Access, excess and ethics

- towards a model for rational use of a new antibiotic -
Table of Contents
Abstract.........................................................................................................................................................4
Background..................................................................................................................................................4
Aim.........................................................................................................................................................4
Methods..................................................................................................................................................4
Results....................................................................................................................................................4
Conclusions............................................................................................................................................4
Swedish summary // Sammanfattning......................................................................................................5
Abbreviations..........................................................................................................................................6
Operational definitions.............................................................................................................................6
Background................................................................................................................................................8
Antibiotic resistance..................................................................................................................................8
Selection pressure....................................................................................................................................8
The burden of resistance........................................................................................................................10
Drug distribution and use in LMICs..........................................................................................................11
Distribution of antibiotics in LMICs.........................................................................................................12
Problem statement....................................................................................................................................13
Aim..........................................................................................................................................................14
Specific objectives....................................................................................................................................14
Method I - Ethic review.............................................................................................................................15
Results I - The ethical considerations of restricting antibiotic availability........................................15
Access to antibiotics as a public good.................................................................................................16
Balancing rights of present and future patients.................................................................................17
Method II – Distribution of ACTs..........................................................................................................19
Results II – Distribution of ACTs..........................................................................................................19
Resistance to antimalarials....................................................................................................................20
Access and resistance............................................................................................................................21
Surveillance.............................................................................................................................................21
Access to quality ACTs........................................................................................................................22
Laboratory diagnosis............................................................................................................................23
Method III - Interview survey................................................................................................................25
Sampling & Participants........................................................................................................................25
Data collection & instruments..............................................................................................................25
Data analysis............................................................................................................................................26
Theoretical framework..........................................................................................................................27
Ethical considerations...........................................................................................................................27
Result III - Interview survey................................................................................................................28
Barriers to access with rational use of antibiotics...............................................................................30
Drivers of resistance.............................................................................................................................30
Patients..................................................................................................................................................31
Public sector...........................................................................................................................................32
Private sector drug sellers.....................................................................................................................33
Governance.............................................................................................................................................33
Balancing access and excess...............................................................................................................34
Access vs rational use...........................................................................................................................34
Restricting availability..........................................................................................................................35
A systemwide intervention...................................................................................................................36
Governance.............................................................................................................................................37
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
<td>38</td>
</tr>
<tr>
<td>Service delivery</td>
<td>39</td>
</tr>
<tr>
<td>Human resources</td>
<td>39</td>
</tr>
<tr>
<td>Medicines and technologies</td>
<td>40</td>
</tr>
<tr>
<td>Finance</td>
<td>41</td>
</tr>
<tr>
<td>People</td>
<td>42</td>
</tr>
<tr>
<td>Learning from other communicable diseases</td>
<td>42</td>
</tr>
<tr>
<td>Malaria and ACTs</td>
<td>42</td>
</tr>
<tr>
<td>H1N1 and Tamiflu</td>
<td>43</td>
</tr>
<tr>
<td>Discussion</td>
<td>44</td>
</tr>
<tr>
<td>Principal findings</td>
<td>44</td>
</tr>
<tr>
<td>Access vs restriction</td>
<td>44</td>
</tr>
<tr>
<td>Ethical aspects of restriction</td>
<td>46</td>
</tr>
<tr>
<td>A systems thinking approach to access with rational use</td>
<td>47</td>
</tr>
<tr>
<td>Governance and Health information systems</td>
<td>48</td>
</tr>
<tr>
<td>Service delivery &amp; Human resources</td>
<td>51</td>
</tr>
<tr>
<td>Medicines and technology</td>
<td>52</td>
</tr>
<tr>
<td>People</td>
<td>53</td>
</tr>
<tr>
<td>Finance</td>
<td>54</td>
</tr>
<tr>
<td>Methodological considerations</td>
<td>55</td>
</tr>
<tr>
<td>Conclusions and recommendations</td>
<td>56</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>58</td>
</tr>
<tr>
<td>References</td>
<td>58</td>
</tr>
<tr>
<td>Appendixes</td>
<td>65</td>
</tr>
<tr>
<td>Appendix I: Scenario letter</td>
<td>65</td>
</tr>
<tr>
<td>Appendix II: Interview guide</td>
<td>66</td>
</tr>
</tbody>
</table>
Abstract

Background
The increasing antibiotic resistance is a global threat to healthcare as we know it and much attention has been given to new business models for research and development on new antibiotics. However, there is no model of distribution ready for a new antibiotic that balances access against excessive or inappropriate use in rural settings in low and middle income countries (LMICs) where the burden of communicable diseases is high and access to quality healthcare is low.

Aim
The purpose of this thesis is to explore how a new antibiotic could be distributed and regulated in LMICs to balance access to patients in poor and rural settings against the risk of excessive and inappropriate use.

Methods
Departing from a hypothetical scenario of rising antibiotic resistance among pneumococci, 11 stakeholders in the health systems of various LMICs were interviewed one-on-one to give their view on how a new effective antibiotic should be distributed to balance access against the risk of irrational use and emerging resistance. Transcripts were subjected to thematic 'framework' analysis. The results were discussed in relation to the ethical debate on antibiotic restriction as well as the experiences from distributing antimalarials in LMICs, also reviewed for this thesis.

Results
The analysis resulted in four main themes: *barriers to access with rational use of antibiotics, balancing access and excess, a systemwide intervention* and *learning from other communicable diseases*.

Conclusions
Barriers to access with rational use exist at all levels of the health system. In the short run access can only be given at the expense of rational use. Looking ahead, a systems thinking approach will be needed to design a distribution model for a new antibiotic that achieves access with rational use. In pursuit of this, strengthening monitoring and surveillance of resistance patterns and antibiotic usage seems crucial.
Swedish summary // Sammanfattning


Syftet med den här uppsatsen har varit att utforska hur en sådan distributionsmodell kan se ut eller vilka egenskaper den bör ha. 11 aktörer ur hälsosystemen i ett flertal låg- och medelinkomstländer har intervjuats om hur de tycker att en distributionsmodell bäst balanserar tillgång mot risken för överanvändning. Utgångspunkten har varit ett hypotetiskt scenario där ett nytt bredspektrumantibiotikum når kliniken och marknaden i en situation där pneumokocker, den vanligaste bakterien vid lunginflammation, blivit resistent mot gängse behandling. Litteraturöversikter skrev också om de etiska aspekterna på att undanhålla antibiotika från en patient liksom distributionen av malarialäkemedel i låg- och medelinkomstländer. Dessa översikter var tillsammans med intervjuerna underlaget till uppsatsens diskussionsdel.

Den kvalitativa analysen av de inspelade och utskrivna intervjuerna visar att det finns många hinder mot antibiotikatillgång med rationell användning på flera ställen och nivåer i hälsosystemet. Detta gör att man kortsiktigt måste hitta en avvägning och acceptera antingen överanvändning eller bristande tillgång i vissa miljöer. Långsiktigt bör ett systemvetenskapligt angreppssätt användas när distributionen planeras för att förekomma oönskade konsekvenser av föreslagna åtgärder. Emedan det är svårt att prioritera bland alla förslag till förbättringar i hälsosystemet som föreslogs av intervjuobjekten verkar övervakning och kartläggning av resistensutveckling och antibiotikaanvändning vara centrande för att kunna säkerställa rationell användning utan att minska tillgången.
Abbreviations

| ACT | Artemisinin combination therapy |
| ADDO | Accredited drug dispensing outlet |
| AMFm | Affordable medicines facility for malaria |
| AMR | Antimicrobial resistance |
| DRA | Drug regulatory authority |
| GDP | Gross domestic product |
| HIC | High income country |
| HGT | Horizontal gene transfer |
| LMIC | Low and middle income countries |
| MoH | Ministry of health |
| NMCP | National malaria containment program |
| OoP | Out-of-pocket (expenditure) |
| OTC | Over the counter |
| PMI | The President's malaria initiative |
| RDT | Rapid diagnostic test (for malaria) |
| WHO | World Health Organization |

Operational definitions

Access is used in this thesis referring only to the ability to obtain quality health technologies when and where they are needed. The reason for this unusually narrow definition is that the aim of the thesis as a whole is to balance access to antibiotics against the risk of inappropriate or excessive use. A definition of access including rational use would thus ignore the tension between getting the product out to the patient and making sure that it is used appropriately.

Rational use in this thesis follows the WHO's definition that “patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community”. (1) This concerns the prescribing, dispensing and consumption of antibiotics and generally assumes that the affected stakeholders refrain from irrational use as this one of the key issues in this thesis.

A health system is defined by the WHO as a national system that “consists of all organizations, people and actions whose primary intent is to promote, restore or maintain health”. (2) This wide
definition enables health system researchers and policy makers to think outside the public healthcare sector when designing interventions.

*Dispenser* is someone who gives out medicines, usually demanding money in return. The dispensing can occur in accordance with or in violation to the regulations. A dispenser can among other things be an informal drug shop, a public health worker or a pharmacy.

*Prescriber* refers to any type of health worker eligible to issue a valid prescription for a medicine. It can be a doctor but also a nurse or a community health worker.
Background

Antibiotic resistance

The discovery of penicillin by Alexander Fleming in 1928 and the subsequent mass production started in the 1940s are among the most influential events in the history of medicine. Together with other classes of antibiotics penicillin further diminished the mortality in bacterial infections already lessened by improvements in living conditions and sanitation. Apart from, for the time being, closing the book on infectious diseases access to effective antibiotics was also vital for several other medical achievements of the 20th century such as aggressive chemotherapy, organ transplantations and treatment of severe burn injuries. Antibiotics are thus incorporated into many fields of medicine today. All those fields in addition to the treatment of infectious diseases are threatened by the rise of antibiotic resistant bacteria.

Selection pressure

Antibiotic resistance among bacteria can be classified as intrinsic or acquired. Intrinsic resistance might require consideration when choosing antibiotic therapy but it is stable over time and does not, like acquired resistance, threaten healthcare practices and outcomes. Acquired resistance can be defined as reduced susceptibility to an antibiotic among bacteria when compared to the wild type of the same species. Clinically, this is not an absolute but a continuum where the minimal inhibitory concentration (MIC), the level of antibiotic where the bacteria stop growing, gets ever higher.

There are four ways through which a previously susceptible bacteria can acquire resistance: mutation, transformation, conjugation and transduction, the latter three being examples of horizontal gene transfer (HGT). HGT is the transfer of genetic material within the same generation of bacteria and may occur within and between species. Even if resistance is acquired through HGT it will be transferred vertically, inherited, when the bacteria replicates.

Antibiotic usage selects for existing resistant bacteria by enriching their representation in the larger population or give rise to resistance among a species of previously susceptible bacteria. When an infected patient takes an antibiotic the selection pressure is applied not only to the infecting pathogen but to all bacteria exposed including patient's the normal flora. Gaining resistance generally comes at the expense of bacterial fitness (growth rate and virulence). (3)

A conclusion drawn from this is that once the antibiotic pressure disappears from the
environment, in this case a patient's body, the resistant bacteria, losing their only advantage, should gradually give way to fitter susceptible strains. While this has been shown, the time between taking the antibiotic course and clearing resistant strains of the normal flora has been several years.(4) There are also examples where new compensatory mutations allow resistant bacteria to regain lost fitness.(5)

Under the influence of antibiotic concentrations lower than the MIC for a given bacteria and an antibiotic, the advantage of resistance has a much smaller impact on relative fitness. This requires resistant strains to maintain most of their fitness for survival regardless of level of resistance since the susceptible strains will continue to grow but at a decreased rate. Sub-MIC-concentrations have been shown to provide a selection pressure for existing resistant bacteria but also de novo mutations associated with only a small loss of fitness and often but not always a weak resistance.(6) Thus lethal and non-lethal (sub-MIC) antibiotic concentrations can select for resistance both through enriching the population of existing resistant bacteria or through the emerging of new ones through de novo mutations or HGT.

Any antibiotic consumption means applying a selection pressure even if the use of the drug is indicated and the patient fully recovers. A whole course might eliminate the infection fully but resistance can be selected for in the normal flora.(4) Not completing an entire course but adhering to the full daily dose might not clear the infecting bacteria and allow strains gaining resistance to survive but the selection pressure on the normal flora is of a shorter duration than with the full course. Under-dosing through poor compliance or sub-standard antibiotics may increase the length of infection and with it the time the bacteria are exposed to selection pressure. Sub-MIC-concentrations also selects for resistant bacteria with fitness more similar to the susceptible wild type.(6) The result is similar to what happens due to the non-lethal concentrations in the environment due to poor cleaning of sewage water or factory and hospital drains. After all, a large proportion of most antibiotics ingested by both humans and animals is excreted in feces and urine still in their active form.(7) Environmental bacteria developing resistance to antibiotics may then transfer that resistance to bacteria of clinical significance for humans through HGT.(6)

To conclude, all antibiotic use among humans and animals is applying a selection pressure for the development of new resistant bacteria or enrichment of the existing population of resistant bacteria. This can affect the infecting pathogen, the normal flora of the patient or the environmental bacteria through excretion. Because of this, there is an urgent need to eliminate unnecessary use of antibiotics.
The use of antibiotics in animal husbandry is not the subject of this thesis and thus it will not be elaborated on further.

