heat and humidity in various types of packaging (from Naidoo et al, 2006).

Table V: A comparative analysis of the percentage of ring breakage of amoxicillin capsules using iodometric titrations at temperatures of 30-35 °C with ± 75% relative humidity on day 1, day 7 and day 14 [Limit < 5 %]

Packaging	Day 1 % ring breakage	Day 7 % ring breakage	Day 14 % ring breakage
PLASTIC PACKET	15.70%	25.00%	41.00%
TB WITH WOOL	13.00%	19.40%	29.00%
AB WITHOUT WOOL	16.20%	23.30%	38.00%
AB WITH WOOL	11.00%	14.60%	25.00%

TB= transparent bottle, AB = amber bottle
Source: Naidoo KK et al, SA Family Practice 2006:48(6).

Deteriorated samples of amoxicillin were distributed across the sample in all types of outlet and in both countries, and were not limited to any one brand or country of manufacture. This reveals the need to pay particular attention to the storage of amoxicillin, and perhaps to invest in better packaging so that this vital drug can be delivered to the patient in good condition. The fact that amoxicillin is also being prescribed in inadequate doses (see below) means that particular attention needs to be paid to both the dosing and the storage of this vital drug.

Objective 3: Analysis of formal health sector treatment of acute respiratory infections and enteric diseases

Teams of consultants visited 11 sites in Uganda and 12 sites in Zambia to collect data on outpatient visits to health centers and hospitals. In Uganda, 10,172 such records were abstracted from patient registers, and in Zambia, 4,218 records were obtained. In addition, interviews were held with prescribers in formal sector facilities (hospital OPDs and health centers), and with attendants at pharmacies and drugshops in the informal sector, regarding their knowledge of treatment of pneumonia and enteric diseases and knowledge about antibiotic resistance.

Certain comparisons of the two countries which share a similar health system structure are very illuminating. For example, the data show that antibiotic use in Uganda is over 50% higher in Uganda than in Zambia; 64% of visits in Uganda result in prescription of an antibiotic compared with 41% in Zambia. Antibiotics made up 24.3% of prescriptions in Zambia, and 28% of prescriptions in Uganda. The average number of drugs prescribed per patient was 2.67 in Uganda and 1.76 in Zambia. Injectible drugs are more widely used in Uganda (5%) than in Zambia (1.4%) whereas for young children, syrups and suspensions are slightly more widely used in Zambia. The table below presents some of the key differences between the two countries in terms of antibiotic use as reflected in the outpatient data.

Table 5. Key differences between Uganda and Zambia outpatient visits.

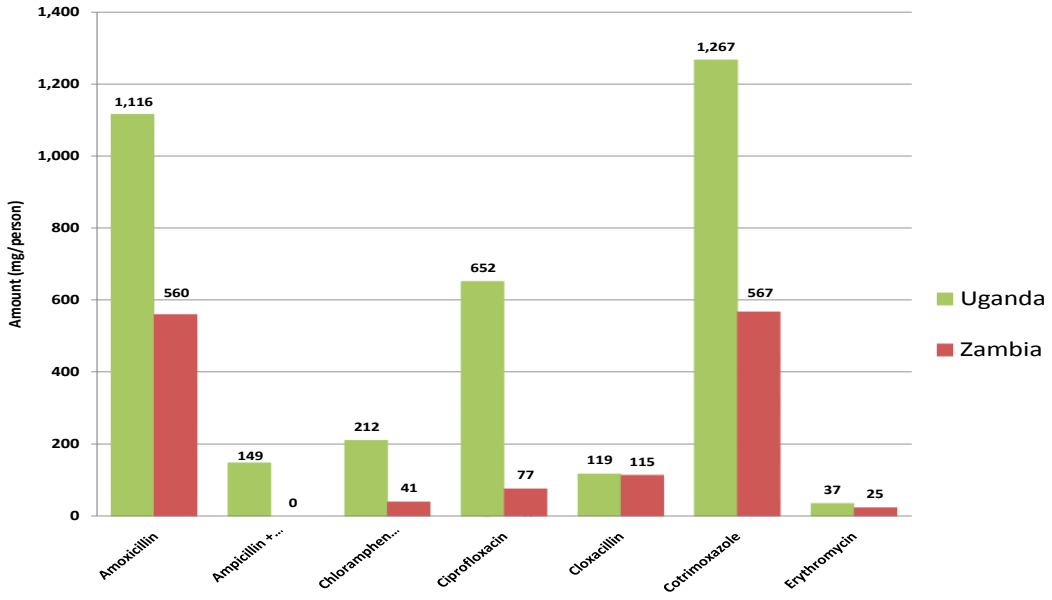
	Uganda (n=10172)	%	Zambia (n=4218)	%
Visits of children under 5	2205	*21.7*	1203	*28.5*
OP visits with an antibiotic	6471	*63.6*	1711	*40.6*
Injectible antibiotic	504	*5.0*	57	*1.4*
Syrup or suspension for under 5	305	*22.6*	303	*25.2*
OP visits with malaria diagnosis	4405	*43.3*	1104	*26.2*
Malaria cases with a blood smear (BS) or RDT	694	*15.8*	57	*5.2*
Malaria BS with positive result	377	*54.3*	8	*14.0*
OP visits with pneumonia diagnosis	430	*4.2*	54	*1.3*
Pneumonia cases with antibiotic	397	*92.3*	41	*75.9*
OP visits with other respiratory diagnoses	2053	*24.2*	884	*21.0*
OP visits with overlapping malaria / respiratory diagnoses	1176	*11.6*	141	*3.3*

There are also important differences in the antibiotics which are being used in the two countries. Despite very high levels of resistance, cotrimoxazole for acute respiratory infections (ARI) continues to be the main drug used in both countries; in Uganda amoxicillin is being used primarily in older people rather than in young children. Injectible antibiotics are more widely used in Uganda, whereas in Zambia, more children receive antibiotic syrups and suspensions. Figure 4 below shows the amount of antibiotics per patient in the samples of both countries, and indicates that Ugandan prescribers prescribe about twice as much antibiotic for a given set of patient visits as their Zambian counterparts. For certain drugs, the difference is much greater; Ugandans use 8.5 times more ciprofloxacin than Zambians and 5 times as much chloramphenicol.

