

MARKET REPORT

Amoxicillin Dispersible Tablets Progress and Opportunities

October 2022

EXECUTIVE SUMMARY

The stakes are high to address childhood pneumonia, which has persistently remained the leading infectious cause of under-five mortality globally, accounting for an estimated 800,000 deaths each year. To reduce childhood pneumonia deaths – especially in low- and middle-income countries hit the hardest – multi-pronged action is needed to address this leading cause of death. This must include increasing access to the WHO recommended treatment, amoxicillin dispersible tablets (DT). Amoxicillin DT is an effective, low-cost and appropriately designed treatment available within the global market. However, access is still not widespread, particularly in countries with the highest burden of childhood pneumonia deaths.

Urgent efforts are needed to scale amoxicillin DT. This market brief aims to document – primarily in qualitative terms – progress seen over the past eight years since the WHO guidance was updated to recommend the use of amoxicillin DT for childhood pneumonia treatment. Importantly, the brief also highlights key remaining opportunities to unlock persistent barriers, and to transform access to this life-saving commodity. Market barriers described in this document focus on aspects of regulatory, financing, supply, demand, and appropriate use of amoxicillin DT at the global level and at the national level in countries with high burdens of childhood pneumonia. The recommendations coming out of this brief provide strong suggestions for where country governments and partners can collectively focus attention in forthcoming years to continue improving access



Client purchase Amox DT at an Accredited Drug Dispensing Outlet (ADDO) in Dar es Salaam. ©Results for Development

to amoxicillin DT by addressing key enduring challenges:

- Need for prioritization of access to amoxicillin DT in national strategies and investment cases targeting reductions in child mortality;
- Significant funding gaps persist, requiring greater prioritization by both donors and governments;
- Limited availability of internationally quality-assured products – at competitive prices – within high-burden countries;
- Need for more robust quantifications and their use to inform procurement decisions; and
- Concerns around appropriate use, supported by evidence of misdiagnosis and incorrect prescription practices

In support of the Sustainable Development Goals to end preventable child mortality, combined and coordinated efforts across partners and governments of high burden countries is greatly needed to prioritize efforts to tackle the barriers documented in this brief, thus enhance scale-up of amoxicillin DT.

THE STAKES ARE HIGH TO ADDRESS CHILDHOOD PNEUMONIA

Childhood pneumonia is a critical global health challenge, accounting for 15% of global under five (U5) deaths each year – amounting to over 800,000 child deaths per year.ⁱ The highest burden of childhood pneumonia deaths falls disproportionately on low and middle income countries in South Asia and Sub-Saharan Africa, and is linked to poverty-related factors such as undernutrition, air pollution, and inadequate access to primary healthcare.ⁱⁱ To reduce childhood pneumonia deaths – especially in low and middle income countries hit the hardest – multi-pronged action is needed to address this leading cause of death. This must include increasing access to effective, low-cost and appropriately designed treatments which are available in the global market, but where access is still not widespread.

Reducing childhood pneumonia deaths is critical to achieving Sustainable Development Goals to end preventable child mortality by 2030.ⁱⁱⁱ The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) also aims to reduce the incidence of childhood pneumonia by 75%, decrease mortality to fewer than three per 1,000 live births, and ensure 90% of cases have access to appropriate treatment with antibiotics. To achieve these goals, GAPPD outlines a comprehensive package of care to protect, prevent, diagnose, and treat childhood pneumonia.^{iv}

To reduce preventable child deaths, it is crucial to scale access to the WHO recommended treatment for childhood pneumonia, amoxicillin. In 2014, the World Health Organization (WHO) updated its guidance to recommend oral amoxicillin as the first-line treatment for non-severe childhood pneumonia, replacing the incumbent drug, cotrimoxazole. The dispersible tablet (DT) formulation was identified as the most suitable for children due to its ease of use compared to other formulations.^v Furthermore, scaling access to amoxicillin DT has additional perceived benefits. Firstly, appropriately designed pediatric formulations are believed to contribute to reduced risks of spreading antimicrobial resistance (AMR) given the ease of use promotes adherence to a full course of treatment.^{vi}

Moreover, access to amoxicillin DT will contribute to lives saved in other leading causes of newborn and child mortality since amoxicillin is also recommended by WHO to treat possible serious bacterial infections (PSBI) and uncomplicated severe acute malnutrition (SAM).^{vii,viii}

OBJECTIVES AND METHODOLOGY

Urgent efforts are needed to scale amoxicillin DT. This market brief aims to document – primarily in qualitative terms – progress seen over the past eight years since the WHO guideline update. Importantly, the brief also highlights key remaining opportunities to unlock persistent barriers, and to transform access to this life-saving commodity.

Market barriers described in this document focus on aspects of regulatory, financing, supply, demand, and appropriate use of amoxicillin DT at the global level and at the national level in countries with high burdens of childhood pneumonia. Other downstream aspects, such as service delivery and supply chain, certainly play an important role in terms of access and appropriate use of amoxicillin DT; however, these aspects are not addressed in this brief, which remains focused on market challenges and opportunities at the global and national levels.

Findings described in this brief were identified from collective partner efforts, but draw heavily upon Results for Development's experiences supporting the governments of Ethiopia, Tanzania, and Uganda to catalytically scale-up amoxicillin DT, as well as additional (less recent) market diagnostics conducted across five other geographies in India, Indonesia, Malawi, Nigeria, and Zambia.^{ix} Additional data was sourced from publicly available secondary resources produced by donors and implementing partners supporting efforts to reduce childhood pneumonia deaths. As a result, the findings are meant to illustrate a thematic trend in the status of amoxicillin DT scale-up but may not be universally experienced across all high burden countries.

MARKET LANDSCAPE

Regulatory

An enabled national regulatory environment is necessary, but not sufficient, to scale access to amoxicillin DT. It is needed to ensure the product can be registered, financed, forecasted, and procured. in national exercises. An enabled regulatory environment includes ensuring alignment between WHO and national policies, as well as alignment between national treatment guidelines and essential medicines lists. In 2014, WHO updated its guidelines recommending amoxicillin – preferably the DT formulation – as the first-line treatment for childhood pneumonia.^x However, countries did not immediately adopt the new WHO recommendation. Among countries which did update their guidelines, there was also variation in which formulation of amoxicillin was included – and in some instances, capsules or tablets were specified rather than a pediatric formulation.^{xi}

At present, broadly speaking, countries which sought to adopt the WHO recommendation have created favorable regulatory environments to support scale-up. Of 74 low- and middle-income countries reviewed for adherence to the WHO recommendation, 58 (78%) adopted amoxicillin DT as the first-line treatment for non-severe childhood pneumonia in their national clinical guidelines, and 61 (82%) ensured amoxicillin DT is included in their national essential medicines lists (Figure 1 and 2).^{xii} These combined efforts ensure that the regulatory environment within countries enables amoxicillin DT to be registered, procured, and ultimately prescribed to treat childhood pneumonia and other leading causes of death in children under five.