The burden of resistance

Resistance to penicillin among previously susceptible bacteria was discovered early on and Fleming himself warned the scientific community against irresponsible use of penicillin for fear of emerging resistance in his Nobel lecture in 1945.\(^{(8)}\) Since then cases of resistance against most antibiotics has been confirmed in almost all bacteria in some time and place.\(^{(7)}\) Resistance arises and spreads where antibiotics are used and a correlation between level of resistance to a certain antibiotic and the amount used by patients have been seen at both hospital and community level.\(^{(9,10)}\)

The burden of antibiotic resistance is hard to quantify but estimates are high. In Europe alone the number of deaths attributed to antibiotic resistance in 2007 was estimated to 25 100, the number of extra hospital days to 2 536 000 and the overall cost to 1 534 100 000 EUR.\(^{(11)}\) There are no estimates of cost or lives lost at country level in Africa or Asia but the level of antibiotic use without prescription is high.\(^{(12,13)}\) In more limited studies, such as one study from Tanzania, resistance to older generations of previously effective antibiotics among Gram-negative bacteria has been shown to be high and antibiotic resistance is a strong predictor for mortality when having blood stream infections.\(^{(14)}\) Multidrug-resistant tuberculosis is claiming 150 000 lives annually and 440 000 new cases emerge.\(^{(15)}\) Gonorrhea is getting harder to treat and first line drugs are failing in various countries with low and middle income countries (LMICs) in south-east Asia being hit especially hard.\(^{(16,17)}\)

Resistance to antibiotics is not a national issue. People travel more than ever and pathogens travel with them. The infamous NDM-1 carbapenemase gene carrying resistance to broad spectrum carbapenem antibiotics, believed to have emerged among Klebsiella Pneumoniae in India in 2009 has already spread to neighboring countries, Europe and South America.\(^{(18–20)}\)

As resistance to earlier generation antibiotics emerges and spreads patients will have to move on to newer more expensive antibiotics with the economic implications that follow for the already strained health systems in LMICs. Even now, due to a high proportion of out of pocket spending on healthcare a quarter of the population of Pakistan can not afford full course treatments with first line antibiotics for pneumonia, shigella or gonorrhea (amoxicillin, azithromycin,
Gabriel Heyman
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(21) Adding to this, the antibiotic research pipeline is looking grim, with only five antibacterial agents with new targets or mechanisms of action (thus prolonging the time until resistance emerges) that have reached clinical trials. (11) In short, new antibiotics are not being developed at the same rate that we are, in some areas, losing the efficacy of the old ones. The need for new business models for financing development of new antibiotics has been brought up in several recent articles. (22,23) However, distribution, dispensing and use of antibiotics must be addressed as well to handle the new antibiotics when they do reach clinical practice. (24)

**Drug distribution and use in LMICs**

The division of countries into developing and developed ones is being replaced by a new one. The world bank has picked arbitrary cut off points in gross national product levels to divide countries into low, middle and high income countries. Thus the taxonomy does not specifically address level of development, state of the health system or public health in the country, but crude income. (25) However, with sinking GDP generally comes the following: higher child mortality rates, shorter life span, higher burden of communicable diseases, less access to basic healthcare with skilled personnel and quality medicines, greater health inequities and less spending on healthcare a higher proportion of which is out-of-pocket (OoP) further increasing the inequities. (25,26)

Drug distribution with rational use and access to quality medicines becomes the responsibility of several stakeholders. As explained by the United States pharmacopeia drug quality and information program: *Government leaders and policy makers* set the rules and boundaries of the distribution system by formulating policy and legislation. They also institute a *drug regulatory authority (DRA)* and support it with legislation as well as the financial and human resources necessary to fulfill its assignment. The DRA is generally responsible for approving medicinal products for use within the country, licensing pharmaceutical establishments along the distribution chain, surveilling these establishments and when need be revoke their licenses or recall defective products. The DRA also oversee the marketing of medicines. *Manufacturers of pharmaceutical products* are responsible to acquire a license from the DRA and adhere to rules and guidelines for that license. They are also responsible for the quality of their products as well as only distributing them to DRA-licensed establishments and keep shipped merchandise traceable throughout the supply chain. *Procurement organizations, wholesalers and distributors*, both public and private, share a similar responsibility to manufacturers of holding a license and adhering to the rules, but in
addition all imported medicines must be approved by the DRA. *Prescribing medical professionals* diagnose the patient to the best of their knowledge and if need be write a prescription for a drug according to or in violation of existing guidelines, if such guidelines exist. *Dispensers*, such as pharmacies and drug sellers provide the patient with pharmaceuticals, hopefully demanding proper prescriptions. *Patients* are ultimately responsible for their own compliance of dispensed therapies as well as their care seeking behavior choosing only licensed retailers and not demanding restricted medicines without presenting a prescription. *Donors* and *non-governmental organizations (NGO)* play a supporting role in relation to the other stakeholders in the system. (27)

In reality the system fails to a varying degree in achieving access with rational use of medicines as stakeholders falls short of living up to their responsibilities. Drug regulatory bodies are often weak and even where rules exists they are not always fully enforced. Less than half of all medicines dispensed in LMICs are taken in adherence to clinical guidelines and instructions on how to take medicines only reach patients in half of all dispensing events. (28)

While some drugs are dispensed and used excessively others, so called controlled drugs, are kept under such tight restrictions that even patients who need them can not access them. Controlled drugs are substances that can be abused such as opiates and psychotropic drugs. For fear of abuse, leakage and black market sales, these drugs are regulated harder than any others and can only be prescribed by doctors in most LMICs. In addition only specially licensed pharmacies and health workers are allowed to handle these medicines making the available distribution channels few. Access to these drugs is recognized as a big problem for patients worldwide compromising among other things the quality of palliative cancer care. (29,30) At the other side of the spectrum antimalarials have been very loosely regulated and made available through all possible distribution channels and dispensing outlets in an effort to decrease the high mortality from malaria in rural and poor communities. (31)

**Distribution of antibiotics in LMICs**

Antibiotics, like other drugs, are subject to irrational use, but in the case of antibiotics one patient's behavior can affect another patient's future access to effective antibiotics. This makes the irrational use a matter of common concern. Antibiotics are often prescribed for viral illnesses such as diarrhea and the common cold. (28) Self-medication with antibiotics is also common and over-the-counter (OtC) sales to patients without valid prescriptions are happening worldwide at a large scale. (12,13,32) In India incomplete courses are sold to poor patients and knowledge on how antibiotic
resistance relates to antibiotic use is lacking among pharmacists regularly dispensing antibiotics OtC.(13,33)

Adding to this, access is also a problem. Looking at pneumonia, a major cause of child mortality in LMICs, one third of all children with pneumonia do not receive antibiotics with poor and rural patients being worst off.(34) If the prescription only-status is to be enforced on antibiotics, there is a concern that poor and rural populations will be deprived of access to antibiotics similar to what has happened with the controlled drugs, with health equities worsening further.(35)

In 2001, the WHO released its Global Strategy for Containment of Antimicrobial resistance. It does not specifically target bacterial infections or antibiotic resistance but it tackles antimicrobial resistance as one big issue. Barriers to sustainable use are identified and various interventions to overcome them are suggested. The strategy guide then goes on to suggest “prioritized areas” for each antimicrobial resistance issue. The high prioritized areas often encompass a great proportion of health system stakeholders (community, patients, dispensers, prescribers, national government and the pharmaceutical industry) making it difficult to go through with everything on a limited national health budget. The strategy does not specifically addresses LMICs nor does it discuss how a new antibiotic could be regulated and distributed differently from older agents.(24)

**Problem statement**

The widespread irrational, excessive use and abuse of antibiotics have a considerable impact on antibiotic resistance. Restricting antibiotics to the providers where adherence to guidelines and regulations can be ensured may mean restricting access for the populations most burdened by communicable diseases where quality healthcare is scarce. When distributing an antibiotic in such a setting access to medicines must be balanced against the risk of irrational use.

Without solving this, the therapeutic life length of any new antibiotic will be brief. There is no system of antibiotic distribution that addresses and minimizes the excessive use while achieving access to antibiotics in remote locations where medical services are scarce.
Aim

The aim of this thesis is to present how a future antibiotic could be regulated and distributed in order to achieve a high level of rational use while at the same time providing access to antibiotics for patients where healthcare resources are scarce.

Specific objectives

1. Write a literature review of the ethical aspects on restriction of antibiotics.
2. Write a descriptive review on how the distribution of antimalarials of the last generation (ACTs) has been designed to achieve wide access and how the risk of emerging resistance has been addressed.
3. Perform an interview survey with key informants from relevant stakeholder groups in the health systems of LMICs on the subject of distribution of a future antibiotic.
Method I - Ethic review

The purpose of this review was to summarize the ethical discussions on imposing restrictions on antibiotic use to prevent resistance from emerging. Articles were obtained through searches for “ethics” and “antibiotics” in PubMed and Google Scholar filtering out non-english articles, articles older than ten years and articles that were not accessible through the Uppsala University Library's online licenses and subscriptions. Articles discussing specific instances of antibiotic use such as treatment of pneumonia among demented patients and presumptive treatment of Lyme's disease were also ruled out. Only five articles remained. Furthermore, a bioethicist was consulted to find more articles. This generated four suggested articles and book chapters, two of which were already included in the review from the database searches mentioned above. Newspaper articles and WHO bulletins were obtained through simple Google searches.

Results I - The ethical considerations of restricting antibiotic availability

“Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X's death? Why Mr. X whose negligent use of penicillin changed the nature of the microbe.” - Alexander Fleming(8)

The hypothetical anecdote above was told by Fleming in his Nobel prize lecture in 1945, mainly to illustrate the importance of using sufficient doses when taking an antibiotic treatment. The anecdote is still relevant today as incomplete antibiotic therapies or insufficient doses are major contributors to the rising burden of antibiotic resistance worldwide. It also highlights the fact that one's decision to consume an antibiotic does not just have an impact on one's own economy and health but also, potentially, the future health of those around us through emerging resistance as a result of antibiotic use. We are, simply put, all in this together. The issue of antibiotic resistance is thus not only a medical one but an ethical one as well where rights of different patients are to be balanced against one another.
Access to antibiotics as a public good

The issue of excessive use of antibiotics as a cause of worsening antibiotic resistance is sometimes discussed as a free market failure or analyzed with economical models. The tragedy of the commons is probably the economical or ethical concept most widely used to describe the nature of the problem of antibiotic resistance. Introduced by ecologist Garret Hardin in 1968, the tragedy of the commons is the depletion of a common resource through rational utility-maximizing actions performed by rational actors, even though they all as a group will suffer in the long run for losing the resource. Applied to antibiotics the tragedy explains why a patient may find it rational to take antibiotics even for a minor infection despite the threat of emerging antibiotic resistance. The risk of emerging resistance (loss of utility) is shared among the entire population and the fraction of it that is carried by this particular patient is small while the chance of a quick recovery may be big.

Battin et al question the current applicability of the tragedy of the commons on the issue of antibiotic resistance. They argue that it is not rational for patients to take antibiotics in a situation where their condition do not pose a serious threat to their health. This is because the patients would risk acquiring a resistant normal flora of bacteria due from consuming an antibiotic treatment. Antibiotic resistance is not something that will arise in the distant future at a point when society has consumed a critical amount of antibiotics, but something that might happen in the normal flora of every individual patient taking antibiotics today. This may happen without them knowing until years later when they get a serious infection that can not be treated with antibiotics. Presented with this risk and thus being given a significantly larger part of the negative consequences of antibiotic use most patients would, in the view of Battin et al, choose to refrain from excessive use of antibiotics.