Another important finding of the study was that in Zambia pneumonia is very rarely listed as a diagnosis, with only 1.3% of cases having a diagnosis of pneumonia recorded, compared with 4.2% in Uganda. In Uganda, 288 of 2347 (12.3%) children under 6 had a diagnosis of pneumonia, of which 95 (33%) were judged to be “severe” and 193 (66%) “not severe.” By contrast, in Zambia, only 23 children (1.7%) of children under 6 had a recorded diagnosis of pneumonia, and only one of these was labeled “severe.” DHS statistics for both countries list pneumonia as a major cause of death of young children, so it appears that pneumonia is greatly under-diagnosed in Zambia (and possibly in Uganda as well), although the reason for this could not be determined from our study data. There is a need to ascertain what is happening with pneumonia diagnosis and treatment particularly in Zambia. It seems that health staff are slow to recognize signs and symptoms of pneumonia in young children, and thus to provide appropriate treatment; this is a potential intervention point.

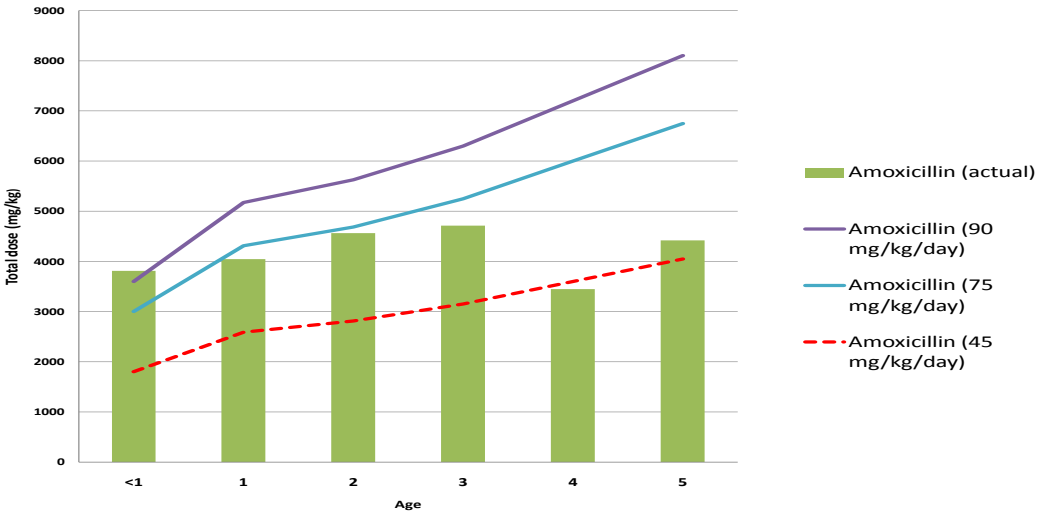
Cotrimoxazole is the most often used antibiotic (38.7%) for treatment of pneumonia in Uganda. *S.pneumoniae* resistance to cotrimoxazole exceeds 80-90% in Uganda (and Zambia). 88 children (30.5%) received cotrimoxazole alone and no antibiotic was recorded for 19 children (7%). Thus, about 37% of Ugandan children with pneumonia who were brought to the health facilities received potentially ineffective antibiotic therapy for pneumonia.

Figure 4. Comparison of antibiotic prescribed per outpatient visit in Uganda and Zambia



Another key finding of the study was that in Uganda, many of those children treated with amoxicillin received a dose which was too low, especially for children above the age of 1 (figure 5 below). Children aged 4 actually received a lower mean dose of amoxicillin than children aged 1 or 2. The current recommendation is tending towards a higher dose of amoxicillin, approximately 90 mg/kg/day (the upper purple line in the graph below) and clearly only the very youngest children are receiving an adequate dose. Comparable dosing data from formal health sector facilities were not available for Zambia, although data from the Lusaka informal sector drugshops and pharmacies indicated that underdosing of amoxicillin was also taking place there.

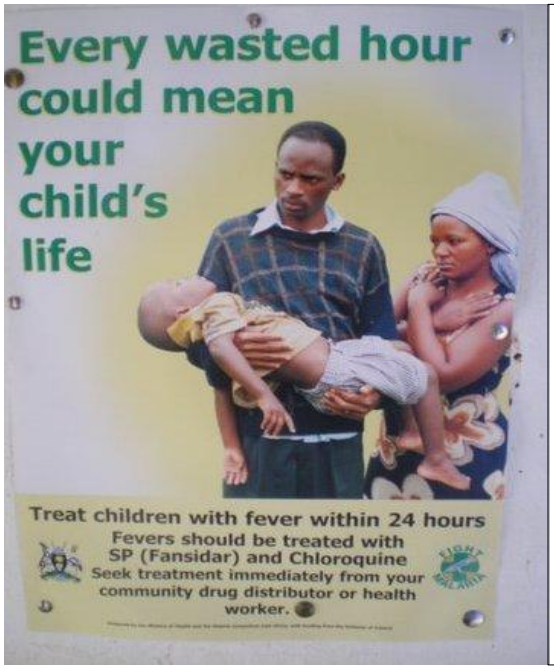
Figure 5. Actual and appropriate doses of amoxicillin for children under 6, by age.