While ensuring guidelines and essential medicines lists are updated to include amoxicillin DT is necessary, it is not sufficient for scale-up. Countries must also include the life-saving medicine in national health strategies to encourage its prioritization among policymakers, providers, and caregivers. This has been achieved across several high burden countries which have included

FIGURE 1. Countries that include amoxicillin DT 250mg in national clinical guidelines (n=74)

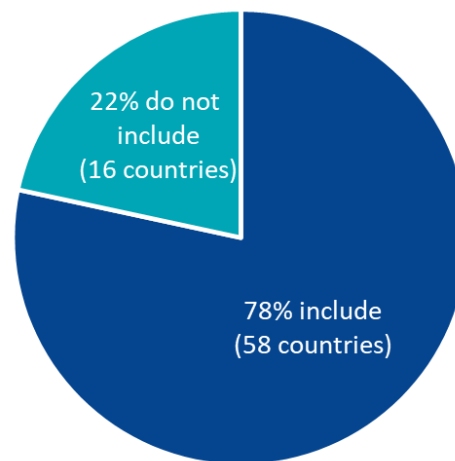
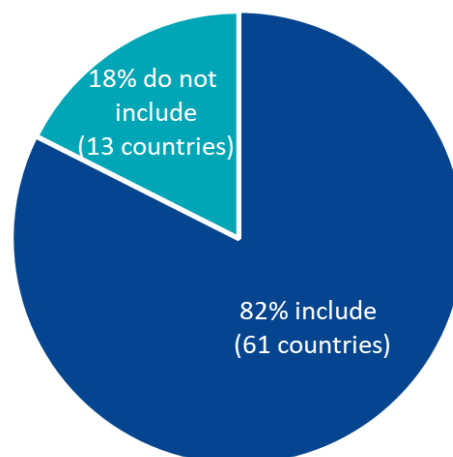


FIGURE 2. Countries that include amoxicillin DT 250mg on national essential medicines lists (n=74)



amoxicillin DT in national strategies for Reproductive, Maternal, newborn, and Child Health.^{xiii} Some high burden countries – such as Ethiopia, Kenya, and Nigeria – have taken this one step further and developed national Pneumonia Control Strategies which specify costed implementation plans to prevent, diagnose, and

treat childhood pneumonia. These efforts to prioritize amoxicillin DT within national policies and strategies play a significant role in enabling further in-country efforts

required for scale-up, and all countries – particularly those with high burdens of childhood pneumonia – should be encouraged to do so.

Recommendations

- For 13-16 countries that do not include amoxicillin DT on the clinical treatment guidelines and EML, ensure they are aware of the updated WHO guidance and its benefits.
- Support more countries to prioritize and cost treatment of childhood pneumonia in national policies as a core strategy to tackle under-five mortality, in addition to including amoxicillin DT in national guidelines and essential medicines lists.

Finance

Financing continues to be one of the most significant market barriers inhibiting scale-up. Ensuring sufficient, sustainable funding is available to procure enough amoxicillin DT to satisfy demand is crucial to increasing access to this life-saving commodity. While some progress has been made by donors and high burden countries, greater efforts are needed to increase both donor and domestically mobilized resources to alleviate short-term funding gaps and ensure long-term sustainable financing.

In 2014, the majority of amoxicillin DT in the market was donated to enhance introduction of the newly recommended commodity. However, by the end of 2015, funding cliffs were imminent as key donor support through the RMNCAH Trust Fund was sundowning.

Since then, a few donors have continued to fund amoxicillin DT procurement for country-specific programs. Governments in some high burden countries have begun to mobilize resources, as well. Nevertheless, significant funding gaps persist, requiring greater prioritization by both donors and governments:

- *Donor funding:* Historically, when compared to other therapeutic areas, donors have not prioritized efforts to tackle pneumonia, despite it being the leading single cause of U5 death. Over a 10-year period, pneumonia received only

7% (\$7.1 billion) of total global donor funding given to malaria and HIV/AIDs combined (\$108.7 billion).^{xiv} Of the funding, which was dedicated to pneumonia, the majority was allocated to vaccines and only 1% (\$80.1 million) went towards treatment-based interventions, such as amoxicillin DT (Figure 3 and 4).^{xv} Of the funding

FIGURE 3. Global donor funding per health area, 2007-2018 (USD)

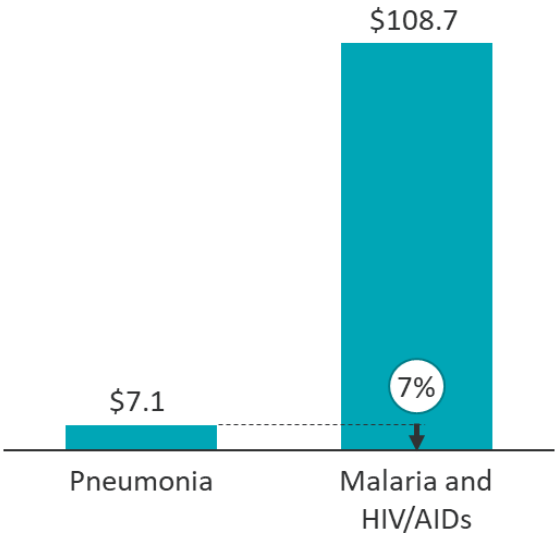
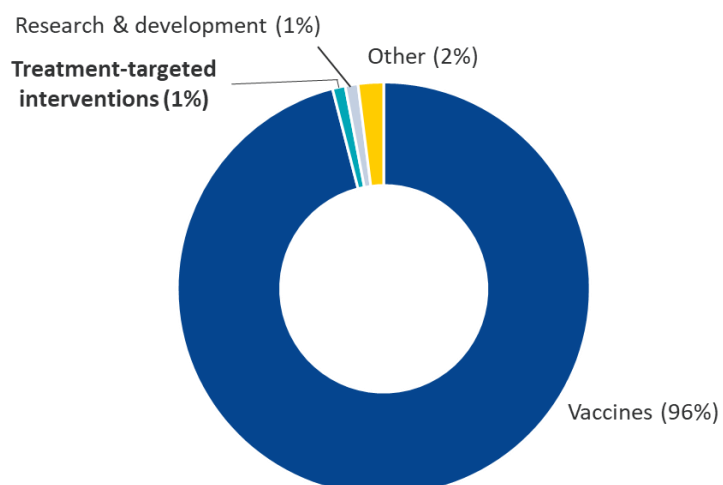


FIGURE 4. Allocation of global donor resources for pneumonia interventions, 2007-2018 (USD)



donors have prioritized for amoxicillin DT, it is often limited to donors' geographical and programmatic priorities (e.g. scaling Integrated Community Case Management).