Selgelid argues that freedom from infectious diseases (partly by access to effective antibiotics) should be treated as a public good, meaning something that should be kept available for the benefit of everyone since no one can be excluded from them and one persons consumption (of freedom from disease) does not come at the expense of someone else's. He states that antibiotics can not and should not be treated as a commodity to be handled by the free market, because of externalities. The use or misuse of antibiotics brings negative externalities, unfavorable outcomes not factored into the market price for a treatment of antibiotics, in this case selection for resistant bacteria. Selgelid goes on to describe how a free market of antibiotics brings under-consumption by the poor not being able to afford full courses of treatment and over-consumption by the wealthy, both resulting in even more resistant bacteria to the misfortune of all as well as bad present
therapeutic outcomes for the poor. He therefore concludes that only those who actually need it should, poor and rich alike, be given access to antibiotics for both egalitarian/just and utilitarian reasons.(40)

Battin et al have suggested a model to internalize the negative externalities by adding a fee to every treatment of antibiotic sold making the consumer bear the cost. The revenues from the fee would be donated to research projects aimed at finding new antibiotics.(37)

Millar expands on the differing access to effective antibiotics within the current generation due to financial differences. He does not agree with Selgelid that under-consumption of antibiotics by the poor is a cause of antibiotic resistance apart from some specific examples such as tuberculosis. Instead Millar argues that worldwide equal access to antibiotics on the level of a high income country (HIC) would as a general rule induce resistance quicker. Thus, according to Millar, when it comes to access to effective antibiotics, intragenerational justice will come at the expense of intergenerational justice or sustainability. He concludes that equal access to effective antibiotics worldwide can only be combined with sustainability if there are multinational treaties on antibiotic restriction and other determinants for communicable diseases such as vaccines and sanitation are improved.(41)

**Balancing rights of present and future patients**

Leibovici et al have analyzed the practice of giving less than maximum empirical antibiotic treatment to save the broader antibiotics for when they are absolutely necessary, even though there is a risk that the infecting pathogen is resistant to given antibiotics. The authors have used the four principles of biomedical ethics (beneficence, non-maleficence, autonomy and justice) and cost-effectiveness deriving the latter from the ethical theory of utilitarianism. When applying the four principles the conflict between respecting the autonomy of the individual patient (wanting broadest possible antibiotics and thus risking to drive the resistance further) and maintaining justice (as in equal access to antibiotics) between this patient and future ones is evident. The same goes for the responsibility that the treatment habits today does not harm future patients thus violating the non-maleficence principle. Leibovici et al conclude that individual autonomy must be overruled in favor of the principles of justice and non-maleficence in the case of antibiotics. This will balance the rights of different generations and also reach the most cost-effective outcome in their view. They also use the ethical construct of Rawl's veil of ignorance to illustrate this claim further saying that people not knowing what group of patients they would belong to would favor recognizing the rights
of future patients' access to antibiotics by restricting the use of broad spectrum antibiotics in some situations. To include those rights in each clinical situation with present patients, Leibovici et al argue that decisions should as much as possible be made in a collective way through centrally written guidelines on antibiotic choice.(42)

In a similar argument, Millar applies Scanlon's contractualism to the issue of antibiotic use and its restriction meaning that antibiotic use is justifiable only if it is based upon principles that no one could reasonably object to. Milliar arrives at the conclusion that the suffering of future patients infected with antibiotic-resistant bacteria must be taken into account when regulating antibiotics today. He goes on to state that antibiotics should only be used when there is “a substantial risk of irretrievable harm” due to infection that can be ameliorated through the use of an antibiotic. This eliminates various antibiotic uses such as animal growth promotion but also the use of antibiotics among patients who will not benefit from treatment such as moribund intensive-care patients. He also discusses the possibility of restricting the use of antibiotics for infections that might be self-limiting and in the case where they are not, the patient will have time to revisit the prescriber before suffering irretrievable harm such as uncomplicated cystitis.(43)

When an immediate risk of irretrievable serious harm presents itself such as a patient in septic chock, Leibovici et al suggest an exception from equalizing present and future patients. This rescue rule would allow for a very broad antibiotic treatment to a present patient regardless of how it would affect future patients.(42)
Method II – Distribution of ACTs

The subject of this review is the distribution of artemisinin combination therapies (ACTs) and how it has been organized to maximize access to quality medicines in remote rural areas while addressing the threat of emerging parasite resistance relating in part to excessive use of ACTs.

Primary sources of information were a key informant interview with a Swedish malaria researcher and the following WHO publications on the issue: World Malaria Report 2011, Global Report on Antimalarial Drug Efficacy and Drug Resistance, Global Plan for Artemisinin Resistance Containment and Guidelines for the Treatment of Malaria 2nd edition. To further assess the results of different interventions various PubMed searches were made.

Results II – Distribution of ACTs

As a global health challenge, the struggle against malaria and resistance to antimalarials have a lot in common with that against bacterial infections and antibiotic resistance. Being communicable diseases, poor countries assume the highest burden of both bacterial diseases and malaria. Insufficient access to medicines is a great source of mortality and morbidity in both cases but at the same time, resistance arise under drug pressure which means that access must be balanced against excessive or inappropriate use of antibiotics or antimalarials. (25,31,34,44)

In 2010 malaria caused approximately 655 000 deaths worldwide out of 216 million cases. 91% of the deaths of which a striking majority (86%) were children under 5 years of age, occurred in Africa. These numbers, while depressing are in fact an improvement from 10 years ago when the number of deaths was estimated to be 755 000 and the total amount of cases was 223 million. (31) This progress is now threatened by emerging resistance to the latest generation of antimalarials, artemisinin-derivates.

The millennium development goal of reducing the mortality and morbidity from malaria is an international venture with stakeholders from a wide range of sectors such as national malaria control programs (NMCP), NGOs, WHO and pharmaceutical companies. The work rests on four legs: vector control, chemo-prevention for especially vulnerable groups, accurate diagnosis through rapid diagnostic tests (RDTs) or microscopy and timely treatment with appropriate antimalarials given parasite species and resistance pattern. (31,45) The last two legs are of importance for this thesis as the other legs have no counterpart in the issue of antibiotic distribution and use in the face
of increasing resistance.

**Resistance to antimalarials**

Büttiens and D’Alessandro have written a thorough historical review of big scale malaria eradication efforts and the emergence of resistance to antimalarials. In it they describe how WHO launched its Global Malaria Eradication Campaign in 1955. Early attempts at achieving good coverage of antimalarials included monthly mass drug administrations and even antimalarials added to the cooking salts. Due to differences in salt uptake among the population the levels of antimalarials differed creating a widespread drug pressure of different amount that is believed to have selected for resistance.\(^{46}\) Since then resistance among plasmodium falciparum, the deadliest of the malaria protozoae, has emerged against all antimalarials used up until the introduction of artemisinin in western medicine in the 90s although patterns of resistance are different depending on region.\(^{47}\) The resistance against older antimalarials has generally emerged in south-east Asia in Cambodia and Thailand and spread from there across the southern hemisphere through Africa.\(^{48}\)

Artemisinin is originally derived from the plant *Artemisia annua* and has been used against malaria in China for centuries. In the face of rising resistance to existing antimalarials artemisinin derivates were introduced into clinical practice worldwide in the 90s. Artemisinin derivates have a short half-life and need to be taken for seven days to cure uncomplicated malaria. The therapeutic course is shorter if they are combined with another antimalarial, a partner-drug with longer half-life to form artemisinin combination therapies (ACTs). This type of combination also decreases the risk of resistance developing, which is why WHO strongly advises against the use of artemisinin mono therapies.\(^{48,49}\) Resistance to artemisinin among P. falciparum, for now in the form of prolonged clearing time of parasites in the blood, has been confirmed in the area where resistance to older antimalarials first emerged, on the border between Thailand and Cambodia.\(^{44}\)

P falciparum resistance to antimalarials is caused by arbitrary genetic mutations that proves to be an advantage under drug pressure. Thus the genes of resistance are inherited, transferred vertically to the next generation of protozoa similar to the way resistant bacteria passes its genes on to the next generation.\(^{44}\) There is no known horizontal transfer of genes of resistance between protozoa within or between species. While there is no normal flora of P. falciparum in humans that is exposed to drug pressure with unnecessary treatments, there is, in endemic areas, a risk of being reinfected through a new mosquito bite while still having sub-therapeutic levels of the artemisinin partner-drug in circulation from an earlier treatment and thus creating a selection for resistance to
the artemisinin partner-drug which has a longer half-life than the artemisinin derivates. (48)

**Access and resistance**

According to the WHO's global plan for artemisinin resistance containment there are three main drivers of artemisinin resistance among *P. falciparum* relating to drug distribution and use (48):

1. Lack of surveillance on therapeutic efficacy prevents the discovery of resistance and thus prevents the timely initiation of counter-resistant measures.
2. Lack of access to quality ACTs cause patients to use artemisinin mono therapies or substandard ACTs increasing the parasite clearing time and with it the risk of emerging resistance.
3. Dispensing of medicines without performing or following the results of laboratory diagnosis such as rapid diagnostic tests or microscopy results in excessive use of ACTs adding to total parasite exposure to artemisinin derivates.

**Surveillance**

Resistance among malaria protozoae can be tested for in three ways: therapeutic efficacy, in vitro and genetic markers of resistance. Therapeutic efficacy, measuring in vivo resistance, is the one most commonly used for surveillance. (50) Patients with confirmed malaria diagnosis return on the third day of treatment and new blood samples are taken and examined with microscopy to determine parasite clearance. Parasite clearance time however, is influenced by patient-dependent factors, mainly age and immunity. (48) If clearance times are prolonged in vitro tests can be performed, by-passing the many confounders of parasite clearance time, and confirm resistance to the antimalarial in question. In addition to these two methods, genetic testing can be done confirming the existence of known resistance genes, but this requires the availability of PCR equipment. (50)

WHO recommends that therapeutic efficacy tests are to be done at special sentinel sites within a country burdened with malaria every two years. The results are used in global surveillance on malaria resistance and national guidelines on first- and second line treatments can be adjusted according to the results so as to keep effective drugs as recommended treatment. (48) However, out of 92 countries endemic for *P. falciparum*, only 31 are performing studies on therapeutic efficacy resulting insufficient knowledge on rising tolerance to artemisinin-derivates or their partner-drugs both on a national and a global basis. The forming of resistance monitoring networks that allow
countries to collaborate on setting up sentinel sites and training staff as well as sharing data is one suggestion by WHO for overcoming this issue. (51)

Access to quality ACTs

To make ACTs affordable for health systems and patients in LMICs others have assumed part of the cost of the drugs. In 1999 the pharmaceutical company Novartis introduced an ACT consisting of artemether/lumefantrin. They sold the medicine under two different brand names. Riamet was to be sold for maximum profit all over the world as is the usual custom when pharmaceutical patents are still valid, but the pharmacologically identical Coartem would be sold without a profit to malaria-endemic countries through the WHO. This initiative had generated 250 million treatments in 2009. (52)

The proportion spent on malaria control by national governments varies greatly between countries. Endemic countries generally spend less per person at risk than countries that are approaching malaria eradication and as a whole, domestic spending on malaria control is less than international spending. National governments generally spends less than 10% of their anti-malarial budget on treatments. (31)

Disbursements to malaria endemic countries by international donor organizations amounted to US$ 2 billion in 2011 with the Global Fund being the biggest donor, followed by the american presidents malaria initiative (PMI), british department for international development (DFID) and the World Bank. 20% of these funds went into providing treatment with antimalarials, mainly ACTs. (31) The Affordable Medicines Facility for malaria (AMFm), managed by the Global Fund, is exclusively devoted to providing ACTs and rapid diagnostic tests (RDTs) at affordable prices for both public and private sector buyers. They do this by negotiating with manufacturers for a reduced price and then paying a substantial part of that price. The idea is that prices will remain low to the end user regardless of wether that person seeks care in the private or public sector. (53)

Because of great variation of care seeking behavior many distribution and dispensing channels have been used to ensure access to ACTs even in remote rural locations. The medication is not regulated as prescription-only products and over the counter (OtC) sales has even been targeted by the affordable medicines facility for malaria (AMFm). By subsidizing ACT courses to allow lower prices in the private sector the intention was to grant access to quality ACTs for those seeking care in the private sector while displacing the cheap less effective and potentially resistance-driving alternatives such as artemisinin-based mono therapies. (53,54) Minimizing the price gap in this way
in a pilot program encompassing several endemic countries did lead to a big increase in courses of ACTs sold in the private sector. However compliance has been shown to be an issue with OtC sales of ACTs, both by patients taking the full course to quickly and not completing it on time.

This indicates that simply ensuring the availability to the drug at the point of care may not be enough.

Another thing that has been tried where conventional healthcare services are not available are community case management (CCM) of malaria, which has been used with some success. A significant drop (but not elimination) of progression to severe malaria and mortality has been seen. Members of the community are trained in basic diagnosing of malaria, basically a child running a fever and recently with the addition of a positive RDT. They are also taught how to properly consume a course of antimalarial treatment, which they dispense to their patients when need be.

The diagnostic accuracy for malaria by briefly trained community case workers has been low as fever among children can have many causes other than malaria. The same goes for more professionally trained health workers when proper diagnostic technology such as microscopy or RDTs is not used.

Presumptive treatment of malaria comes with two great drawbacks when treating patients not suffering from malaria. One is the cost of many unnecessary ACTs and the other is the risk of missing the actual disease that might demand another treatment.

Laboratory diagnosis

In order to reduce excessive dispensing of ACTs causing both risk of resistance and unnecessary spending, WHO recommends that all patients with fever should be subjected to diagnostic testing with rapid diagnostic tests (RDTs) or microscopy before receiving antimalarials. RDTs have a clear advantage over microscopy because it can be used in settings where the human resources or lab equipment to use microscopy are not available.