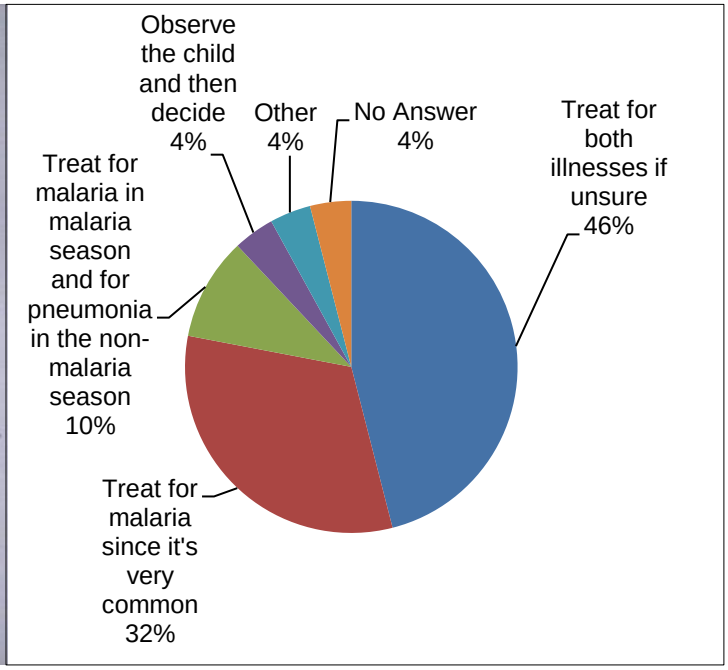


One of the unexpected findings of the study was the important role of malaria in driving antibiotic use in Uganda and the confusion and uncertainty evident in the prescribing practices of the staff. Approximately 43% of outpatient visits are for malaria in Uganda as compared with 26% in Zambia. Most important for

antibiotic use is that in Uganda, two-thirds of persons visiting with a diagnosis of malaria also receive an antibiotic. Given the high number of visits for malaria this means that about 30% of antibiotic use is for people whose main reason for visiting the health services was stated as malaria. For some time now the official policy in Uganda has been to treat all fevers in young children as malaria as seen in a poster photographed in a Ugandan clinic in 2008 (figure 6 below) advising parents to get malaria treatment for all febrile children (note that the treatment recommended is now outdated, and that such outdated messages are difficult to retrieve once launched). This policy is clearly reflected in the treatment practices of the health staff. When asked what they would do if they were unsure of the diagnosis, about half would treat for both malaria and pneumonia, and a third would treat for malaria only, as reflected in Figure 7.

Figure 6. Ugandan poster advising to treat all children with fever for malaria, and Figure 7, Treatment preferences of Ugandan health staff who are unsure of a malaria/pneumonia diagnosis





Work by Kallander et al in Uganda (2) illustrates how difficult it is for clinicians to distinguish between malaria and pneumonia in young children. We compared our (non-laboratory confirmed) rates of malaria diagnosis with data on laboratory-confirmed rates of malaria in various transmission zones in Uganda from Nankabirwa et al (3). We were thus able to make an estimate that about 21% of cases of malaria were overdiagnosed in our data (Table 6 below). This has important implications on many levels. First, the unnecessary exposure of both antibiotics and antimalarials can accelerate the development of resistance to both classes of drug. Secondly, it has major economic implications, especially as more expensive drugs, such as the artemisinin-containing therapies (ACTs) and amoxicillin come into wide use. Our estimate is that over $800,000 in antimalarial costs alone could be saved per year in Uganda if more accurate diagnosis was implemented. These funds could be used for more effective antibiotics for serious cases, more effective but expensive pediatric formulations, or as a contribution to the cost of pneumococcal vaccine.

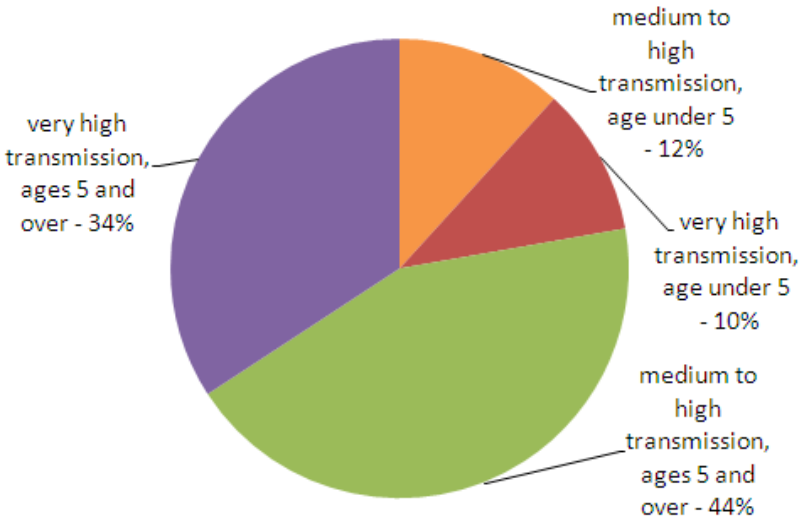
Table 6. Estimate of malaria misdiagnosis in Uganda using laboratory-confirmed data

	ARSANA project data		Nankabirwa et al (1) data		Difference	
	Malaria Transmission Zone:		Malaria Transmission Zone:		Malaria Transmission Zone:	
Age group	Very high	Med/high	Very high	Med/high	Very high	Med/high
Age under 5 (n)	1312	893			224	252
% diagnosed with malaria	67.6%	62.2%	50.5%	34%	17.1%	28.2%
Age 5 and above (n)	3683	4284			733	934
% diagnosed with malaria	39.0%	35.7%	19.1%	13.9%	19.9%	21.8%
Total	4995	5177				
Difference					957	1186

(1) Nankabirwa et al, *Malaria Journal* 2009 8:66.