Moreover, of the donor resources which are available, countries identified it is often difficult to navigate the various terms and conditionalities across resources. This in turn limits how effectively countries may be able to access existing resources. For instance, the Global Financing Facility (GFF) is a potential resource which countries may leverage to mobilize funding for procurement of life-saving commodities, including amoxicillin DT. There is evidence that a few countries, such as Uganda, leveraged the GFF mechanism to utilize the GFF Trust Fund, IDA loans, or other partner resources under GFF to fund commodity procurement. However, this does not seem to be widespread across country investment cases.^{xvi} Moreover, as of 2021, for Global Fund, countries may now leverage their co-financing requirement for non-malaria commodities, including amoxicillin DT.^{xvii} To-date, there are limited insights as to whether countries are utilizing this opportunity.

Governments have identified that it would be helpful to have greater clarity on what resources are available – including the GFF – and how they can be most effectively accessed.

- *Domestically mobilized resources:* In addition to increasing access to donor resources, mobilizing domestic resources is crucial to ensuring sustainable financing is secured. Evidence suggests government-allocated resources are the primary funding source for Maternal, Newborn, and Child Health medicines, including amoxicillin DT.^{xviii} High burden countries have employed a variety of domestic financing strategies to fund amoxicillin DT, such as securing direct government donations to the public health system or including amoxicillin DT in national Revolving Drug Funds or facility commodity budgets. In specific countries, partners have provided technical assistance to support governments to generate a strong evidence base to mobilize domestic resources for amoxicillin DT. Such evidence includes developing clear funding gap analyses and/or return on investment analyses.

Looking holistically, to increase the power and effectiveness of donor financing mechanisms, co-financing arrangements can be leveraged to catalyze domestic resource mobilization and allocations. In fact, since 2017 a high burden country benefiting from such support has allocated a total of \$1.1 million, which amounts to about 5.6 million courses of treatment.^{xix} Prior to 2017, amoxicillin DT was solely donor funded in the country – signifying a significant transition to securing more sustainable financing for amoxicillin DT. This example also suggests that similar catalytic donor support could be applicable in other high burden countries to mobilize domestic resources for sustainable amoxicillin DT funding.

Recommendations

- Prioritize more donor funding for amoxicillin DT, perhaps via co-financing mechanisms, to (1) address short-term funding gaps, and (2) catalyze greater domestic resources over-time to secure sustainable financing.
- Improve coordination efforts between partners and governments to ensure countries have a deliberate discussion around and an action plan for resource mobilization for pneumonia treatment.
- Develop a guidance tool to clarify the various terms and conditionalities of donor financing mechanisms available for amoxicillin DT, including GFF.
- Support countries to develop an investment case for amoxicillin DT, among other MNCH commodities, which can be used to inform resource mobilization from donor and domestic resources.
- Support countries to develop clear evidence and strategies to mobilize greater domestic resources for amoxicillin DT in order to support sustainable financing in the long-term.

Supply

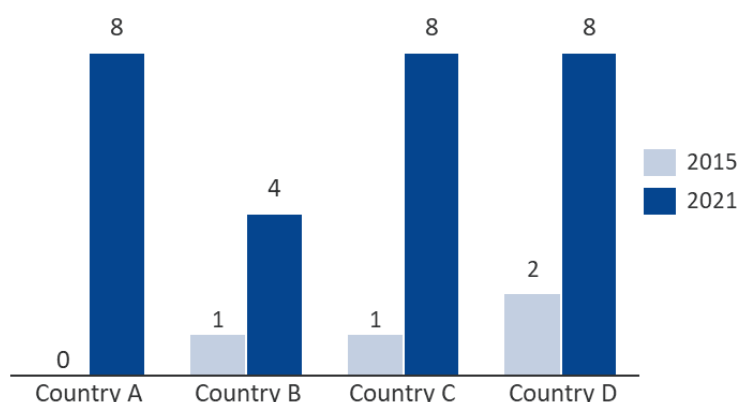
In addition to an enabled regulatory environment and ample financing, markets must also have sufficient, accessible, high-quality, and affordable supply capacity to effectively satisfy demand. In 2014, partners estimated there was ample manufacturing capacity to fulfill five times the global demand – so the existence of sufficient supply has not been a challenge.^{xx} Rather, ensuring supply is accessible, high-quality, and affordable – especially within high burden country markets – has been an area targeted for market improvements. Significant progress has been made in recent years, but further efforts are needed to address persistent challenges in these areas.

In 2014, when amoxicillin DT was being introduced in high burden countries, UNICEF held long-term agreements (LTA) with quality-assured manufacturers to procure the life-saving commodity for these markets and secured waivers to facilitate importations. However, countries themselves did not have direct access to supply. This was due to few international manufacturers registering their products in countries and, specifically in Sub Saharan Africa (SSA), an absence of local manufacturing capacity. In general, international manufacturers have cited multiple reasons for not registering their products in-country, including need for more transparency on in-country market size, ambiguous or lengthy registration processes and perceived challenges doing business in the public sector.^{xxi}

However, since 2014, the supply landscape for amoxicillin DT has improved in terms of (1) access to supply at the country-level, as well as ensuring the supply is (2) quality-assured and (3) affordable, but further efforts would strengthen quality and affordability of amoxicillin DT across high burden countries.