Even though RDTs are sensitive, specific and affordable implementation of testing and adherence to the results has not been successful or at least slow. While doubled in sub-saharan Africa, testing of feverish children in the public sector is still only at 40% with the private sector lagging even further behind. In Cambodia, testing of suspected cases of malaria has been similarly low in both public and private sector and adherence to positive test results (dispensing of any antimalarial) was 42-61%. Adherence to negative results, not prescribing or dispensing unnecessary antimalarials in the case of a negative RDT, is also an important measurement for this thesis since withholding therapy might prevent resistance development among both malaria...
parasites and bacteria. There are some success stories such as Senegal where the proportion of feverish patients receiving ACTs in the public sector dropped from 72.9% to 31.5%, roughly the equivalent of confirmed malaria cases from other studies.(61) Then there are worse cases such as Ghana where studies have shown that ACT treatment of patients with fever and negative RDTs or microscopic slides remains as high as 50%.(58) There is no known reason as to why some NMCPs succeed in their upscaling of RDTs and some do not. Focus group interviews with Cameroonian health workers have shown that the RDTs were looked upon as a placebo for the patient to assure him or her that the clinical diagnosis was correct and that presumptive treatment often persisted even in the face of a negative RDT to show the patient that malaria and fear of it indeed was taken seriously by the provider.(62) Summing up, RDTs, while strong clinical tools have yet to become the success stories they were expected to be.
Method III - Interview survey

Sampling & Participants

Sampling for the participants was purposive to ensure knowledge on the health systems from several LMICs. The following stakeholder groups were represented: clinicians, policy/regulatory, HIC donor agencies, NGOs, WHO and pharmaceutical industry. 19 such stakeholders were identified through the extended professional networks of ReAct and the study's supervisor, a professor of global health. Of the 19 presumptive participants emailed, 13 accepted to be included in the interview survey. One additional participant was added to the list following the suggestion of another participant belonging to the same NGO. Three participants were indisposed at the date of the interview and declined to answer further propositions for new dates and were thus not interviewed. The final eleven participants showed a pluralism in respect to nationality, stakeholder group and profession as seen in Table 1. Stakeholder 1 and 2 belong to the same NGO and were interviewed together. The other participants are not known to work together. Not one stakeholder emailed actually declined to take part in the survey. Those who did not answer the initial email were both from Europe and Africa. They belonged to all the stakeholder groups and among them were DRA and WHO officials.

Data collection & instruments

A letter (Appendix I) emailed to participants prior to the interview outlined the purpose of the survey as well as describing a scenario of rising airway pathogen resistance to existing treatments in a LMIC. Two scenarios for the distribution of a new and for the time being effective antibiotic were included as well. One of these scenarios was derived from the descriptive review of the strategies used in the distribution of ACTs. The other was inspired by the restrained model used for controlled drugs and was included as an opposite to the first one as they both were to serve as basis for the discussion on antibiotic distribution and use. A semistructured interview guide (Appendix II) was created to cover issues of sustainability and equity in antibiotic distribution and use with the two scenarios as a starting point.
Table 1 – Participants

<table>
<thead>
<tr>
<th>#</th>
<th>Profession</th>
<th>Operational Setting</th>
<th>Stakeholder Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Leader of access to ACTs project</td>
<td>International</td>
<td>NGO</td>
</tr>
<tr>
<td>2</td>
<td>Malaria NGO official</td>
<td>International</td>
<td>NGO</td>
</tr>
<tr>
<td>3</td>
<td>Health NGO coordinator</td>
<td>Tanzania</td>
<td>NGO</td>
</tr>
<tr>
<td>4</td>
<td>Health advisor on development research</td>
<td>International</td>
<td>HIC donor agency</td>
</tr>
<tr>
<td>5</td>
<td>MD</td>
<td>Uganda</td>
<td>Clinician</td>
</tr>
<tr>
<td>6</td>
<td>MoH official</td>
<td>Ghana</td>
<td>Clinician</td>
</tr>
<tr>
<td>7</td>
<td>Project coordinator</td>
<td>Pakistan</td>
<td>NGO</td>
</tr>
<tr>
<td>8</td>
<td>Pediatrician</td>
<td>Uganda</td>
<td>Clinician</td>
</tr>
<tr>
<td>9</td>
<td>CEO, Pharmaceutical company</td>
<td>Uganda</td>
<td>Industry</td>
</tr>
<tr>
<td>10</td>
<td>AMR Task force member, MoH</td>
<td>India</td>
<td>Government</td>
</tr>
<tr>
<td>11</td>
<td>Head of research, Pharmaceutical company</td>
<td>India</td>
<td>Industry</td>
</tr>
</tbody>
</table>

Interviews were carried out in person, over the telephone and with Skype. The interviews were held in English and lasted for 25 to 45 minutes. One interview was a group call with two participants and the other were carried out one on one. With the verbal consent of the participants, the interviews were recorded for later transcription by the researcher. Each respondent was promised confidentiality and that his or her name was not to be published within any presentation of the results of the survey.

Small changes in the interview guide were made as the survey moved along. Less emphasis was put on the general questions on antibiotic resistance due to time constraints and more emphasis was put on necessary health system strengthening efforts, this being a reoccurring theme in all of the initial interviews.

**Data analysis**

The audio recordings from the interviews were transcribed verbatim by the researcher. The qualitative method of analysis used was 'Framework' analysis as described by Ritchie & Spencer. (63) The transcripts were then read through for familiarization. Based on research notes from the familiarization process an initial thematic framework of seven main themes was created. The interview transcripts were then read through once more and indexed according to the thematic
framework using qualitative software TAMS Analyzer. The attitudes of the respondents towards different key themes and concepts were abstracted, summarized and put into charts to construct an easily read overview of the results. Upon review of the thematic map and the chart the initial seven themes were rearranged into four main themes with several sub-themes to better suit the research question. The new thematic framework was used to index the transcripts, again using TAMS Analyzer. The sub-themes were kept as sub-headings in the results section.

**Theoretical framework**

The theoretical framework used in this thesis is that of the health system as it is presented by de Savigny and Adam in their WHO report *Systems Thinking for health systems strengthening* (Figure 1). In this model, the health system is constructed by six subsystems, here referred to as service delivery, human resources, information, medicines and technologies, financing and governance. *People* are added as a seventh subsystem. In this thesis people only refers to the community as present or future patients. Health workers are addressed under human resources.

All the subsystems are vital in generating health systems outcomes and must be considered when designing bigger interventions. In addition, there are connections through which the different subsystems are dependent on and influence each other sometimes resulting in unexpected outcomes. To address this, interventions should be designed in close contact with stakeholders from all subsystems.(64)

**Ethical considerations**

All participants were informed of the study's purpose by an email prior to the interviews. They were also promised confidentiality. The participants gave verbal consent to take part in the study as well as to be recorded over Skype.
Result III - Interview survey

An initial thematic framework was devised after coding all ten transcripts. It consisted of seven themes: causes of antibiotic resistance, access & excess, restriction, awareness, monitoring & surveillance, health systems strengthening and miscellaneous. Upon review of the themes and the research notes four new themes were constructed to encompass the original seven while addressing the research question better. The final four themes were barriers to access with rational use of antibiotics, balancing access and excess, a systemwide intervention and learning from other communicable diseases. Each of the themes had their own sub-themes as shown in Table 2.
Table 2 – Final thematic framework

<table>
<thead>
<tr>
<th>Theme</th>
<th>Sub-theme</th>
</tr>
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<tbody>
<tr>
<td>Barriers to access with rational use</td>
<td>Drivers of resistance</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
</tr>
<tr>
<td></td>
<td>Public sector</td>
</tr>
<tr>
<td></td>
<td>Private Sector drug sellers</td>
</tr>
<tr>
<td></td>
<td>Governance</td>
</tr>
<tr>
<td>Balancing access and excess</td>
<td>Access vs rational use</td>
</tr>
<tr>
<td></td>
<td>Restricting availability</td>
</tr>
<tr>
<td>A systemwide intervention</td>
<td>Governance</td>
</tr>
<tr>
<td></td>
<td>Information</td>
</tr>
<tr>
<td></td>
<td>Service delivery</td>
</tr>
<tr>
<td></td>
<td>Human resources</td>
</tr>
<tr>
<td></td>
<td>Medicines and technologies</td>
</tr>
<tr>
<td></td>
<td>Finance</td>
</tr>
<tr>
<td></td>
<td>People</td>
</tr>
<tr>
<td>Learning from other communicable diseases</td>
<td>Malaria and ACTs</td>
</tr>
<tr>
<td></td>
<td>H1N1 and Tamiflu</td>
</tr>
</tbody>
</table>

*Barriers to access with rational use* explains how, in the view of the participants, we have ended up with a considerable amount of antibiotic resistance as well as why it is so difficult to achieve rational, sustainable distribution and use of antibiotics. The theme encompasses patient and provider behavior, shortcomings of the health systems of LMICs and the lack of governmental awareness and engagement.

*Balancing access and excess* explores the present day tension between maintaining rational use of an antibiotic and ensuring access for those in need. Because of the barriers brought up in the first theme, using the distribution channels available in remote rural districts will grant access to patients at the expense of rational use and the sustainability of the antibiotic in question. Different levels of suggested restriction, the role of private sector drug dispensers and ethical standpoints are presented in this theme.

*A systemwide intervention* is about the future of antibiotic distribution in LMICs. This theme expands on the previous theme's one-dimensional tension between access and rational use using
health system strengthening efforts to improve access while maintaining a given level of rational use and vice versa. The suggestions are ordered under the six subsystems of the health system as presented by Adam and De Savigny.(64)

Learning from other communicable diseases summarizes the participants' statements concerning drug distribution and use in other communicable diseases and what, if anything, can be learned from them.

**Barriers to access with rational use of antibiotics**

Some participants cited the failure of the medical industry to develop new antibiotics as an important reason for the current shortage of effective antibiotics in the face of rising resistance. The research for new antibiotics is not the subject of this thesis and that topic was left without further discussion.

Barriers to access with rational use of antibiotics were covered from two angles. One was discussing the stakeholder behaviors and health system properties that are believed to have caused the current level of resistance. The other was identifying potential obstacles when the participants suggested solutions to the interview scenario.

**Drivers of resistance**

Excessive use of antibiotics, insufficient doses and incomplete courses of therapy were perceived as the big drivers of resistance. Under-dosing was mainly considered a habit due to strained financial situation for the patient or lack of understanding of how to take antibiotics. Counterfeit and substandard drugs were also mentioned as a source of sub-therapeutic antibiotic doses.

“I mean the entire duration of treatment is not taken by the patient. So if half of the duration or half dosages are taken then again that will lead to drug selection pressure or increase in resistance.” - #10 Indian AMR task force member

“Then sometimes we have a lot of adulterated drugs, some drugs come into the market and they somewhat miss being uh regulated the national drug authority […] and you find that in reality none of those drugs in the combination that they are supposed to be within that drug. So you find people ingesting drugs which are probably under-dosed...” - #8 Ugandan pediatrician
Patients

There was a widely shared position that the end user must be considered to achieve a sustainable model of antibiotic distribution. Knowledge on antibiotics, financial situation and care seeking behavior were all identified as important aspects of the patients' situation in understanding why antibiotics were misused. Lack of antibiotic awareness was seen as a barrier throughout the entire supply chain as well as at all levels of the health system. With OtC sales of antibiotics in parts of the private sector (see below) and insufficient patient knowledge on the function of antibiotics and the dynamics of resistance inadequate use will continue to be a problem.

“I think if you ask an ordinary person about malaria, they can tell you that, you know, there are malaria that are resistant to so-and-so so you must use this, but I don't think people really can say: oh, there is resistance to antibiotic...an ordinary person I think in the street. I'm not sure that...and I'm not sure that they understand the magnitude of the problem” - #3 Tanzanian health NGO coordinator

“...the knowledge of how to take these antibiotics and the fact that you've got to finish a course etc is also really pretty unknown amongst...particularly if you go out to the villages...you know where our care is very very poor, really.[...] you know they will go and buy two capsules of amoxicillin in case of...they got a soar throat for instance or a chest infection. And of course, that's gonna do you more harm than good.” - #9 CEO at Ugandan pharmaceutical company

The poor and/or rural populations that were the subject of discussion in many of the interviews may under-consume antibiotics for financial reasons. Those who can not afford an entire antibiotic course were believed to buy part of it hoping for some boost in their or their loved ones' recovery from infection. Those who can not afford a consultation might by-pass the physician and go straight to the (often private) drug shop or pharmacy and consult the staff on what medication to buy, thus receiving a lower level of expertise as well as consulting someone who sell drugs for profit.