Surprisingly, our data showed that the majority of the overdiagnosis was not predominantly in the children under five, in whom differentiating between malaria and pneumonia is particularly difficult. Instead, three-quarters of these cases were in older children and adults (figure 8 below). This is a potentially useful intervention point.

Figure 8. Overdiagnosis of malaria by transmission zone and age group in Uganda



Another finding was that antibiotic resistance to cotrimoxazole has increased dramatically in the past decade, to nearly 100%. This is likely caused by its widespread use for HIV prophylaxis in HIV patients. The cost of amoxicillin which is replacing cotrimoxazole is approximately double (more if liquid formulations are used). This rise in resistance was predicted (4) and raises the issue of how to balance the needs of one patient group (e.g. HIV patients) with the needs of another group (e.g. children with

pneumonia). Decisions made by one part of the public health community with regard to antibiotic use can have much wider impact, which is often not factored into the decision-making process.

Finally, the key finding of the study with regard to diarrhea and enteric disease was that first of all, it is very rarely recorded as a diagnosis at health services in either Uganda or Zambia. Only 2.1% of visits in Uganda, and 2.3% in Zambia, recorded a diagnosis of diarrhea or gastroenteritis. This suggests that most cases of diarrhea are not reaching the formal health services, and thus that it is crucial to improve the practices and advice being given in the informal drugshops. Secondly, the use of zinc for reducing the severity and duration of diarrhea is almost non-existent in either country. Zinc was not even registered for this use in Zambia until very recently. In Uganda a zinc formulation ("Zinkid") is available in the private sector pharmacies and drugshop, but rarely in public health facilities. Despite a fairly widespread publicity campaign including billboards and other mass media about "Zinkid" in Uganda about 15% of Ugandan health staff had not heard of the use of zinc for diarrhea.

Objective 4: Analysis of informal sector distribution and use of antibiotics

In both countries, many patients visit the private sector pharmacies and drugshops to purchase antibiotics for self-medication before seeking other professional care. Such outlets run the gamut from licensed pharmacies to unlicensed "no name" shops (to avoid detection by pharmaceutical regulatory authorities), kiosks and market stalls. We conducted interviews of attendants at these outlets to ascertain their levels of knowledge about antibiotics, and their treatment practices with regard to pneumonia and enteric diseases. Some of these outlets stock a fairly extensive range of antibiotics, while others are more limited (figure 9). Note the IMCI chart affixed to the countertop in the photograph on the right.

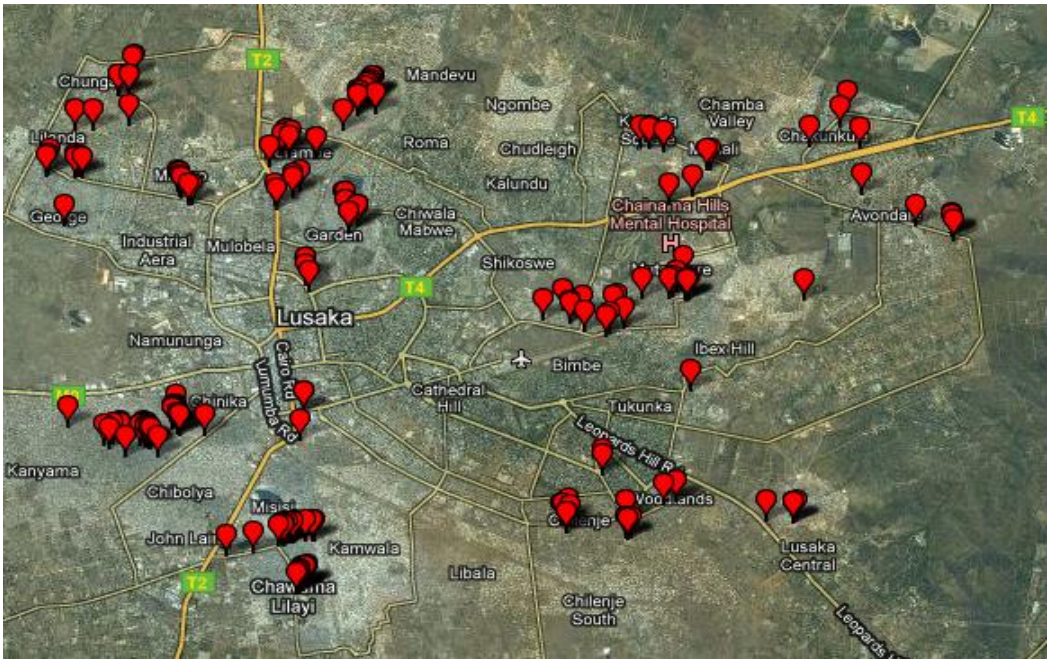
Figure 9. Range of antibiotics available at two drugshops in Uganda.

In Uganda, the study found a high level of training of attendants at both pharmacies and drugshops – two-thirds of attendants had a nursing background. Almost no pharmacists were in attendance at any of the outlets, however. In Zambia, attendants tended to have a primary education but no specific health training. Attendants at all types of outlet were eager to learn more about proper antibiotic use, especially through written guidelines and booklets.

Zambia is a highly urbanized country, with over 50% of the population living in urban areas. Accordingly we wanted to know more about the availability of drugs in urban areas. In Lusaka, Zambia, 19 young community workers from an HIV support and counseling center were trained to purchase samples in July

2010. Over 600 samples of amoxicillin, ciprofloxacin, and cotrimoxazole were purchased in Lusaka urban drug outlets (licensed and unlicensed). GPS coordinates of the shops were noted, and workers assessed the quality and appearance of the shop. About 10 samples were expired (of those 500 or so for which a date could be determined). They were asked for a prescription in about ten shops, especially for ciprofloxacin. The location of the drug outlets is shown below in Figure 10. Surprisingly, the quality of 380 samples of drugs purchased in these informal outlets was as good as that found in the public facilities, with only 5.5% failing quality testing. Ten samples were expired of approximately 500 for which an expiry date could be determined.