- **Accessibility:** Registering pharmaceuticals with countries' national drug regulatory authority (NDRA) is a vital step towards ensuring products in the market are safe and of good quality. In a positive development, the number of manufacturers active in high burden countries has expanded over the last few years. Across four high burden countries, the number of registered amoxicillin DT products have doubled since 2015 (Figure 5). While the number of manufacturers registered in each country varies, this is likely indicative of trends experienced in other high burden countries, as well. Local manufacturing capacity for amoxicillin DT also improved during this period in Sub Saharan African countries. This may be at least partially attributed to the rise in policies across Sub Saharan African countries which seek to promote domestic manufacturing capacity in key sectors, including the pharmaceutical industry.^{xxii}

FIGURE 5. Comparing number of amoxicillin DT 250mg manufacturers registered in four countries, 2015 vs. 2021



Additionally, a variety of manufacturers are actively participating in the market and have successfully won tenders in public sectors of high burden countries. In fact, looking at just three high-burden countries across 2016-2020, public sector tenders were awarded to seven different manufacturers^{xxiii} – providing a positive indication of improved market access and amoxicillin DT’s supply security.

- Quality:** A healthy market for amoxicillin DT also requires attention to quality. In addition to national drug regulatory authorities, multiple global quality designations are available for amoxicillin DT 250mg as a finished pharmaceutical product. These include Stringent Regulatory Authority (SRA) approval, WHO Expert Review Panel (WHO ERP) recommendation,^{xxiv} and, as of 2020, WHO Prequalification (PQ)^{xxv}. However, manufacturer participation in these global quality mechanisms remains low for amoxicillin DT. Currently, only four amoxicillin DT 250mg manufacturers hold a global quality designation for their finished pharmaceutical product (Figure 6). While some manufacturers expressed interest applying for WHO PQ, none have been awarded WHO PQ to-date. In addition to quality-assurance for finished pharmaceutical products, WHO Good Manufacturing Practice (WHO GMP) can be awarded to the facility in which amoxicillin DT is produced. When WHO GMP is awarded to a facility via a WHO- or SRA-led process, this is also

viewed as a positive indication of quality – albeit not an indication of quality for the finished pharmaceutical product. At least two additional manufacturers – Medopharm and Milan Labs – to the four referenced above hold WHO GMP for the facility in which their amoxicillin DT product is produced.

Manufacturers’ interest in global quality designations for amoxicillin DT appears to be largely driven by the perceived value-add – i.e., if their primary clients are interested in such quality designations. Clients in the NGO sector – such as UNICEF – appear most interested in global quality designations, viewing them as favorable, or even required, in order to award contracts. Alternatively, manufacturers have shared that they have not experienced the same degree of interest in global quality assurance from public and private sector clients in high burden countries, particularly when procurement is financed from domestic sources. In fact, when looking at tenders awarded in countries funded by government resources across three high burden countries since 2016, one-third of tenders were awarded to

FIGURE 6. Manufacturers with global quality designation

Manufacturers	Quality Designation
Medrieck	WHO ERP
Micro Labs	WHO ERP
Remedica	WHO ERP & SRA
Sandoz	WHO ERP & SRA

international manufacturers without global quality assurance (Figure 7).^{xxvi} Moreover, national procurement agencies have indicated that when they do wish to prioritize a global quality designation- such as SRA, WHO PQ, or WHO ERP - it can be difficult and time consuming to identify and verify manufacturers' certifications, given there is no single database which tracks such information. This may further contribute to lack of perceived interest in global quality designations. Strengthening the business case for national drug registration authorities to prioritize global quality designations would likely increase manufacturer participation.

- Affordability:** Affordability is also key to ensuring sustainable access to amoxicillin DT. In a positive market development, over time, the range in amoxicillin DT manufacturers' average retail price decreased by 35% between 2016 and 2019 (Figure 8).^{xxvii} In 2019, manufacturers' global average price for amoxicillin DT 250mg ranged from \$1.00 - \$2.77 per pack of 10x10. Manufacturers report that competition both at the global level and within high burden countries, reduction in input costs, and increased market share facilitated lower prices in the pre-COVID era.

Furthermore, price does not necessarily appear to be tied to manufacturers' ability to attain global quality designations. In fact, manufacturers with prices at the higher end of the spectrum are a mix of local manufacturers in Sub Saharan African countries and those who hold global quality designations and supply to UNICEF (Figure 9). Providing further transparency around global pricing for amoxicillin DT and supporting manufacturers to take necessary measures to be price competitive may lead to further reduced prices, particularly among higher priced manufacturers. This would in turn increase the number of perceived affordable, quality-assured manufacturers accessible in high burden countries, thus enhancing supply security.

FIGURE 7. Manufacturers awarded tenders across three high-burden countries, 2016-2021

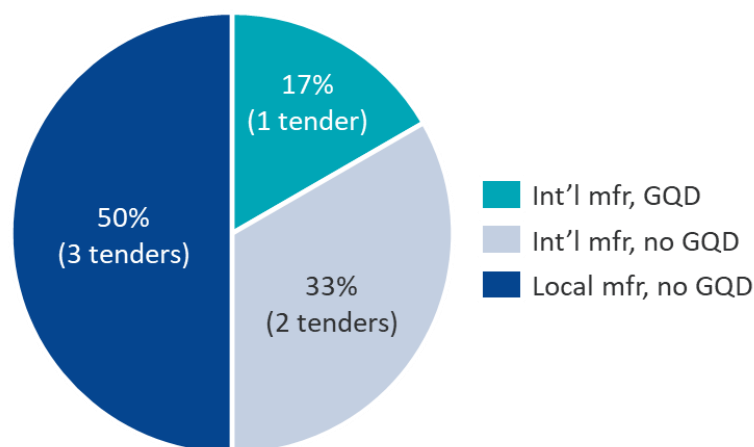


FIGURE 8. Range in amoxicillin DT 250mg manufacturers' global average prices, 2016 vs. 2019 (USD, 10x10 pack)