“depending upon the country you're in [...] a lot of help seeking is in the private sector...and very often is directly to the pharmacy or to the drug shop because people cannot afford to pay the prescriber.” - #2 Malaria NGO official

“access is denied in terms of maybe of finances for example: Somebody cannot afford the full course, they take a bit of it. You take a part of it. Now that's a huge selection for antibiotic resistance.” - #3 Tanzanian health NGO worker

Ensuring access to effective antibiotics for poor patients and those living in remote rural areas as
well as ending their economizing of antibiotics was given much thought when suggesting new models of distribution (see below under A systemwide intervention).

Public sector

The public sector healthcare system was held in higher regard than the private sector not having the conflicting economical interests. As such it was believed to have more drug dispensing procedures. However, the public sector was also viewed as a system with many shortcomings obstructing the rational use of antibiotics and other drugs both within its own facilities and through pushing disappointed patients away to private drug shops. These shortcomings exist at different levels of the system and affect the supply and stocking of antibiotics, availability of skilled health workers and the diagnostic tools at their disposal. Different types of misuse of antibiotics were believed to occur. To be on the safe side, public health workers may offer antibiotics for non-bacterial diseases. Stockouts or long waiting times may result in insufficient access which may lead to future care seeking in the private sector or dispensing of unnecessary broad spectrum antibiotics that are available in the public sector at that time.

“the public sector is also to be blamed because...either there is not enough clinically trained people but even where there are, the system for quality control to ensure adherence to standards are inexistent so many people don't follow guidelines. There is almost no proper supervision system [...] there are no diagnostic facilities or they are not adequate. So we end up giving antibiotics.” - #5 Ugandan MD

“in primary care public facilities, maybe second, third generation antibiotics are available and some of the primary, first generation antibiotics which should be there are not available and availability varies there depending upon the supply of antibiotics in the medical stores. So the inappropriate availability of antibiotics may lead to, or it leads to inappropriate use of antibiotics.” - #10 Indian AMR task force member

There is also concern about professional awareness on antibiotic resistance among both private and public doctors. Some participants raise the issue of insufficient education on antibiotics while others are concerned that doctors get their information on antibiotics from unreliable sources such as market representatives from the pharmaceutical companies.

“the doctors' education on antibiotics is through the five minute meeting with the man...with the sales representative.” - #11 Indian head of research at pharmaceutical company
Private sector drug sellers

Private sector pharmacies and drug shops were acknowledged in succeeding where the public sector has failed in providing access to medicines in remote and rural locations. But they were also seen as dubious partners putting profit before public health by selling antibiotics over the counter to anyone who would ask regardless of whether they had a prescription or not. Poorly trained staff, unable to properly diagnose the patients, were also believed to sell incomplete courses of therapy or wrong doses. There were contradictory opinions on the intentions of the private sector drug sellers.

“I wish we could use the private sector in a way that provides access and protects antibiotic 'cause they're there. They are in the village. Might be a small place, but they are there.” - #3 Tanzanian health NGO coordinator

“[help seeking] very often is directly to the pharmacy or to the drug shop because people cannot afford to pay the prescriber. So a lot of this is being driven by...by pharmacies who are not necessarily...staffed by people with the right skills, who are handing out any medication including antibiotics. And, and I think that's one of the biggest concerns as well.” - #2 Malaria NGO official

The term “private sector”, although often referring to pharmacies and drug shops is not very specific and might encompass a wide range of providers from an informal drug seller in the market to a properly staffed pharmacy in the city.

Governance

Although antibiotics are prescription-only by law in many of the countries discussed in the survey, weak drug surveillance systems and regulatory institutions were seen as major barriers to enforcing those rules.

“the major problem is...mismanagement, mainly at deliver of the state in terms of...in case of Uganda, in terms of...rules and the ability to implement and operationalize the rules and regulation.” - #5 Ugandan MD

“They [the drug regulatory authority] have recently increased their man power but still they don't have that much man power to restrict the use [of antibiotics].” - #10 Indian AMR task force member

Antibiotic resistance was perceived as a significant but mostly silent issue. Insufficient mapping and record keeping of resistant bacteria keeps governments from properly assessing the situation. Regrettably lack of antibiotic awareness at government level was seen as a major obstacle for political will to attack the resistance problem head on. This leaves antibiotic resistance as a sort of
second class health issue not getting the financial support or political attention of more firmly established public health challenges.

“unfortunately all diseases except HIV/AIDS and malaria suffer here because the government focuses almost totally on those [...] most of the funds go towards you know...three diseases: malaria, HIV/AIDS and TB of course.” - #9 Ugandan CEO at pharmaceutical company

**Balancing access and excess**

How one patient's use of antibiotics may increase resistance and affect another patient's access to antibiotics is what makes them unique as drugs. When rationing and restricting antibiotics within a health system ethical considerations as well as medical research and data must be taken into account. This means that everybody must find their own middle ground between access and restriction.

**Access vs rational use**

The scenario of access to subsidized antibiotics without prescriptions was dismissed as a final solution by all the participants as abuse would be wide and resistance would emerge quickly with huge increases in mortality and treatment costs.

“When it's free without a prescription then...I would fear that people may take it as just another paracetamol.” - #3 Tanzanian health NGO coordinator

The tension between delivering equal access to antibiotics and keeping the dispensing and use rational in a flawed health system was evident in all the interviews. The distribution channels and providers that were seen as able to handle an antibiotic in a responsible and sustainable way simply were not accessible for many rural and poor populations and thus in the short run access could only be given at the expense of rational use and the life length of an antibiotic.

“one worry that is always at the back of your mind is misuse of the drug and then you get antibiotic resistance occurring and then that requires you to purchase something that is much more expensive and all that. But at the same time you want to save lives.” - #8 Ugandan pediatrician

“...it's so much easy to say these things from a city or a developed country perspective. From a perspective of an undeveloped nor...or developing country access...any restriction affects access.” - #11 Indian head of research at pharmaceutical company

No common middle ground existed when balancing antibiotic access for current patients against future ones. Some were very firm about access to effective medicines being a fundamental human
right while others argued decisively for prioritizing rational use. Most participants were in favor of starting out with a looser restriction while working towards a stronger more sustainable system of distribution.

“in the initial term, we need to make these drugs available. It is ethical and also a human right” - #5 Ugandan MD

“we can not get up and say: the new antimicrobial or antibacterial should...should be available to lowest end when we don't have a structure out there to support the management of the product.”” - #6 Ghanian MoH official

Restricting availability

In search of an acceptable combination of access and rational use of antibiotics restricting the use of a new antibiotic at different levels of the referral system was discussed. The suggestions varied from restriction of the drug within infectious disease departments at hospitals with prescriptions being countersigned by the head of department down to community health workers. To address the poor health infrastructure in rural settings some participants would suggest different restrictions in different places, combining a tight restriction in the cities with community health workers dispensing the drug in rural settings where no functional health facility was within reach.

“Like in India, we have national rural health mission and through that we have many uh health centers and trained people or trained health worker [...] for India I can say that this medicine or this antibiotic can be distributed through that channel in the rural areas but in urban areas it should be in restricted or at designated retail pharmacies and for tertiary care public or private sector facilities.”” - #10 Indian AMR task force member

The role of private hospitals within these regulated distribution models was seen as mostly similar to public sector facilities. General practitioners, pharmacies and drug sellers however were singled out as actors that due to insufficient knowledge on the issue and economical incentives to over-prescribe/-dispense and were given special supervision. Some participants ruled them out as a distributors and providers all together. Licensing or accreditation of pharmacies were discussed and the importance of surveillance to ensure adherence to rules and guidelines was stressed on several occasions.

“[drug regulatory authorities] chose a certain standard of private sector partner or distributor or drug seller to step up to the plate to be engaged in this pilot study that we did. What's powerful about that? You get to raise the standard of a private distributor, a private retailer, by saying 'you're
gonna be using a super drug, but we need to know what your minimum standards are. You’ll be monitored and supervised”” - #1 Leader of ACT-access project at malaria NGO

“I strongly feel that the private sector should be allowed to sell only to the hospitals, no selling through the pharmacy....which also will affect their commercial value but the...if the...if the government can subsidize the rate then the hospitals can charge...they can charge the hospitals slightly higher amounts but no selling to the pharmacy.” - #11 Indian head of research at pharmaceutical company

Public trust in the health system's institutions was discussed in relation to restricting the availability of the new antibiotic. The predictions of change in trust were dependent on properties of the health system not necessary present everywhere. One view was that trust would be unaffected or even improved by restriction if there was public awareness of the importance of antibiotic conservation. Some stressed that trust would remain the same if weaker previous generations of antibiotics were still widely available at lesser outlets as an OtC or GP's prescription first line. Finally one participant expressed concern that restricting an antibiotic within public facilities would risk corrupting public health workers and damage patients' trust in their intentions.

“I think that you know that [trust will decrease] as soon as you...take an important drug and ration it in that way. […] There'll also be trust issues related to if you have a genuine stockout of the drug will people will actually believe that it's not a stockout but that the drug is being withheld because of cost or...or eh preference for other patients or something like that and so there would be huge pressure that would come on...public sector providers.” - #4 Health advisor on development research at a HIC's donor agency

**A systemwide intervention**

In pursuit of a model of antibiotic distribution that balances access against excess a wide scope of suggestions for policy and intervention design were suggested. These suggestions were seen as important in overcoming the barriers from the first theme and supporting the various types of restriction and regulation presented in the second theme. Some of the ideas could be categorized as system strengthening efforts while others were only expected to have an impact on antibiotic access and rational use alone. Implementing these suggestions are associated with varying costs and difficulties but given the dynamic nature of antibiotics and resistance all were expected to be worthwhile in the long run.

“...also distributing it, the storage, the rational use of it and regulation that comes and so it is a
whole system approach that must be required to deal with the issue of any new agent that will be found.” - #6 Ghanian MoH official
“...with these drugs we must not only invest in the commodity we must also invest in the system...” - #5 Ugandan MD

One thing all the suggestions had in common is that they aimed to improve the conditions for antibiotic distribution making a certain level of restriction more accessible or raising the rationality of prescription and use while maintaining the same level of access thus offering a brighter future than the current stand-off between rational use and access to effective antibiotics. The suggestions are presented below sorted into the six subsystems of the health system as described by Don De Savigny with people added as a seventh subsystem covering the patients.(64) While the use of an existing theoretical framework as sub-themes in a thematic analysis might seem somewhat unorthodox, this categorization does not rule out any suggestions made by the participants. In return, the categorization enables the inclusion of these findings into the existing discussion on systems thinking in health system research.

**Governance**

There was a strong consensus that the distribution of new antibiotic must be regulated to prevent excessive use. The different types of restriction brought up are listed under the previous theme. Regulation in both the public or private sector needs to be supported by controlling authorities so that both prescribers and dispensers of antibiotics can be rewarded for judicious use and reprimanded for irresponsible use. Drug regulatory authorities were seen as weak institutions, in some countries able to effectively oversee the restriction of one or two new drugs but not all later generations of antibiotics. Therefore strengthening drug regulatory authorities and the systems for monitoring of prescribing and dispensing habits were regarded as a crucial steps toward controlled distribution and use of antibiotics.

“If you could strengthen that, then even the private sector knowing that there is a monitoring system that's going to kind of insure, in a way that the antibiotics I am entrusted with are used in a proper manner...dispensed to and prescribed in a proper manner. Then that I think would be my suggestion. Investing...invest more into strengthening a system that has also got some control and monitoring mechanism.” - #3 Tanzanian health NGO coordinator

Raising governmental awareness and engagement in antibiotic resistance as an emerging threat comes with several benefits according to some participants. By raising governmental awareness on
the issue it was expected to land on the agenda of the highest level of government much like HIV or malaria in some countries and in turn achieving faster implementation of new regulations than if it was the responsibility of the ministry of health alone. How that awareness was to be raised was not evident from the interviews.

“most of our countries...they move the HIV management issues into the office of the president of the republic. I think that it is about time we begin to look at antibacterial resistance issues in a similar function [...] why do we want to handle it in a very small corner of our countries and begin to think that we will achieve the same results?” - #6 Ghanian MoH official

Recognizing the global implications of antibiotic resistance international agreements on drug regulation were requested by several participants to ensure the longest therapeutic life possible for the new antibiotic. To keep track of resistant bacteria and raise awareness at the international level one participant suggested instituting a UN Rapporteur on antimicrobial resistance. This would also illustrate how antibiotic resistance has the potential to be an important issue of development for LMICs in the coming decade.

Information

Improved health information systems was requested mainly for two purposes. The first was to keep records of prescribing and dispensing practices of the new antibiotic in order to make both public and private providers accountable to rules and guidelines. The increased pharmacovigilance from governance is in large dependent upon this type of data.