Figure 10. Location of Lusaka drugshops in high-density residential areas.



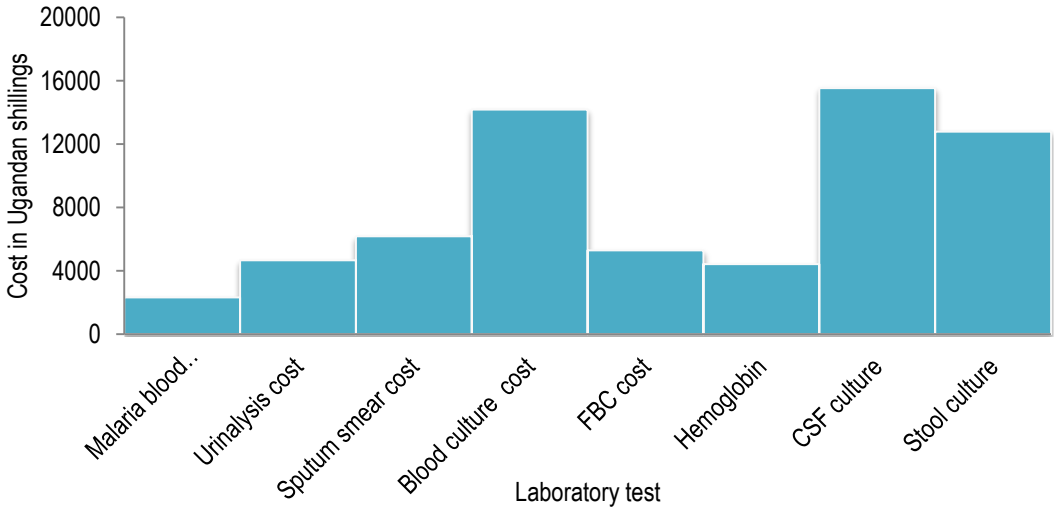
Objective 5: Assessment of laboratory capacity and costs to conduct antibiotic resistance surveillance and translate into policy and clinical practice

A total of 17 laboratories in Zambia and 29 laboratories in Uganda were surveyed to examine their capacity to reliably provide clinical diagnostics, perform antimicrobial sensitivity testing (AST), and transmit the data to be used by policy makers for clinical management and decision making. The following aspects of these laboratories were examined: the ability of laboratories to detect pathogens and perform AST; availability of a system for quality control; availability of mechanisms for dissemination of laboratory/surveillance data; availability of a system for collection, analysis and transmission of the data to be used for antibiotic management decisions; ability of laboratories to deliver accurate results; and availability and use of the WHONET software for antimicrobial resistance surveillance.

Most surveyed laboratories had qualified staff with diplomas and degrees in their respective fields. Staff training on biosafety, isolation and characterization of microorganisms, and quality control assurance was generally good in most laboratories, and records of laboratory consumables and tests performed were also well maintained in both countries. However, overall, in both countries, laboratory capacity to conduct AST was poor, and only a few facilities were able to provide routine clinical diagnostics and AST. The majority of hospital laboratories are not conducting any AST and the demand from both clinicians and patients for obtaining cultures from patients seems to be low, because laboratory diagnosis of enteric and acute respiratory pathogens was not a priority. In addition, the cost of the testing is often not affordable for patients. Figure 11 shows the mean costs of various laboratory tests in Uganda shillings. Blood culture

and CSF culture are the most expensive tests, at around 15,000 UGX or US $8 – as much as or more than 30% of an average monthly salary of 30,000-50,000 UGX, and far more than the cash income of many subsistence farmers.

Figure 11. Mean costs of laboratory tests in Uganda (Uganda shillings, UGX)



At present, most of the data on antibiotic susceptibility are coming from large urban centers, and thus may not be representative of the situation throughout the country.

Table 7 below provides assessment of the laboratories, based on their performance on the survey. Those laboratories listed under level I had almost no infrastructure required for laboratory diagnosis of the most common acute enteric and respiratory pathogens. These laboratories also showed inadequate staff training in aspects of antibiotic susceptibility testing, lack of authenticated standard operating procedure manuals, lack of equipment and unsatisfactory maintenance of available equipment, unsatisfactory quality assurance and lack of quality reagents and kits used for antibiotic susceptibility testing. Even though there was an expectation that some regional and missionary hospitals would do better in terms of the surveyed aspects, this was not always the case. Conversely, there was more happening in certain sites than expected. Three hospitals designated as regional referral hospitals (Lira, Masaka, and Arua) in Uganda had low scores; mission hospitals and some other referral hospitals were better performing. In Zambia, only a few national hospitals and research facilities had high scores.

Laboratories listed under level II had an average performance in terms of staffing, equipment availability and reagent availability, staff training in diagnosis and antibiotic resistance testing. A relatively small investment could upgrade these laboratories to a more functional level in terms of laboratory diagnosis of enteric and respiratory pathogens and the antibiotic susceptibility testing of these pathogens. In both countries, there were a limited number of laboratories under level 3 (designated by * in the table below), which are currently conducting AST, and which with minimal additional investment in equipment, supplies, and training could be improved and strengthened to form a small nucleus of a data collection network. Such data could be used to monitor treatment effectiveness from various locations around each country. Most laboratories also lacked proper networking, and most information from the laboratories was not channeled or captured to inform policy or to design interventions. Most clinicians were either not aware of, or ignored the potential benefits of using laboratory diagnosis of acute respiratory and enteric pathogens. Despite having or knowing the benefits of using WHONET software, only two laboratories in Zambia and Uganda were using it. One other major issue facing laboratories in both countries was the supply and distribution of laboratory consumables by the National Medical Stores and other commercial suppliers due to irregular demands of the laboratory consumables. For the most part, laboratory

strengthening efforts have been limited to malaria, HIV, and tuberculosis, with little done to improve the diagnosis of pneumonia.