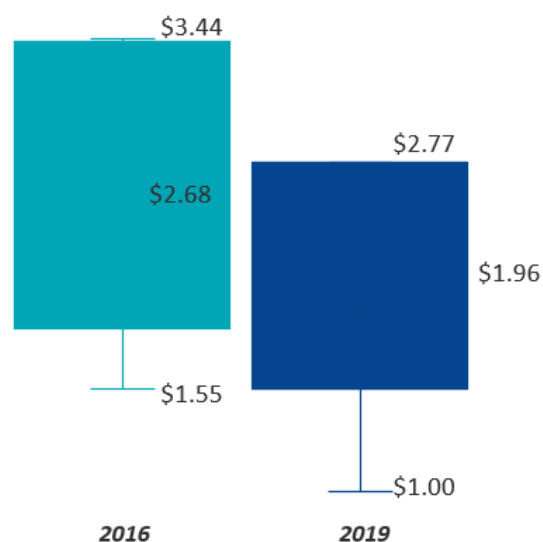
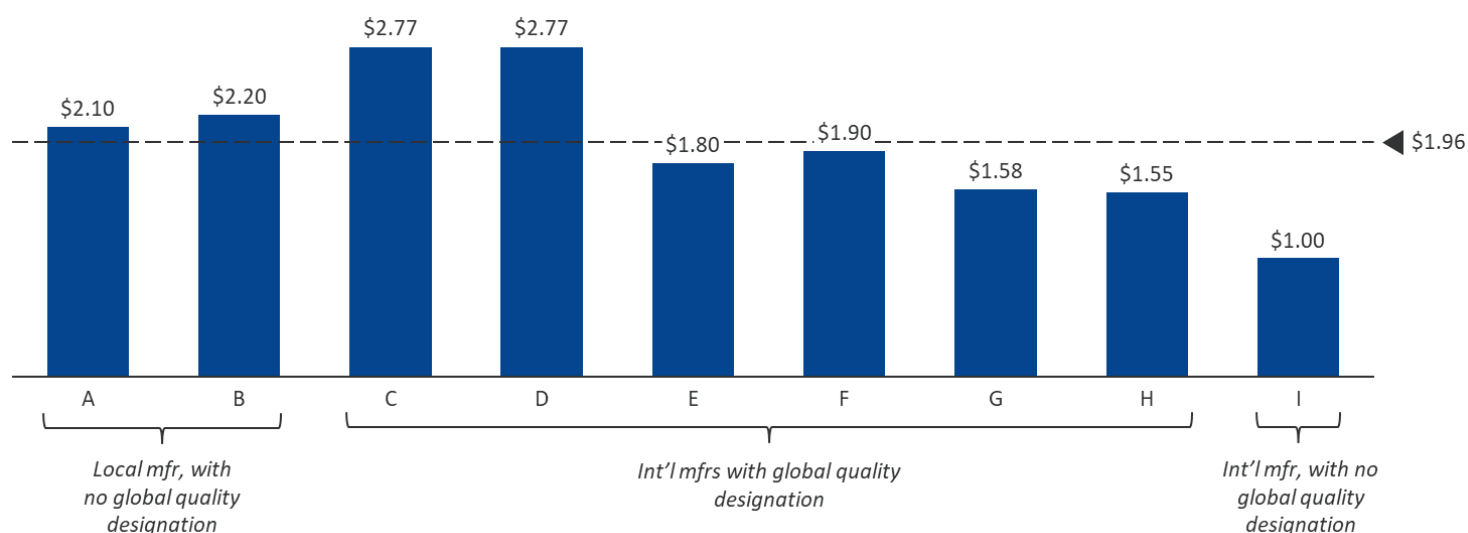


FIGURE 9. Global average retail prices of nine manufacturers (\$USD, 10x10 pack)



Recommendations

- Support efforts to reduce market asymmetry by providing manufacturers with updates on demand across high burden country markets and clarifying the process to register their products.
- Clarify the process and business case for manufacturers to participate in global quality mechanisms – SRA, WHO PQ, and WHO ERP. This may include liaising with existing amoxicillin DT manufacturers to clarify the process and timelines to submit applications and providing return on investment analyses.
- Develop a list of amoxicillin DT products which hold global quality designations for national procurement agencies to refer to when evaluating tenders. This would make it more efficient for procurement agencies to include global quality assurances as a criteria in their bid evaluations, and thus increase the likelihood of them doing so.
- Encourage national drug regulatory authorities (NDRAs) to consider global quality designations in their dossier reviews to increase efficiencies for manufacturers, and thus provide a tangible benefit to pursuing both global quality designations and registering their product in countries. A potential benefit would be reduced timeline to review dossiers when the product holds a global quality designation.

Demand

Lastly, in addition to market aspects around regulatory, financing, and supply, scaling access to amoxicillin DT requires accurately quantifying demand and ensuring capacity exists to efficiently procure the life-saving commodity across high burden countries. Significant progress has been made in terms of increasing levels of demand and countries improving their procurement capacities. However, further support is needed to improve quantifications and ensure national quantifications are utilized to inform resource mobilization and procurement decisions. Additionally, insights from Tanzania's private sector indicate that more progress may be needed to improve demand in the private sector.

In 2014, the DT formulation of amoxicillin was a new product for many country markets and was more established in Asia compared to other areas of the world, such as in Sub Saharan Africa.^{xxviii} The life-saving medicine was procured through UNICEF programs rather than national procurement agencies. There were also significant challenges in quantifying demand for amoxicillin DT at the country-level; this was attributed to challenges with quality and availability of data and a need to strengthen quantification methodologies – issues seen across a range of essential medicines.

Significant progress has been made in demand for amoxicillin DT since 2014. To begin, demand for the life-saving medicine has steadily increased. UNICEF remains the single largest global procurer of amoxicillin DT – their order volumes are viewed as indicative of global demand. In fact, since 2015, UNICEF's procurement volumes have increased threefold (Figure 10).^{xxix} This progress has been mirrored by increased demand for amoxicillin DT at the country-level where now in addition to UNICEF, national procurement agencies have increasingly procured amoxicillin DT as part of their portfolio; this includes forecasting, supply planning, tendering, and bid evaluations. Country-level demand for amoxicillin DT is estimated to be significant and

FIGURE 10. UNICEF procurement volumes, 2015-2020 (tablet, millions)