“[Drug leakage] will happen, unless it's not just a restriction. It's a restriction that goes with accountability. It's a restriction meaning that you, a private pharmacy for example, and if you're allowed to have a thousand doses of that antibiotic, okay? Unlike, if we have a system that says ’at the end account for me how you use those a thousand doses. I need to see sensitivity tests for example or lab tests or...okay, what is it that led you to use those a thousand?'” - #3 Tanzanian health NGO coordinator

The other purpose was to gather data on antibiotic resistance to properly assess the problem at hand. Given the presumed cost of deploying a later generation antibiotic, treatment failure can not be taken to be caused by resistant bacteria at face value. Cost was mentioned both as increased drug pressure and as money spent by the government subsidizing health care in the public sector or the patients paying out of pocket at private providers.

“I think step one has to be to improve...the...through straight forward research done quickly about
what level of antibiotic resistance we really have. And, and is this related to the drug or is it related to compliance by the patient or is it related to the quality of the...drugs that are available?” - #4

Health advisor on development research at a HIC’s donor agency

Service delivery

Access to antibiotics in a rational fashion in remote places played a key part in the scenario drawn up for the interviews. As the patient population most frequently discussed in the interviews were poor the public sector was seen as the most important provider of health care. Community health workers while generally viewed as an important point of care for village people were not regarded as a stand alone solution but the widest reaching lowest level of the public referral system. Participants requested a stronger more accessible referral system and stressed that lower levels must function well to provide a link between the community and the hospitals. The public referral system needs to be kept strong to prevent equity issues given the higher prices of private providers. Failing first level facilities with stockouts of effective antibiotics were also feared to lead to blocking up of hospitals at higher level. Because of this, strengthening the community level at the expense of the referral system would in fact risk creating a weaker health system.

“There should be a combination of strategies so in my view...community case management as a standard alone is quite not a very good strategy. It needs to be integrated within a broader context.” - #5 Ugandan MD

“if the referral system doesn't work [...] then the system fails because either A) I will go out and look for it in the private sector where I can get it or I will by-pass the referral system and go on to the next level where of course, the different drugs are there, I clog the system. [...] So you would need a good referral system.” - #3 Tanzanian health NGO coordinator

Human resources

The public healthcare workforce was seen as lacking in both numbers and knowledge. It is a potential corner stone in the controlled distribution and use though, both as competent resistance-aware village health workers and nurses, pharmacists and doctors manning the first level health facilities. A well functioning public health facility system was seen as vital for increasing care seeking in public sector and decreasing it in the informal private sector. If the MoH wants to increase the staff in rural districts, educating more doctors might not suffice as life in the village comes with a set of drawbacks over the cities that would call for higher salaries.
“the longer term solution would be to for government to train more doctors and pharmacists and incentivize them to be able to go to the rural areas. And the only way you can do that is to pay them good salaries. Because you know for most middle class ugandans with children, would want to stay in near the big cities because that's where the good schools are. That's where you got a decent life...” - #9 CEO at Ugandan pharmaceutical company

Participants stressed the importance of health worker training on antibiotic use and resistance regardless of profession, preferably before the new antibiotic is to be released into the system. Professional awareness about antibiotic resistance was believed to decrease drug leakage at the first health facility level.

“I think [leakage] would be less if awareness is increased that in this particular antibiotic is not...to be used because it is not so...means if used inappropriately it may cause some adverse effects.” - #10 Indian AMR task force member

Across the board participants also recommended increased training for health workers in properly diagnosing pneumonia or recognizing the danger signs and referring to higher level of healthcare system where both antibiotics and infections could be handled with better outcomes.

**Medicines and technologies**

Investing in the supply systems to prevent further stockouts was seen as an important part in ensuring the public sector's delivery of access to antibiotics where and when they are needed.

“I would...advise this government...to invest more on their supply chain to the facilities where they know things will be done properly.” - #3 Tanzanian health NGO coordinator

Relatively simple interventions to reduce leakage of drugs between the factory and the patient were brought up by participants drawing on previous experience. Marking the capsules intended to be sold exclusively in the public sector would make prosecuting private actors buying these drugs on the black market easy. Prepackaging entire course of antibiotics before distribution was brought up to address the dispensing or purchasing of incomplete therapies.

“...all our tablets have also got to be embossed 'UG' on the capsules and on the tablets. And so, anybody found selling a product that has UG on it, it's completely illegal [...] The leakage is...I can't say it's stopped because I don't know but I know that it has dramatically reduced.” - #9 CEO at Ugandan pharmaceutical company

Diagnosing bacterial disease particularly isolating bacterial pneumonia from viral infections is a difficult task at any point of care. To improve the diagnostic certainty at health facilities and
community level more research for an easy-to-use diagnostic tool was suggested. Governmental subsidies for each individual test was expected to speed up the implementation process when such a test was made available. Until that time the use of diagnostic algorithm was regarded as a feasible way to ensure some kind of rationality among health worker dispensing habits.

“It's got to be...point of care diagnostics which are cheap. [...] Or at least it should be subsidized by the government. For example TB, the gene expert uh is 30 dollars a test but the government has now made it available at less than uh...nine dollars and I heard it's going down to three dollars.” - #11 Indian head of research at pharmaceutical company

Finance

The financial subsystem was only brought up in regard to the potentially steep price for a new antibiotic being an overpowering financial burden for poor patients or poor countries. Making the full course of antibiotic treatment and the preceding health worker consultation free of charge in the public sector or at least heavily subsidized in the private sector was expected to solve some health equity issues as well as reducing the purchasing of incomplete courses or economizing of antibiotics.

“the poorest who, wether it is available or not, can only afford a third of the course, what are we going to do about them? So there needs to be a system that catches this....this group as well.” - #3 Tanzanian health NGO coordinator

Higher up in the supply chain offering LICs a discount when procuring the new antibiotic was suggested to lessen the strain on the poorer health budgets as well as reducing corruption within the health system.

“if the new antibiotic is at very high cost then...you know having in place some sort of...advanced market arrangement so that the...the price in the low income countries would be much lower...than the price in the developed countries I think that would be a very important step forward. Then you have...as soon as the price comes down to a more sensible level then the risks of corrupt practice and so on are...are somewhat reduced.” - #4 Health advisor on development research at a HIC’s donor agency
People

There was a concern that the people, the patients to be, lack any significant knowledge of antibiotic use and how it affects the emergence and spread of resistant bacteria. However there was also great hope that an increased awareness on the issue might decrease the excessive use of antibiotics. Therefore it was suggested that both doctors and pharmacists who are licensed to prescribe or dispense the new antibiotic should be obliged to inform patients of the importance of following the instructions and taking the full course so as to avoid treatment failure and risk of ending up with resistant bacteria.

“if a doctor administer a drug to the patient, so he should say that you should take this as a whole, not single. Otherwise you will get the future…the consequences” - #7 Pakistani project coordinator at NGO

The possibilities of media campaigns were brought up as a way to spread the word in the community and not only to one patient at the time. A knowledgeable group of patients was even considered able to put pressure at the health care provider to improve his or her knowledge and use of antibiotics and instead of the other way around.

“But if people know common cold you don't treat with antibiotic and you go and somebody gives you an antibiotic you say 'Okay, why? Why are you giving me an antibiotic? I've got a cold. I've...I've got a running nose. What is it that has made you decide I need an antibiotic and not just vitamins and good rest and so on?''” - #3 Tanzanian health NGO coordinator

Learning from other communicable diseases

The participants made several statements concerning drug distribution and use in other communicable diseases as well as discussing what, if anything, could be learned from those examples.

Malaria and ACTs

Using malaria and the distribution of ACTs as a model for antibiotic distribution was met with both positive and negative responses. While it was acknowledged that a lot has been achieved within the malaria field as of accurate diagnosis under poor clinical circumstances and improved compliance (education of health workers and prepackaged courses of therapy) results are mixed. Nevertheless, prepackaged courses of therapy and a simple field kit were suggested as successful concepts that
could play a role in antibiotic distribution.

The in retrospect unnecessary presumptive treatment before the introduction of RDTs was brought up as was the remaining use of artemisinin mono therapy in many places. Malaria and bacterial diseases are seen as differing on several important points such as PoC diagnostics and the potential number of patients that are liable to misuse antibiotics (ie everyone with the common cold).

“[ACTs] came with a package, a package of distribution, a package of the products, a package of diagnostic tools and a package of...laboratory work and so I think that package or that system is a best practice we can look at and review it and adapt it to suit antibacterial resistance challenges.” - #6 Ghanian MoH official

“Cause with the artemisinin it's strictly for malaria, but then with the antibiotic they'll realize that they can use it for pneumonia, they can use it for whatever so they'll try all other different things to use that drug not solely for pneumonia.” - #8 Ugandan pediatrician

**H1N1 and Tamiflu**

The restricted distribution of Tamiflu in India during the 2009 H1N1 outbreak was brought up as a potential model for antibiotic distribution by the two Indian stakeholders interviewed for the survey.

“They did something right I'm pretty sure because H1N1 came to India. There were lots of cases of H1N1. But there was no panic. There...drug was available. It was restrained and the system handled it. Of course we did not have millions of people but we...system handled it. So what did we do right?” - #11 Indian head of research at pharmaceutical company
Discussion

Principal findings

Through interviews with stakeholders in the health systems of LMICs, barriers to controlled distribution and use of antibiotics were identified throughout the health system and at several levels of government. In response to this, not one of the stakeholders interviewed favored a distribution system for new antibiotics without regulation and control in the long run though many stressed that access to effective drugs was a fundamental right which might demand substantial compromises with the rationality of dispensing and use in the short run. The use of different distribution channels and restrictions in different settings depending on local availability of health services was one unorthodox way to minimize irrational use while working for access to antibiotics in a flawed health system. Private sector drug sellers provide access in remote locations but they must, in the view of the participants, be both regulated and incentivized in order to minimize leakage in OtC sales.

Looking ahead, the need for a systemwide approach to controlled distribution and use of antibiotics is evident from the interviews. In a systemwide approach, the success of an intervention depends on more than one of the building blocks of the health system and how they influence each other. For example any regulation of antibiotics must be accompanied by monitoring and surveillance of prescribing and dispensing as well as level of resistance. Awareness on antibiotic resistance and how it relates to use was also addressed as lacking among health workers but also at government level and in the general population. There were many additional suggestions for improving the distribution and use of antibiotics, some drawing on the handling of ACTs such as improved point of care diagnostics and prepackaging courses of therapy.

Access vs restriction

The short term tension between access and rational use of a new antibiotic in LMICs was acknowledged in the interviews. Unregulated access through any outlet that decides to carry the drug was not suggested by any participants. Finding the middle ground between universal access and rational use is of course no easy thing. While all participants favored some form of restriction and regulation of the new antibiotic the choice of distribution channels to be used varied from
private sector drug shops, community health workers, primary care health facilities and hospital level.

The private sector has, as brought up by several participants, accomplished a lot in terms of access in places where the public sector distribution does not suffice. Private actors of varying degrees of expertise have been used to deliver pharmaceuticals to remote places, two prominent examples being AMFm's subsidizing of ACTs sold through private drug shops generating large volumes reaching patients and the ColaLife project where ORS kits are strapped onto Coca Cola-bottles as the popular soft drink seems to be available everywhere while the cheap and effective diarrhea treatment is not.\(^{(55,65)}\) The major drawback of distributing through private providers is as stated by several participants the risk of low medical rationality in advising and dispensing, especially in the informal private sector, in part due to incentives to increase sales, a lesson learned from the ACT distribution.\(^{(48,60,66)}\) This may not be a big issue with ORS but due to the special nature of antimicrobials irrational use is a concern for others than the individual patient.

Regulating and incentivizing the private sector to ensure a higher level of rationality in dispensing and adherence to regulation is no easy thing to do. Both are mentioned in the WHO Global Strategy for Containment of Antimicrobial Resistance. How incentives for rational dispensing of antibiotics are to be created is not elaborated on in the WHO strategy guide.\(^{(24)}\) Incentives discussed in the interviews were directly linked to the antibiotic in question such as the status of being a shop allowed to stock prescription-only medicines but also the possibility of losing that privilege if caught breaking the rules. Regulations suggested were classifying the new antibiotic as a prescription-only product, deciding what level of health worker would be allowed to prescribe it and what type of venue that would be allowed to stock and sell it. The issue of provider accountability was brought up as well and it will be addressed further on in this discussion.

Addressing that we are stuck with the currently available healthcare infrastructure in the short run the Indian interviewees suggested restricting the new antibiotic to in-patient use at infectious disease wards in urban areas while allowing community health workers to dispense the drug in remote rural areas where facility care was poor. This “one size does not fit all” solution where level of restriction is adapted to locally available healthcare institutions is interesting as it provides a way to maintain highest possible rationality in handling of the antibiotic in a variety of different settings. However, determining what healthcare services are available and functioning in a given districts needs a certain type of health system data, placing demands on the health information system. Still, it offers a way to address the well known issue of the widespread practice of OTC
dispensing of antibiotics in urban areas without leaving the rural patient in an even worse position as has been feared to be the case with general restrictions. (67) Currently amoxicillin and other antibiotics are dispensed through integrated community case management programs in a lot of LMICs, usually following some kind of diagnostic algorithm, but the numbers needed to treat and leakage of antibiotics with that particular type of providers are not known. (34, 61)

As a long term solution, we should hope for something more rational, both for the sake of the rural patients receiving better care and for all of us that antibiotics will be used with greater precision.