Table 7. Scores of hospitals included in the hospital microbiology laboratory assessments.
** designates a hospital carrying out AST which could be targeted for improvement.*

Assessment scores of Ugandan Microbiology Laboratories

Level I: Score Range 0-49%	Level II: Score Range 50%-74%	Level III : Score Range >75%
Kibuli Hospital	Soroti Hospital	Mbarara Regional Referral Hospital *
Kisubi Hospital	Kuluva Hospital	Kitovu Hospital *
Lira Regional Referral Hospital	Masaka Regional Referral Hospital	Mulago National Referral Hospital *
Cure Hospital	Arua Regional Referral hospital	Mengo Hospital *
Jinja Hospital	Lacor Hospital	Mbale Hospital*
	Kiwoko Hospital	International Hospital Kampala *
	Kagando hospital	Butabika Regional Referral Hospital
	Nsambya Hospital	
	Kitovu Hospital	
	Tororo Hospital	
	Entebbe Hospital	
	Kibuli Hospital	
	Gulu Independent Hospital	
	Rubaga Hospital	

Assessment scores of Zambian Microbiology Laboratories

Level I: Score Range 0-49%	Level II: Score Range 50%-74%	Level III : Score Range >75%
Lundazi District Hospital	Maina Soko Military Hospital	University of Zambia Teaching Hospital *
Mutendere Mission Hospital	Mansa General Hospital	Tropical Disease Research Center * (research facility)
Livingstone General Hospital	Chikankata Mission Hospital	Arthur Davidson Hospital Laboratory*
	Mpika General Hospital	Chest Disease Laboratory * (national laboratory)
	Kasama General Hospital	
	Kitwe Central Hospital	
	Ndola Central Hospital	
	Monze Mission Hospital	
	Nchanga South Hospital	
	Lusaka Trust Hospital	

Objective 6: Project management
Project management was comparatively smooth and was greatly facilitated by the work of the APUA chapters in each country, who paved the way for administrative, banking, ethical review, and logistical arrangements. In each country there was a part-time country manager. The first Zambia country manager, Dr Chileshe Lukwesa, left to pursue a Master's degree in microbiology in the UK. She was replaced by a colleague, Mr. Darlington Mwenya, who did an excellent job of picking up the reins with the assistance of Mrs. Edna Mulenga, the administrator. In Uganda the country manager, Dr. Florence Najjuka, had taken on many other activities and much of the project work fell to the pharmacist, Ms. Annette Naggayi, who ably managed both the administrative and the pharmacy sides of the Uganda project, and also tested nearly 700 drug samples using Minilab ® in the APUA project office in Kampala. In Zambia a part-time pharmacist, Mr. Billy Mweetwa, oversaw the pharmacy aspects. Two Boston University MPH interns provided crucial support for the data collection exercises in Uganda (Joe Novotny, MPH) and in Lusaka (Kate Cerwensky, MPH). A number of other interns assisted in Boston with data cleaning and analysis.

Unexpected results:

- The predominant role of malaria in driving antibiotic overuse was not previously documented in these settings, and presents an important target for intervention and education. The potential for saving nearly $1 million a year in antibiotics and antimalarials in Uganda, plus the reduction of antibiotic and antimalarial exposure, should place this issue high on the list of priority interventions.
- Underdosing of amoxicillin as documented in our data, combined with deterioration of product due to tropical storage conditions, pose a high risk that subtherapeutic doses are being administered – thus leading to unnecessary mortality and additional drug resistance to this vital drug.
- We were expecting a higher rate of counterfeit and substandard drugs in our sample. Based on our study, counterfeit antibiotics can be eliminated from consideration as a major driver of resistance in these two countries.

References:

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III. Accomplishments

- A review of published and unpublished data on antibiotic resistance was brought together for the first time in one document for each country. We also documented the scarcity, quality problems, and urban bias inherent in available data.

- Hospital microbiology laboratory assessments were performed at 29 laboratories in Uganda, and 17 laboratories in Zambia, outlining the steps needed to improve the situation with regard to microbiology laboratory strengthening. We identified a low-cost way for those few laboratories already conducting antibiotic susceptibility testing to be upgraded to form the nucleus of a network for monitoring of treatment effectiveness.

- Data were obtained on over 14,000 outpatient records by a team of 92 Ugandan medical students who examined and abstracted data from 10,172 outpatient records at 11 sites in Uganda, and a team of 16 Zambian pharmacy interns who examined and abstracted data from 4,218 outpatient records at 12 sites in Zambia, giving us a valuable cross-sectional dataset on use of antibiotics in the outpatient setting in the two countries. This dataset highlighted important shortcomings in the prescription and use of antibiotics in both countries, and the overlap of malaria and pneumonia diagnoses, particularly in Uganda.

- Interviews were carried out with formal health staff and attendants at drugshops and pharmacies, which highlighted their confusion in distinguishing between malaria and pneumonia, not only in young children but in older children and adults as well.

- Assessments of the pharmaceutical import and distribution system, focusing on antibiotics, was performed for both countries, identifying the main sources of antibiotics, brands, formulations available, and the prices at various types of outlet. Over 1,000 drug samples were collected and 800 submitted for quality testing, and the results indicate that with the exception of amoxicillin (see below), the quality of antibiotics in these countries is generally acceptable.

IV. Impact:

This project was the first such comprehensive assessment of drivers of antibiotic resistance and treatment of pneumonia in either Uganda or Zambia. It has contributed to a deeper understanding of the causes of ineffective treatment of pneumonia and enteric diseases, so that government and funding agencies can better target their interventions.