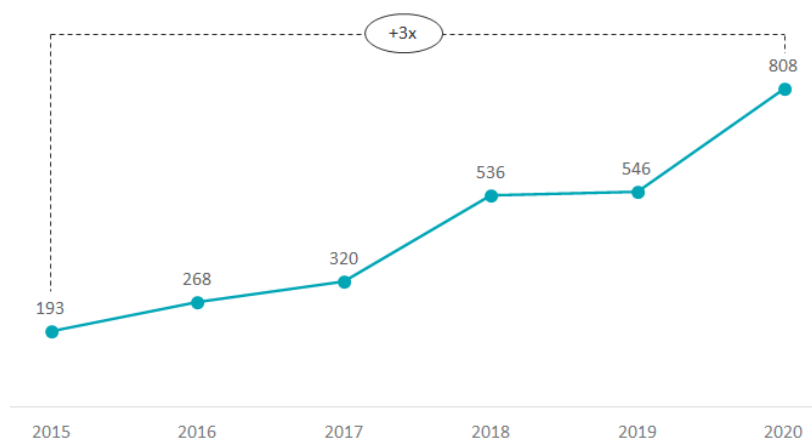
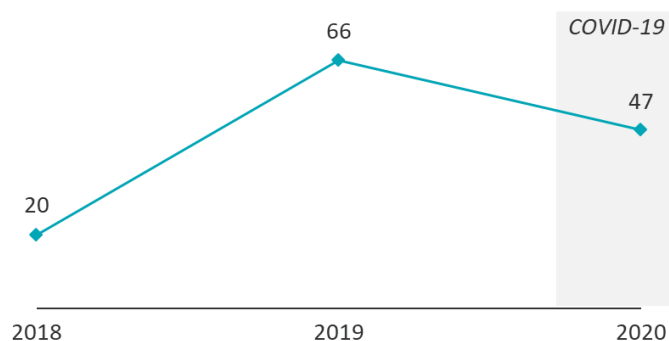


FIGURE 11. Country A procurement volumes, 2018-2020 (tablet, millions)



growing. A detailed look at one high burden country (Country A) illustrates how demand has increased over time since the national procurement agency first began procuring amoxicillin DT in 2018 (Figure 11).^{xxx}

However, while demand has increased at both the global- and national-levels and countries have improved their procurement capacities, barriers remain related to quantification methodology and its utilization:

- *Quantification:* Accurately quantifying demand at the country-level is necessary to inform both resource mobilization and procurement. Amoxicillin DT would benefit from further country-level support to strengthen underlying data, assumptions, and methodologies used in national quantification exercises. In 2014, partners developed the RMNCH quantification supplement to offer guidance for country-level quantifications on key life-saving commodities, including amoxicillin DT.^{xxxi} This is a useful resource and tool, however, further in-country technical assistance is needed to support countries to implement global guidance and address key challenges unique to amoxicillin DT. Cited challenges in conducting quantifications for amoxicillin DT include accounting for seasonality, including other conditions where amoxicillin DT is prescribed, and ensuring demand across both community- and facility-levels are forecasted in a harmonized manner. In one country (Country B), collective partner support provided to the Ministry of Health led to significant updates to quantification methodology and assumptions, including harmonizing data and methodologies to quantify demand across community and facility levels, ensuring assumptions followed recommended guidelines regarding dosages, and including additional indicators for which amoxicillin DT is prescribed in the health system. This ultimately led to a nearly twofold increase in quantified volumes of amoxicillin DT (Figure 12). This suggests previous quantifications were significantly underestimating national need, and thus potentially contributing to under-financing

and under-procurement of the life-saving commodity. Similar impact would likely be experienced in other countries if greater quantification technical assistance were provided.

- *Utilization of quantification in national planning:* Additionally, it is important to ensure national quantifications for amoxicillin DT are utilized to inform resource mobilization and procurement decisions. Multiple high burden countries have been seen to have a disconnect in the utilization of national quantifications. For instance, the formulation of amoxicillin quantified may not match the formulation procured (i.e., only capsules quantified but both capsules and DT procured), or national quantifications may include the DT formulation, but the quantification is not used to inform donor and government resource mobilization or procurement planning exercises. These disconnects in the utilization of quantifications in national planning increase the chances of misalignment with financing and procurement decisions.

Moreover, while demand for amoxicillin DT has grown in the public sector, these gains have not cascaded into the private sector – which accounts for over 50% of childhood pneumonia careseeking in some high-burden countries.^{xxxii} Low private sector demand for amoxicillin DT has been cited throughout the value chain, from importers to wholesalers, and down to points of care.^{xxxiii} The root causes are not fully understood, but further exploration of market challenges in the private sector, and possible solutions, are needed.

Recommendations

- Provide direct technical assistance to leverage global guidance and support countries to strengthen their national quantifications for amoxicillin DT in a sustainable manner, and which includes all levels of the health system.
- Prioritize and allocate technical assistance to ensure national quantifications are utilized to inform national planning for amoxicillin DT – including resource mobilization and procurement planning.
- Support further investigation of amoxicillin DT market challenges in the private sector and identify solutions to improve scale-up in the private sector value chain, e.g., sensitization workshops and marketing campaigns.

Appropriate Use

Once procured and distributed to points of care, additional challenges exist around appropriate use of amoxicillin DT, regarding both correct diagnosis of childhood pneumonia and ideal prescription practices. Misdiagnosis and mis-prescription have been cited anecdotally in multiple high burden countries. This has direct implications on access to amoxicillin DT for those in need, as well as implications on broader risks for AMR. While there is no known spread of AMR for amoxicillin DT specifically, emerging evidence on high antibiotic prescription rates in LMIC settings is noteworthy. On average, children in LMICs are estimated to receive over 24 antibiotic prescriptions before their fifth birthday.^{xxxiv} Appropriate use of antibiotics are of particular concern for respiratory illnesses, such as childhood pneumonia, which can be difficult to correctly diagnose in limited resource settings. While limited data currently exists to understand the degree of and root causes for the challenge, a variety of studies provide important insights into the challenge. These helpful insights point to areas in which governments and partners may focus their attention to improve appropriate use of amoxicillin DT.

It is estimated that across low and middle-income countries, 40-75% of children under-five seeking care for pneumonia receive appropriate antibiotics for treatment. For comparison, an estimated 55-85% of children seeking care received appropriate treatment for diarrhea.^{xxxv} This has been corroborated by additional studies. For instance, in 2017 a health facility observational study was conducted in Tanzania to support of the government's objectives to understand –

and then improve – diagnosis of childhood pneumonia. Findings from the study indicate high rates of misdiagnosis in the limited resource setting where only 18% of under-five children presenting with signs of pneumonia were correctly diagnosed. Furthermore, the studied identified high occurrence of undesirable prescription behavior where of those children correctly diagnosed as pneumonia positive, only 72% were then correctly prescribed amoxicillin.^{xxxvi} An additional study conducted in India suggests that the prevalence of misdiagnosis and mis-prescription may be driven by a “know-can” gap among healthcare providers. This study revealed low correct knowledge of clinical signs of pneumonia (27-37% of providers), and then even lower ability to follow clinical guidelines to diagnose pneumonia (3-18% of providers).^{xxxvii}

Governments and partners have implemented a range of interventions aimed at improving correct diagnosis and prescription behaviors for childhood pneumonia. At a convening of the Child Health Task Force's Child and Newborn Commodities subgroup, partners identified a range of interventions that have been deployed in a variety of geographies to improve appropriate use. Interventions mentioned included distributing and disseminating clinical guidelines and job aids, holding provider trainings, as well as supporting supervision and mentorship programs at facilities. Notably, a single intervention was not seen to “unlock” appropriate use challenges, however a variety of interventions applied together are likely needed to improve provider knowledge, skills, and practices.