**Ethical aspects of restriction**

As mentioned in the ethic review, negative externalities in the form of antibiotic resistance make antibiotic use in the community a common concern. (40) All participants favored some form of restriction of a new antibiotic, at least in the long run, the motivation being to minimize unnecessary use and prolong the therapeutic life of the drug. Being that pharmaceuticals hold no value in themselves outside their potential use or existence as a second line when needed it is a reasonable interpretation to say that the participants hold intergenerational justice and the recognition of future patients' rights as important principles.

Intragenerational justice was addressed in two ways in the interviews: access to effective antibiotics when needed was seen as a fundamental right to be honored regardless of the locally available healthcare infrastructure and the instituting of clinical guidelines on when to prescribe antibiotics making each doctor's visit equal no matter where the patient decides to seek care. Instituting guidelines on antibiotic prescription, as mentioned by Leibovici, can also be seen as a concrete example of using Rawl's veil of ignorance to balance the interests of present patients against future ones. (42)

While a large part of the ethic review covers antibiotic restriction when treating infections of unknown bacteria empirically the dilemma in the health systems of LMICs is similar. Patients in rural areas are denied autonomy when the antibiotic is made inaccessible in that time and place. The rational for restricting availability is to decrease the resistance pressure and risk of emerging och increasing antibiotic resistance, to protect the rights of future patients. When balancing access and excess, some participants were inclined to accept differing access to antibiotics as long as it did not endanger the life of the patient if rationality of use was increased which means that conversely, rationality can be compromised with to save lives. This of course echoes the rescue rule referred to
As several participants brought up the financial situation of some patients and high out-of-pocket expenditure as a barrier to rational use of antibiotics, adding an additional fee to every course sold as suggested by Battin et al might only add insult to injury resulting in even more care seeking directly to drug sellers and consumption of incomplete courses of therapy.

The participants did not discuss access and restriction using the same terms as the authors referred in the ethic review but the guiding principles can be found in the interview transcripts: balancing inter- and intragenerational justice, non-maleficence principle extended to future patients, collective decisions through clinical guidelines and the presence of a rescue rule for present patients risking serious harm trumping the interests of future patients.

However, the ethical principles only tell us what values and interests to consider, not where we will find our middle ground. In a situation where a variety of distribution channels are available, some more accessible and affordable and some more rational in their prescribing and dispensing habits, how inconvenient or expensive can accessing the new effective antibiotic be before breaking the rescue rule? The answer will depend on hard facts such as pattern of resistance, projected health outcomes and the state of antibiotic pipeline but also on ethical reasoning and as such, the issue can not be left to medical experts alone but must also be the subject of political and hopefully public discussion.

A systems thinking approach to access with rational use

In the interviews, barriers to access with rational use of antibiotics were identified throughout the health system and not least on the demand side. This illustrates the complexity in balancing access against excessive use. Clearly, a systemwide approach is needed if the interventions made are to achieve desired results and not fail because of an overlooked crucial barrier.

Care seeking behavior at the community level and its motivations must be taken into account if an increased rationality in the use of antibiotics is to be achieved. To put it more concretely: if a majority of patients buy their antibiotics in the private sector it might not matter if public sector health facilities are stocked with quality antibiotics and staffed with workers trained in their appropriate use. Furthermore, in a complex adaptive system such as a national health system, the connections between the subsystems mean that the influencing go both ways. An intervention aimed at restricting excessive dispensing of antibiotics in public facilities might, as discussed in the interviews, decrease trust in the public healthcare sector while increasing
corruption and informal payments for medicines as well as care seeking in the informal private sector. On the other hand if done with great transparency such a restriction could possibly, according to one participant increase the trust in the system, illustrating the complex relationships within the health system.

On a similar note, Bigdeli et al have called for a systems thinking approach to access to medicines in LMICs arguing that the distribution and use of pharmaceuticals is influenced by and influences external factors and other health system subsystems than medicines and service delivery alone.(68)

Starting off from the barriers mentioned in the first theme, the third theme consists of numerous solutions to overcoming most of them and then some, the idea being that with system strengthening efforts, a higher degree of rational use can be achieved without sacrificing access. The results of the interviews run the risk of becoming a utopian wish list much like the WHO Global Strategy for Containment of Antimicrobial Resistance.(24) Since funds are limited and changes take time the suggestions for intervention design and health systems strengthening must be judged both according to their cost-effectiveness and ability to eliminate key barriers to already existing or future interventions. Some form of prioritization must be done as to which intervention should be implemented first and what interventions must go together to achieve results.

The solutions suggested by the participants and how they relate to each other will be discussed in pursuit of such a prioritization under the headings of the different health systems building blocks. Using a systems thinking approach, these subsystems are not seen as isolated systems but interconnected ones which is why some are grouped together in the same section and aspects of one system may be briefly touched upon in another section.

Governance and Health information systems

The role of government nationally was in the views of the participants to institute regulation and guidelines on antibiotic distribution, stocking, prescription, dispensing and use. The licensing of private pharmacies was also brought up as a governmental responsibility, both by the participants and earlier by the WHO.(24) The DRA is the governmental body tasked with enforcing a lot of these responsibilities. For this to be done, monitoring and surveillance is critical. Record keeping at and monitoring of providers both public and private are essential for upholding any regulation on antibiotic use and holding providers responsible. Without it strengthening the DRAs with more manpower and authority might not achieve its full potential in controlling the drug dispensers
adherence to rules and guidelines. There can be no accountability without some form of record keeping or data. It is no easy thing to introduce this kind of record keeping among private sector providers but the example of Tamiflu brought up by an Indian participant offers some interesting starting points.

The scientific literature on the Indian regulation and distribution of Tamiflu in 2009 is non-existent as of this time. Newspaper articles describe the regulation as follows: Initially, for fear of resistance developing if Tamiflu was widely used it was only available for in-patients at hospitals. However, in September 2009 after pharmacies were allowed to stock and sell it under a set of rules known as schedule X, meaning that it could only be sold at 480 accredited pharmacies nationwide, 28 of which were situated in Delhi. The drug was prescription only and pharmacies had to keep a copy of every prescription they received complete with the names of the doctor and the patient to account for every course of Tamiflu dispensed. In 2011 the regulation status of Tamiflu was downgraded to schedule H meaning that any one of the nation's 600 000 pharmacies could stock and sell it, albeit only when presented with a valid prescription. There are no estimates on what amount of Tamiflu were sold OtC without prescriptions nor what amount of patients in need were given access to the drug so at this time, we do not know whether the restriction was a success or a failure regarding access with rational use. What is known is that India has an area of 3.3 million km² and a population of 1.2 billion, 70% of which are living in rural areas. It is no wild guess that 480 pharmacies were not enough to provide equal access to Tamiflu for everyone. If the entire 600 000 pharmacies under schedule H are considered instead, excessive OtC sales are sure to have been a problem if demand was high as self-medication without prescription has been shown to be common practice in Indian pharmacies. Still, the controlled distribution and use of Tamiflu under schedule X should be studied. It did after all contain a system of record keeping at the dispenser's which provided accountability in a pharmaceutical distribution system that severely lacks it. Accountability was raised as a condition for successful inclusion of private sector providers by several participants. If the accountability was shown to improve dispensing behavior and adherence to regulations, scaling up a mechanism of record keeping and control, while an expensive and cumbersome task, has never been easier than in this computerized age. A strong governmental commitment as suggested by several participants will probably be needed to allocate the funds necessary for such a control mechanism.

There is a project in Tanzania called ADDOs in which small private drug shops were accredited by the DRA as ADDOs (accredited drug dispensing outlets) through staff training and
thus were allowed to stock and dispense prescription-only medicines in an attempt to expand access to quality medicines to remote areas where no proper pharmacies existed. This project was referred to by one of the participants as “creating a super drug shop”. If the rules, such as only dispensing some drugs against a valid prescription, where not adhered to the accreditation would be taken away by the government. Ten years in the project has expanded access to medicines into previously neglected areas. However, the DRA has yet to revoke one license from an ADDO for breaking the rules even though dispensing of antibiotics to patients without prescription is higher than that of the unqualified drug shops that still have not received any staff training illustrating the need for proper surveillance and accountability when evaluating interventions.(73)

Mapping resistance, another aspect of the information sub-system, is crucial if informed decisions are to be made on when and where to deploy the new antibiotic. Sometimes, as previously discussed, this must be done through less than rational distribution channels if access is to be ensured. As cited by a participant, treatment failure may be caused by many things other than resistance (wrong diagnosis, poor compliance etc) and deployment of a new antibiotic without confirmed resistance runs the risk of leading to unnecessary use. Returning to the ethical aspects of antibiotic restriction, writers referenced in the ethic review and quite a few participants were in favor of a rescue rule under which the interests of future patients were ignored because a present patient risked suffering “irretrievable serious harm” and thus received broad spectrum antibiotics. Honoring the rescue rule while knowing the state of resistance to older antibiotics in a region to be high would make the MoH able to allow a looser regulation of the antibiotic in that area to ensure access for those who can only reach the less rational providers (community health workers and private pharmacies) while keeping a stricter policy in other areas where susceptibility to older antibiotics is still high. Resistance data could thus reduce selection pressure and spending on a new expensive antibiotics outside areas with confirmed resistance. The same case was made in relation to distributing ACTs in the mid 00s for guiding introduction of the new drugs while protecting them since no others were waiting in the immediate pipeline.(51) As mentioned in the ACT distribution review, monitoring and investigating treatment failure with ACTs is still very much a work in progress.(48)

Mapping resistance also serves a bigger purpose if data is shared internationally enabling the international health community to properly assess the emerging antibiotic resistance threat, where to deploy resistance containment efforts and evaluating them as the work progresses. Grundmann et al have suggested building on existing WHO networks for epidemiological data to create a global
database on antibiotic resistance. A system of national and regional reference labs and external quality assurance institutions could ensure uniformity in data collections methods used at field and hospital microbiological labs as comparing antibiotic resistance data requires consistency in measurements (pathogens to be monitored etc) and laboratory methods. The 2001 WHO global strategy for containment of antimicrobial resistance stresses that surveillance on both resistance levels in hospitals and the community as well as antimicrobial usage is an important responsibility for national governments. However, a lot of countries do not collect sufficient data on antibiotic resistance today nor is there a system to share data between national systems.

Service delivery & Human resources

As discussed earlier, access could possibly be increased without giving up rationality in areas with good healthcare coverage if different levels of restriction are used in different settings depending on available healthcare services. Another way to increase rationality of providers without losing access is to attend to the healthcare infrastructure improving the referral system and services available at first level health facilities. This was brought up as vital if restriction of a new antibiotic within the public sector would be successful in achieving access and maintaining the trust of the community. If the community health workers are not seen as fit to handle rational use of a new antibiotic, the health facilities and referral system must be stocked and staffed to handle the patients when the need arises. While certainly a big and expensive project it ties in with the past few years discussions on strengthening health systems with universal healthcare coverage as a major development goal.

Considering the possible future impact on public health by antibiotic resistance both in mortality and in financial terms, rational use of antibiotics should be a priority when training new health workers or strengthening the referral system. Strengthening the referral system does not rule out the need for surveillance on prescription and dispensing habits as public sector providers including its doctors are also known as a source of irrational prescription and dispensing. No matter if the distribution of a new antibiotic is restricted to the public sector, providers and distributors will have to be monitored and audited.

The training of new health workers, pharmacists and doctors as brought up by several participants is an important but expensive long term plan in raising the level of expertise in the clinical setting, even in rural areas. The lack of skilled and trained healthcare professionals however is substantial in a lot of countries and together with expanding the public sector healthcare system is
one of those issues that risks making this survey and its result an unrealistic wish list. Adding antibiotic resistance and rational use of antibiotics to the curriculum of future healthcare professionals and health workers being trained anyway would seem like a cheaper system strengthening effort in relation to the lack of knowledge at all levels that existed according to the participants. This of course will have little or no impact on the use of a new antibiotic were it to reach the clinic tomorrow.

Working with the existing infrastructure and resources, the ADDO project brought up in the previous section was intended to expand access to medicines while maintaining rationality in dispensing and use, mainly through training the staff and owners of already existing private drug shops. Some ADDOs shops have failed to maintain trained workers over time meaning that the cost effectiveness of training private sector health workers can decrease as time after the intervention passes.