Three main findings of the project were met with both surprise and concern at country level:

1. The majority of the overdiagnosis of malaria in Uganda is in children over 5 and adults, not in young children as commonly believed. The project adds to the growing evidence of overdiagnosis of malaria and overprescription of antibiotics for people diagnosed with malaria particularly in Uganda, but also in Zambia; it made even clearer that there is a need to increase the of use diagnostics particularly the malaria RDTs, and for health staff to adhere to the findings in making treatment decisions.
2. In Zambia, there were very few cases of pneumonia recorded in the outpatient data. Clearly there is underdiagnosis of pneumonia and whether these cases are not being recognized as pneumonia or as severe respiratory infection, or perhaps are being treated outside of the formal health services, could not be determined. Improving recognition of pneumonia and ensuring appropriate treatment is an urgent intervention in Zambia.
3. Priority needs to be given to improving the storage and use of amoxicillin, the new recommended therapy for pneumonia if it is to remain a viable treatment for pneumonia. In Uganda, the underdosing of children 1-5 with amoxicillin was of concern to the medical staff who attended our stakeholders' meeting and they felt it was urgent to bring it up at the next meeting of the Pediatric Association of Uganda, and to inform the Government. Zambian data were not sufficient to determine whether the situation is similar there. The fact that amoxicillin is also subject to deterioration due to tropical storage conditions makes it all the more crucial that an adequate dose is provided. Improving the packaging and storage of amoxicillin should be given high priority.
4. The results of the drug quality testing seem to indicate that quality is overall acceptable in both public and private outlets, including drugshops, so with the caveats expressed above regarding amoxicillin, it seems safe to prioritize other interventions for the treatment of pneumonia and reduction of antibiotic resistance, and for the drug quality effort to focus on other drugs such as antimalarials and antiretrovirals.

5. Dissemination: We established contacts with a wide range of health professionals working on different aspects of acute respiratory and enteric pathogens and presented preliminary findings:

    a. In the two countries, presentations were made to the public health and medical community ("Grand Rounds" at University Teaching Hospital in Zambia; Public Lecture at Makerere University) at the start of the project; at Country Advisory Team meetings, and at Stakeholders Meetings in both countries.

    b. Dissemination efforts beyond the two countries have also been undertaken. Two posters were presented at ICAAC 2010, the ASM annual meeting; abstracts have been submitted for ICIUM 2011, Global Health Council, and ASTMH 2011. UNICEF hosted a meeting on "Priority Essential Medicines for Child Survival" in Copenhagen, in September 2010. The project PI Susan Foster attended for one day and made a brief presentation on the project findings to a group including WHO and UNICEF staff, and NGO representatives regarding levels of resistance, underdosing of amoxicillin, and quality problems with amoxicillin to a varied group who had largely not been aware of the issue of antibiotic resistance and were not factoring it into their discussions of medicines for children. A lively discussion ensued after her brief presentation. UNICEF posted the slides at http://www.unicef.org/supply/index_56401.html. Publications and presentations on the findings of the project are being prepared for further dissemination.

V. Lessons learned

The project period of 24 months was short for the scope of the project, especially given that we collected human subjects data and were thus required to obtain ethical committee review both in the US and in Zambia and Uganda. This impinged on the time available for training of data collectors, data collection, cleaning, analysis, writing up, and dissemination activities. In this regard the APUA chapters in both countries more than proved their worth – both chapters were invaluable in facilitating and expediting a quick start for activities, including ethical committee review. We would not have been able to deliver many of the products in the time frame without the assistance of the chapter members. We encountered hidden expenses which stretched the budget – bank transfer fees of $50 per transfer, fees for ethical review committee submissions, and a variety of other permits and fees. It was essential to have a full time person in the field to assist with administrative matters, and we were fortunate to have identified such persons in each country. The project provided many opportunities for internships for US-based students as well as for Ugandan and Zambian students, and they need very clear terms of reference and supervision in order to perform at their best. In retrospect, it would have been useful to establish a contract with each individual rather than with a more senior person who is responsible overall, so that each student is made aware of the expectations, pay levels, time frame, etc. before agreeing to take on the work.

VI. Challenges

The project time frame was short for the ambitious nature of the project. Obtaining ethical clearance from all relevant ethical review boards (Tufts University IRB, three sequential boards in Uganda, and one in Zambia) took nearly eight months of a 24 month project. Fieldwork could not begin until all approvals had been obtained.

Some elements of the proposal could not be completed due to lack of disaggregated pharmaceutical import and consumption data on antibiotics. No pharmaceutical data older than 2004 were available in either country, thus precluding a comparison of older antibiotic procurement and consumption patterns with newer data. Regarding antibiotic consumption in children, the suggested Defined Daily Doses (DDD) Protocols are not currently available for use with children. In view of this limitation, we agreed that instead of trying to devise a way to calculate a new pediatric DDD, we would emphasize learning what antibiotics were prescribed, the usual daily dose (dose/kg) and days of therapy to provide useful information on under/over dosing. Data on dosing were not available in the Zambia outpatient records, so we relied primarily on the Uganda data which did provide enough dosing information to calculate mean doses.

Drug testing issues: In both countries we endeavored to work with the national drug regulatory authorities. In Zambia, the Pharmaceutical Regulatory Agency (PRA) was very enthusiastic to work with us and promised to test the samples using Minilab ® technology which they already possessed. However they have only one analyst for the needs of the entire country and it became clear that they would not complete the testing before the end of the project, and before many of the samples would have expired. Accordingly we transported the remaining untested samples to our APUA office in Uganda where they were tested by the Uganda project pharmacist. In Uganda, we tried very hard to work with the National Drug Authority, attended multiple meetings, produced several documents and letters, and made several presentations to various NDA staff on the project. However we continued to encounter conflicting advice, delaying tactics, and no cooperation, so on the advice of local experts and chapter members, ultimately we decided to continue without NDA participation and made alternative plans.