Recommendations

- Support further data collection and monitoring of the degree to which misdiagnosis and mis-prescription occurs in their geographies. This may be achieved through leveraging adaptations to ongoing means of data collection (i.e., DHIS systems, household surveys) and supporting additional surveys.
- Coordinate to ensure a package of interventions are resourced, and then deployed, to address provider knowledge, skills, and ultimate practices (i.e., the “know”, “can”, and “do”)
- Recognizing that cultural and resource differences across geographies may influence the effectiveness of interventions, dedicate greater research to identifying what interventions are (or are not) the most effective in improving provider practices in their unique setting. This can be done in a leveraged manner, such as ensuring interventions include a basic baseline and endline measurement of desired outcomes.

CONCLUSION

In conclusion, the market for amoxicillin DT has greatly improved compared to its status in 2014 when WHO first recommended the product for treatment of childhood pneumonia. Since 2014, governments, donors, and implementing partners have supported efforts to address a multitude of market barriers which were inhibiting scale-up. This includes (1) creating an enabled regulatory environment at the country level, (2) making inroads to mobilize domestic resources in some countries while also securing some continued donor financing, (3) encouraging manufacturers to participate in country markets and offer competitive prices, and (4) increasing demand for amoxicillin DT within public sectors while developing the capacities of countries to procure the life-saving product.

In addition to these great successes, as identified above, there are also continued opportunities across regulatory, financing, supply, and demand aspects of the amoxicillin DT market which would benefit from further interventions on behalf of governments, donors, and partners. This brief aims to highlight these additional opportunities for progress in an effort to encourage appropriate prioritization, and pivoting as needed, to ensure remaining barriers to amoxicillin DT scale-up may

be addressed in the coming years. Moreover, while not discussed in this brief, alongside continued efforts to address national- and global-level market dimensions, challenges related to service delivery (e.g., supply chain, correct prescription, etc.) must also be prioritized. In particular, evidence generated around high rates of misdiagnosis and mis-prescription for childhood pneumonia highlight the limitations of improving access to amoxicillin DT if correct diagnosis and appropriate use of the life-saving medicine are not improved.^{xxxviii xxxix} These challenges are a critical component to ensure amoxicillin DT is not only accessible, but appropriately used.

As the leading infectious cause of mortality in children under-five, ensuring access to a comprehensive package of care to prevent, diagnose, and treat childhood pneumonia is essential to achieving the Sustainable Development Goals of ending preventable child mortality. Amoxicillin DT, as the recommended treatment for non-severe childhood pneumonia, is a critical component to achieving these goals. As such, building upon progress since 2014 to further prioritize efforts to enhance scale-up should be a priority among governments, donors, and partners.

Annex A: Summary of recommendations for partners and country governments to support further scale-up of amoxicillin DT

To further ensure amoxicillin DT is prioritized on a policy-level:

- For 13-16 countries that do not include amoxicillin DT on the clinical treatment guidelines and EML, ensure they are aware of the updated WHO guidance and its benefits.
- Support more countries to prioritize and cost treatment of childhood pneumonia in national policies as a core strategy to tackle under-five mortality, in addition to including amoxicillin DT in national guidelines and essential medicines lists.

To further ensure sufficient, sustainable financing exists:

- Prioritize more donor funding for amoxicillin DT, perhaps via co-financing mechanisms, to (1) address short-term funding gaps, and (2) catalyze greater domestic resources over-time to secure sustainable financing.
- Improve coordination efforts between partners and governments to ensure countries have a deliberate discussion around and an action plan for resource mobilization for pneumonia treatment.
- Develop a guidance tool to clarify the various terms and conditionalities of donor financing mechanisms available for amoxicillin DT, including GFF.
- Support countries to develop an investment case for amoxicillin DT, among other MNCH commodities, which can be used to inform resource mobilization from donor and domestic resources.
- Support countries to develop clear evidence and strategies to mobilize greater domestic resources for amoxicillin DT in order to support sustainable financing in the long-term.

To further ensure affordable, high-quality supply exists:

- Support efforts to reduce market asymmetry by providing manufacturers with updates on demand across high burden country markets and clarifying the process to register their products.
- Clarify the process and business case for manufacturers to participate in global quality mechanisms – SRA, WHO PQ, and WHO ERP. This may include liaising with existing amoxicillin DT manufacturers to clarify the process and timelines to submit applications and providing return on investment analyses.
- Develop a list of amoxicillin DT products which hold global quality designations for national procurement agencies to refer to when evaluating tenders. This would make it more efficient for procurement agencies to include global quality assurances as a criteria in their bid evaluations, and thus increase the likelihood of them doing so.
- Encourage national drug regulatory authorities (NDRAs) to consider global quality designations in their dossier reviews to increase efficiencies for manufacturers, and thus provide a tangible benefit to pursuing both global quality designations and registering their product in countries. A potential benefit would be reduced timeline to review dossiers when the product holds a global quality designation.

To further ensure demand is accurately quantified and procured in public and private sectors:

- Provide direct technical assistance to leverage global guidance and support countries to strengthen their national quantifications for amoxicillin DT in a sustainable manner, and which includes all levels of the health system.
- Prioritize and allocate technical assistance to ensure national quantifications are utilized to inform national planning for amoxicillin DT – including resource mobilization and procurement planning.
- Support further investigation of amoxicillin DT market challenges in the private sector and identify solutions to improve scale-up in the private sector value chain, e.g., sensitization workshops and marketing campaigns.