Medicines and technology

Point-of-care diagnostics are an appealing solution to the problem of low rationality in use of antibiotics among community health workers and drug shop staff. Investing in research on affordable easy-to-interpret diagnostic tools were suggested by several participants. Other researchers have pointed out the lack of diagnostics as “the achilles heel of antimicrobial resistance containment” and the cause of excessive use of antibiotics all the way from physicians in HICs to less sophisticated health workers in rural areas of LMICs. Thus, there is an optimism as to what a strong diagnostic can accomplish in terms of rational use of antibiotics.

The example of ACTs and RDTs paints a slightly different picture with implementation of testing as well as adherence to both positive and negative results still lagging behind as described in the ACT distribution review. There might also be unforeseen consequences to introducing a test into the clinic. RDTs' main benefits are believed to be a decrease in excessive use of ACTs saving the NMCPs money and preventing emergence and spread of resistant parasites but they also present an opportunity to catch and treat other dangerous causes of fever among the population. Since bacterial infection is another potentially fatal cause of fever, prescribing antibiotics to those tested negative for malaria has been common practice in some places. Putting an end to presumptive treatment with antimalarials may thus cause a rise in presumptive treatment with antibiotics. This illustrates the complexity of health systems and the need to use system thinking to predict the consequences of interventions. To conclude, rationality in the consultation and
dispensing of antibiotics by health workers, will most likely demand a lot more than a strong diagnostic tool. Field diagnostics might have a key role to play in the pursuit of rational use of antibiotics but other factors than the lack of diagnostic accuracy influencing patient and health worker behavior must be addressed as well.

The antibiotic distribution chain was also addressed in the interviews, both as a source of leakage of drugs into the informal sector and something to invest in on the public side to prevent stockouts at public facilities. As a source of leakage of antibiotics, the distribution must of course be monitored. Embossing tablets to be sold exclusively in the public sector or specialized pharmacies as suggested by the director of a Ugandan pharmaceutical company is a starting point but it can be expected to have a stronger effect if a monitoring system is in place.

People

There are several established theoretical frameworks for analyzing how and why access to a medical intervention is achieved and all of them address the end users situation, knowledge and behavior. No matter if they are referred to as the demand side, patients, community level or the people subsystem, the patients themselves are central in ensuring access with rational use. They may as identified in the interviews put pressure on providers to prescribe or dispense antibiotics when their use is not indicated, seek care at informal drug sellers not fit to diagnose infections nor dispense antibiotics and they may fail to adhere to courses of therapy dispensed and purchased.

In the interviews, the consultation between provider and patient was viewed as an opportunity to convey advice on the importance of adhering to the full treatment. One suggestion was to make it compulsory for doctors and pharmacists to explain how and why to take the antibiotic upon prescribing or dispensing it. This could serve as a way to target each specific patient at the time of treatment. But it also means putting the responsibility of patient knowledge onto the provider, not all of which might be fit to handle it. Private drug sellers in Kenya selling ACTs subsidized by the AMFm were revealed to give poor advice to care givers of children resulting in poor adherence to therapy. Reasons stated were insufficient time in the retail situation as well as forgetting the information given at training before the intervention. Similarly a large proportion of Tanzanian ADDOs workers failed to give one study's “mystery shoppers” correct advice on antibiotics dispensing tetracyclins for newborns (against guidelines) and instructed patients to apply penicillin powder topically in wounds.

Reaching the entire community through media campaigns has been tried in many settings
concerning a big variety of health issues and raising the community awareness on antibiotic resistance and its relation to antibiotic use was stressed as a key target by several participants. A decrease in consumption of antibiotics has been seen following media campaign targeting the general population in some HICs. (78,79) Looking at LMICs, some success has been seen with a multi media campaign featuring youtube videos (that went viral) and radio service announcements on the importance on bed net use for malaria prevention in Cameroon. (80) This suggests that campaigns targeting the community may be a feasible cost-effective way to counter the issue of irrational use bottom-up but, considering the lag between intervention and end line in these studies, that such campaigns should preferably be launched before the introduction of a new antibiotic.

**Finance**

While community awareness on antibiotic use and how it relates to resistance were believed to improve compliance and care seeking behavior financial incentives against seeking care at skilled providers' and purchasing full courses of therapy were also identified.

The finance subsystem challenges in ensuring rational use while maintaining a wide access to a new antibiotic can be discussed at two levels: individual patients and national healthcare systems. A new antibiotic with a valid patent can be expected to be quite expensive compared to those near or after expiry. (81) This will most certainly make it unaffordable for the poor patient populations frequently discussed in this paper. As described earlier, high prices are believed to be a strong driver for purchasing incomplete courses and saving tablets for other members of family or future diseases. This type of economizing of medicines for financial reasons has been found to occur at already heavily subsidized ACTs in rural Kenya. (66)

If access to those in need with a minimum level of irrational use is the desired outcome poor patients can not be expected to assume the cost of a new antibiotic. No mechanism of financing was suggested in the interviews other than making the new antibiotic available through the public sector where both the consultation with a physician and medicines were already free or subsidized.

If the new antibiotic is only to be used at hospital level or in settings where resistance has been mapped and proven high in the community the amount of therapies and thus the cost can be kept down for the national MoH.

There is a growing opinion, both in the industry and academia that profits from developing new antibiotics should be de-linked from volumes sold so as to keep them effective for as long as possible. (22,23) Looking again at malaria and the financing of ACTs in LMICs there are several
successful examples of non-governmental actors in HICs assuming part of the cost such as Novartis selling Coartem without profit and the AMFm being financed by donors from all over the world through the Global Fund. Perhaps similar actors can be made partners in this venture as well although as is clear from the discussion leading up to this, external financing might be needed for more interventions to ensure rationality in distribution and use than lowering the price of a new antibiotic alone.

This might be in the self-interest of wealthier nations as well since antibiotic resistance as stated in the background knows no borders and we might all have to pay the price for irrational use somewhere else.

**Methodological considerations**

Measures of methodological trustworthiness defined for qualitative content analysis will be used because of its similarities with framework analysis and the fact that no such measures are specifically addressed in framework analysis.(63) Graneheim and Lundman suggest **credibility, dependability and transferability** as means of measuring trustworthiness.(82)

**Credibility** depends on how well the data and method of analysis adequately address the research question. For this survey, participants were recruited from a wide range of countries and professions but the private sector drug sellers and DRAs, although frequent topic of conversation, were regrettably not represented, nor were the patients even though their motives and incentives are discussed as a significant determinant on antibiotic use. Furthermore the complex nature of health systems calls for a large number of interviewees and probably longer interviews as well to sufficiently cover the dynamics of the system.

The hypothetical scenario used served as a triangulation and as such it might have limited the interviewees trail of thought on the distribution issue as well as signaling what type of actors are to be considered relevant when addressing the issue. However, it should be noted that many described a middle ground between the two models of distribution outlined as the ideal scenario. The case of pneumonia was picked because of its urgency and relevancy in rural settings where healthcare services are scarce.

The choice of framework analysis without a structured form of open coding saves time but comes at the expense of transparency in the theme creating process. In this case, since the entire data set was read through while making notes, the process of familiarization was in fact quite similar to that of an open coding process. To strengthen the thematic framework's credibility a rich
amount of quotes was embedded into the analysis.

**Dependability** is defined as stability in data collection methods during the survey. This being the first interview survey performed by the researcher and the interviews being rich on factual information relevant for the research question dependability can be expected to be low. The interview guide was constructed using quite general questions making the interviews less structured and left a lot of follow-up questions to be thought up during the interviews further decreasing the dependability. As the purpose of this survey is not to compare the views and suggestions for solutions by different stakeholders a low dependability is not necessarily a significant problem. But it should be noted that the order of the interviews probably influenced the follow-up questions posed and subjects emphasized during.

**Transferability** answers wether the conclusions drawn from a survey can be generalized and applied onto other similar situations. Since the approach here is to discuss LMICs generally the question should be posed the other way around: can the conclusions from this survey be applied onto *any* country? The short answer is that they can not. LMICs might share public health challenges but one solution, as evident from this survey, does not fit all, not even within one country. The state of the national health system must be mapped and assessed to find out what barriers are most significant in that context, but the results and conclusions from this thesis can serve as a starting point and a checklist in that venture.

**Conclusions and recommendations**

The task of distributing a new antibiotic in LMICs calls for creative solutions. In the short run access will come at the expense of rational use, but distribution and dispensing can be restricted to different levels of healthcare in different settings using community health workers or nurses in rural areas where speciality care is not available and infectious diseases specialists in urban areas to ensure highest possible level of rationality and access in all settings.

A new antibiotic must, according to most participants be restricted and regulated to ensure longest possible therapeutic life. For long term solutions a systems thinking approach should be used to address the barriers to access with rational use identified throughout the health system. Taking into account the connections and influences flowing between the subsystems offers the possibility to forestall undesired outcomes, such as trust issues and changes in care seeking behavior, in relation to the new distribution model.

When strengthening health systems in LMICs, rationalizing antibiotic use should be put on
the agenda. Prioritizing at this early stage, it seems as though monitoring and surveillance of both resistance patterns and use of the new antibiotic are crucial for a majority of suggested approaches to rational distribution and use as well as some earlier interventions for rational dispensing of medicines in rural settings with outcomes now being questioned such as the ADDOs project in Tanzania. The provider accountability requested and the enforcing of regulations require, in addition to record keeping and monitoring systems, stronger national DRAs. Controlled distribution and use of a new antibiotic is not expected to be easy but considering the state of the antibiotic pipeline and all studies showing irrational dispensing and use of antibiotics a new approach to antibiotic distribution and regulation clearly is needed.

Finally, any form of service delivery and financing must cater to the poorest population since they have strong financial incentives to by-pass the prescriber and if need be seek care in the informal private sector where OtC sales of incomplete courses of antibiotics are normal practice and quality of medicines can not be ensured.
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Appendixes

Appendix I: Scenario letter

To whom it may concern

Thank you very much in advance for participating in this interview survey. The survey is part of my master thesis at the MD program at Uppsala University. I am writing the thesis in collaboration with ReAct – Action on Antibiotic Resistance (www.reactgroup.org). The aim of the thesis is to present the properties a model of distribution and use of future antibiotics must possess in order to balance access with the risk of excessive use and selection for antibiotic resistance. This will be done through stakeholder and key informant interviews. The results will be used by ReAct in its mission to influence the global health community in pursuit of a new system of controlled distribution and use of antibiotics. Your answers will be treated with full confidentiality, i.e. your name will not in any way or manner appear in any publication or presentation of this thesis or its results.

During the interview we will discuss the following scenarios:

A low or middle income country (LMIC) faces a substantial rise of resistance to standard antibiotic treatment among pneumococci, the main causative agent of pneumonia. Meanwhile, a new antibiotic with a new mechanism of action enters the market. The susceptibility to this new drug among pneumococci is high for now. The ministry of health (MoH) in the LMIC considers the available options for regulation and arrive at the following possible plans of action:

1. Having significantly reduced the mortality in malaria the MoH decides to transfer the model of distribution and regulation of artemisinin combination therapies (ACTs) to this new problem with resistance to standard antibiotic treatment for pneumonia. The new effective antibiotic will be broadly available without prescription. The ministry also explores the possibilities of community case management and point-of-care diagnostics to minimize excessive and unnecessary use.

2. To ensure the effectiveness of this new antibiotic for as long as possible, the MoH decides to put a tight restraint on the distribution. Not only will a doctor's prescription be required, the drug will only be available within the public sector and at certain authorized pharmacies.

In the interview I will ask for your comments on each plan of action and we will discuss them from the perspective of access, excess, sustainability, equity, private vs public sector etc. I am also interested in what improvements you might suggest for any of these plans to make them acceptable and sustainable. If you have any questions about the contents of this letter, the interview or the survey and thesis in general please feel free to contact me at gabriel.heyman@gmail.com

Yours sincerely Gabriel Heyman ReAct, Uppsala University
Appendix II: Interview guide

1. How do you perceive the problem of antibiotic resistance?
   ◦ Main causes
   ◦ Potential solutions
2. What are your reflections on the first plan of action and what consequences do you expect?
   ◦ **Health outcomes – System outcomes**
   ◦ Access/Excess/Resistance/Sustainability
   ◦ Point of care diagnostics and community case management
   ◦ Public sector vs Private sector
   ◦ Equity issues
   ◦ Possible improvements to prevent further resistance
3. What are your reflections on the second plan of action and what consequences do you expect?
   ◦ **Health outcomes – System outcomes**
   ◦ Access/Resistance/Sustainability/Black market access/leakage
   ◦ Level of restraint - Public vs private, hospitals vs pharmacies
   ◦ Equity issues
   ◦ Trust in health system
   ◦ **Possible improvements to ensure access**
4. How would you organize the regulation and distribution of a new antibiotic given the current state of the antibiotic pipeline?
   ◦ Sustainability
   ◦ Equity
   ◦ Feasibility
5. Conclusion – is there anything you would like to add to the discussion?