In order to keep costs low and also to build expertise and capacity, we used students, interns, and community members to collect and enter data wherever possible. While this did allow the collection of large amounts of data and created greater awareness of the issues surrounding treatment of pneumonia, malaria and antibiotic resistance, it was not without its problems. In Uganda we used the Community Based Education and Service (COBES) program of the College of Health Sciences of Makerere University to collect and enter data from the 11 sites around the country. This program places medical, dental, and pharmacy students (most of whom have an urban, middle-class background) at health centers and hospitals around the country for 3-5 weeks each year of their training. The COBES Director played the role of “gatekeeper” and controlled access to the students, but although he is nominally the

director of the program, he was misinformed about the dates of the field work. Their planned departure was a month earlier than we had been told, which meant that they departed for data collection only one day after ethical approval had been obtained. Their training program also was more rushed that would be ideal. In Zambia the data were collected by pharmacy interns and pharmacists from the University Teaching Hospital, some of whom found the work was harder than they expected and decided that they were underpaid, so they delayed transmitting the data and returning the equipment. However despite these issues, the use of students and interns was overall both an effective way to collect and enter a large amount of data from a wide geographical area, and a way to develop capacity. In Uganda, about 10% of the COBES students stated that they would like to continue to carry out research as part of their future career. The community workers in Lusaka were very enthusiastic and although they had no prior health training, they responded very positively to the training we provided and carried out the work very well. For some it was their first experience of receiving a paycheck.

The presentation of a complex project set in two developing countries to the Tufts University School of Medicine's Institutional Review Board posed some challenges. The IRB found the project too complex and confusing, and required us to divide the proposal into two (one for the informal sector / drugsellers survey and the rest in a separate proposal) but the combined proposal had already been submitted to the Ugandan and Zambian boards as one project. This led to some confusion at country level and at the Tufts IRB about which official documents related to which proposal. The Tufts IRB also refused to approve the use of a short form which would have collected limited data (age, sex, main complaint, and drug(s) sold) from informal sector drugsllers on ten sequential sales of antibiotics they made, even though it had already been approved by ethical review boards in both countries. The condition they imposed was that each of the drugsellers would obtain written informed consent from each client to whom they made a sale of antibiotics, which was not possible under the circumstances. The time was too short to try to argue the case, find an acceptable alternative procedure, and resubmit the proposal in time for the data collection to be completed, so this form was dropped from the project.

VII. Sustainability

Although the project was not designed to be a freestanding intervention which would continue after the project period, there are indications that the impact will continue beyond the project end. There is a sense of urgency at country level to implement measures to address the problems identified through the project. Several of the local professionals involved in the project have already obtained further small amounts of funding to continue research on some of the issues identified. There is considerable interest in obtaining funding to implement interventions to address the key findings of the project in both countries.

The project managed to test drug samples very cheaply for about $12, and about 2/3 of this cost is the initial investment in the Minilab ® (equipment, reagents and reference samples) which can be used for many more tests. The testing of suspensions and syrups was much more expensive, at $290 per sample, and could not be done using Minilab ® in-country.

VIII. Other sources of project support

Reasonably priced (below market rate) office space in both countries was made available by fellow NGOs -- in Uganda from the Mulago-Mbarara Joint AIDS Program (MJAP) project and in Zambia from Management Sciences for Health (MSH) Zambia. Free space for training of community workers and a facilitator to help select, train and supervise the workers was provided by Hope House /Kara Counseling in Lusaka; the workers themselves worked for very low pay. Particularly the COBES students of Makerere University College of Health Sciences in Uganda worked very long hours to complete the task of abstracting the data and entering it into the computer for very low reimbursement.

IX. Budget variances

Although there were variances over and under budget in excess of 10% for the overall project period in several categories, these did not cause any adverse impact on the project.

1. **Travel costs** were above the total project budget by 15% due to rises in air fares to Africa; several visits that were longer than planned due to the exigencies of the field work; and several additional trips were made to keep the project on track and on time. Several US-based interns also traveled to Africa to assist with field data collection which was not initially provided for in the budget. In addition,

non-refundable air tickets had been purchased for Advisory Board members to travel to Boston which could not be refunded or reissued when the meeting was canceled because of the volcanic ash in Europe.

2. **Supplies:** Overall project supplies were under budget by 14%, because we did not purchase laboratory supplies as initially planned. Other supplies were underspent when fewer members were able to attend the rescheduled Advisory Board meeting. Supply costs for Country Advisory Team meetings and the final Stakeholder Meetings were also less than projected when attendance was lower than expected, due to many competing meetings and time constraints on the part of the participants.
3. **Sub-contract for testing:** The subcontract for testing was 64% below the budget, because Uganda's National Drug Authority did not agree to perform testing. As reported in Year 1, $15,000 was reallocated to equipment to purchase a Minilab ® for testing of samples in Uganda. Additional drug quality testing of liquid formulations is nearing completion by MEDS Laboratory in Nairobi, and contract negotiations took longer to complete than anticipated.
4. **Equipment:** Equipment costs were above the project budget by 175% (total expenditure of $20,323 instead of $7,400). Changes in the plans for drug quality testing were necessitated when the Uganda National Drug Authority did not reply to our request to carry out drug quality testing after multiple approaches, and other arrangements had to be made. We did not use tablet computers as originally planned when we found out how fragile they are for fieldwork and how costly programming our questionnaires for tablet use would be. Instead we used cheap refurbished laptop computers at $400 each purchased in the US. In addition, fieldwork was done at seven more sites in Uganda than initially planned, so seven additional laptops were purchased for these sites.