To further improve appropriate use:

- Support further data collection and monitoring of the degree to which misdiagnosis and mis-prescription occurs in their geographies. This may be achieved through leveraging adaptations to ongoing means of data collection (i.e., DHIS systems, household surveys) and supporting additional surveys.
- Coordinate to ensure a package of interventions are resourced, and then deployed, to address provider knowledge, skills, and ultimate practices (i.e., the “know”, “can”, and “do”)
- Recognizing that cultural and resource differences across geographies may influence the effectiveness of interventions, dedicate greater research to identifying what interventions are (or are not) the most effective in improving provider practices in their unique setting. This can be done in a leveraged manner, such as ensuring interventions include a basic baseline and endline measurement of desired outcomes.

Annex B: Who manufactures amoxicillin DT 250mg?

The list of amoxicillin DT manufacturers is constantly growing – a positive development in the market since 2014. Below is a list of manufacturers known to be registered in high-burden countries and/or hold an LTA with UNICEF Supply Division. The list is not comprehensive but is meant to provide an indication of supply sources.

Manufacturer	Location	Additional notes
Agog	India	
CSPC	China	
Daily Need	Nigeria	
EPHARM	Ethiopia	
IPCA Laboratories Limited	India	
Kampala Pharmaceutical Industries	Uganda	
Kopran Limited	India	
Lab and Allied	Kenya	
Medicef Pharma	India	
Medopharm	India	Previously received UNICEF LTA.
Medreich	India	Current LTA with UNICEF. WHO ERP recommendation in 2015.
Micro Labs	India	Current LTA with UNICEF. WHO ERP recommendation in 2015.
Milan Labs	India	Previously received UNICEF LTA.
Nem Laboratories	India	
PT Caprifarmindo Laboratories	Indonesia	
Regal	Kenya	
Remedica	Cyprus	Current LTA with UNICEF. SRA approval. WHO ERP recommendation in 2015.
Reyoung	China	
Sanbe Farma	Indonesia	
Sandoz	Germany	Current LTA with UNICEF. SRA approval. WHO ERP recommendation in 2015.
Sparsh	India	
Square	Bangladesh	
Theon Pharmaceuticals	India	
Vapicare	India	

Results for Development

Results for Development ([R4D](#)) is a leading non-profit global development partner. We collaborate with change agents around the world — government officials, civil society leaders and social innovators — to create strong systems that support healthy, educated people. We help our partners move from knowing their goal to knowing how to reach it. We combine global expertise in health, education and nutrition with analytic rigor, practical support for decision-making and implementation and access to peer problem-solving networks. Together with our partners, we build self-sustaining systems that serve everyone and deliver lasting results. Then we share what we learn so others can achieve results for development, too.

R4D's [Market Shaping Practice](#) has deep experience in addressing inefficiencies across global and country-level markets to dramatically expand access to affordable, high-quality essential commodities, towards helping people lead healthier, more productive lives. R4D achieves this by aligning priorities and incentives of change agents, such as policymakers, procurers, financiers and manufacturers at the global- and country-levels to develop and execute solutions for underserved markets at scale. Using practical and business-driven approaches — from increasing market transparency, improving demand forecasting, developing purchasing strategies, to crafting cost-effectiveness analyses — R4D works with local government officials and others to systematically identify and address market and delivery barriers to secure sustained availability and affordability of essential products. Previously designed market-shaping solutions by R4D have the potential to achieve over a billion dollars in savings and availability of high-quality products, including for HIV/AIDS, malaria, childhood pneumonia, maternal health, and neglected diseases prevention and treatment.

Citations

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- ^{vii} WHO, [Guideline: Managing possible serious bacterial infection in young infants](#), 2015 and WHO, [Integrated management of childhood illness: management of the sick young infant aged up to 2 months: IMCI chart booklet](#), 2019.
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- ^{xi} UNICEF Supply Division, [Amoxicillin Dispersible Tablets \(DT\): Product Profile, Availability and Guidance](#), 2013.
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- ^{xiii} Example includes Uganda's 2016 National Reproductive, Maternal, Newborn, and Child Health Sharpened Plan which prioritized tackling childhood pneumonia to reduce child mortality.
- ^{xiv} Bartlett, [Trends in international development assistance to combat pneumonia](#), 2020. From 2007-2018, of the total \$7.1B spent on pneumonia, only about \$285M was spent on pneumonia diagnostics and treatment, combined.
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- ^{xvi} All GFF country investment cases were not reviewed as part of this market brief. However, a preliminary [review](#) of country investment cases conducted by the GFF Secretariat in 2016 revealed they were focused on aspects of health systems strengthening, and as such did not delve into commodity procurement or distribution. To-date, R4D has only learned of two countries utilizing GFF to fund commodity procurement; one is procuring multiple RMNCAH products, including amoxicillin DT, and the second country is only procuring family planning products.
- ^{xvii} Global Fund, [Prospective Country Evaluation](#), 2021.
- ^{xviii} R4D analysis of financing for MNCH medicines across five geographies in Sub Saharan Africa revealed 70% of MNCH medicine volumes procured for the public sector from 2016-2018 were funded through government resources.
- ^{xix} Total domestic resources allocated to amoxicillin DT 250mg in a high burden country between 2017-2020. The country benefited from partner support to mobilize domestic resources for amoxicillin DT 250mg since 2016.
- ^{xx} R4D, Challenges inhibiting scale-up of amoxicillin dispersible tablets market diagnostic, 2015.
- ^{xxi} R4D, Challenges inhibiting scale-up of amoxicillin dispersible tablets market diagnostic, 2015.
- ^{xxii} Countries have enacted policies which give preferential treatment to local manufacturers. Examples include "Buy Uganda, Build Uganda" and "Buy Kenya, Build Kenya" policies.
- ^{xxiii} Awarded tenders sourced from national medical stores.
- ^{xxiv} UNICEF, [Amoxicillin dispersible tablets market and supply update](#), 2018. In 2015, UNICEF and WHO released an Expression of Interest (EOI) for Expert Review Panel (WHO ERP) for amoxicillin DT 250mg. UNICEF utilized the WHO ERP recommendations to identify quality assured manufacturers when awarding its 2017 LTA. UNICEF awarded an LTA to four manufacturers, and this LTA is currently still in place.
- ^{xxv} [Expression of Interest](#) for WHO PQ, first invitation to manufacturers of medicinal products for treatment of infections in newborn and young infants for childhood pneumonia. Released in 2020.

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- ^{xxvii} Pricing data collected by R4D through annual interviews with amoxicillin DT manufacturers, 2015-2021.
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