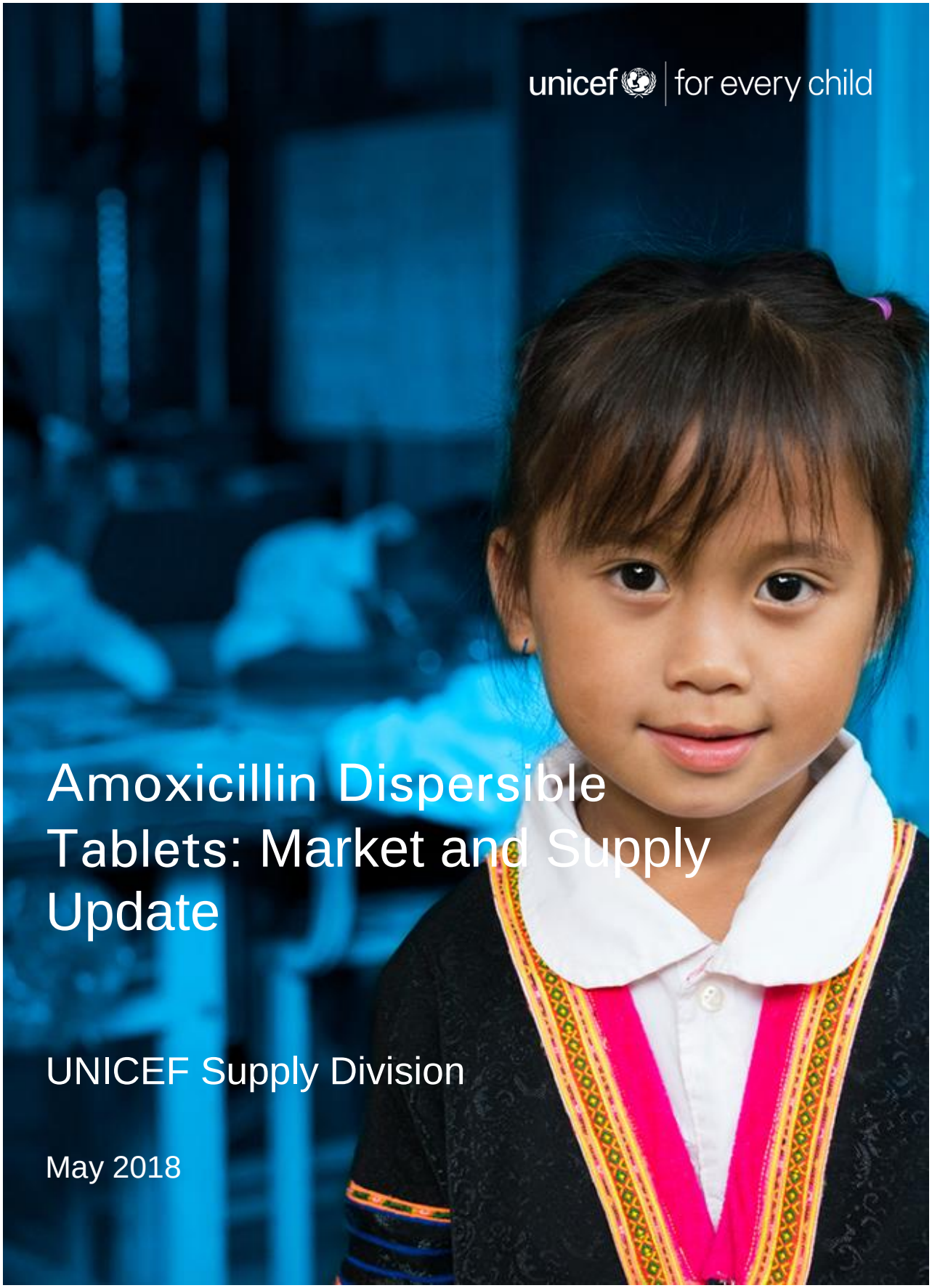

Amoxicillin Dispersible Tablets: Market and Supply Update

UNICEF Supply Division

May 2018

Amoxicillin Dispersible Tablets
Market and Supply Update – May 2018

This update provides information for the period 2018-2019 on amoxicillin dispersible tablets, including supply, and demand across low- and middle-income countries. The product has demonstrated higher effectiveness as a first-line treatment for pneumonia, and there is sufficient supply to meet current and anticipated demand. However, countries must continue to scale-up use and access to amoxicillin dispersible tablets. UNICEF continues to encourage advocacy efforts to support the adoption of WHO's treatment guidelines and product inclusion into national essential medicine lists.

1. Summary

- This note profiles amoxicillin dispersible tablets (DT) products and describes product availability through UNICEF, summarizing its use under the World Health Organization's (WHO) guidance for pneumonia treatment.
- Amoxicillin is an effective broad-spectrum antibiotic for use against bacterial infections and especially the treatment of children with bacterial pneumonia.
- However, its use as first-line treatment for pneumonia in countries with a high-burden caseload remains limited, despite higher effectiveness compared to existing alternative treatments.
- UNICEF introduced amoxicillin DT tablets into its supply catalogue in 2011. The most recent tender increased amoxicillin DT availability and supported increased supply to critical markets. To further increase product accessibility and use, UNICEF encourages advocacy efforts to support changes to national treatment guidelines and national Essential Medicine Lists (EML) to include dispersible formulations of amoxicillin.
- UNICEF's last tender concluded with the evaluation of four suppliers compliant with UNICEF specifications and awarded them long-term arrangements (LTAs) to supply amoxicillin 250mg DT to increase quality assured supply to countries implementing WHO's protocol for childhood pneumonia.

2. Pneumonia Epidemiology and Amoxicillin

World leaders at the United Nations (UN) Sustainable Development Summit adopted the Sustainable Development Goals (SDGs) in 2015, and included the target to end preventable deaths of children under-five years of age; and to reduce under-five mortality to 25 deaths per 1,000 live births by 2030.[1] The global under-five mortality rate in 2016 was 41 deaths per 1000 live births.[2] Pneumonia killed over 900,000 children aged under-five In 2015, accounting for 16% of all deaths of children under-five globally,[3] mostly in South Asia and sub-Saharan Africa. Pneumonia is a preventable and curable infectious disease and the leading cause of death in children under five years of age worldwide. It is a form of acute respiratory infection that affects the lungs. The air sacs (alveoli) fill with fluid, rendering breathing painful, and limiting oxygen intake. Several infectious agents can cause pneumonia, including bacteria,

[1] United Nations, *Sustainable Development Goal 3, Ensure Healthy Lives, and Promote Well-being for All at All Ages*, UN, New York, 2015.
[2] UNICEF, World Health Organization, World Bank Group, United Nations, *Levels and Trends in Child Mortality: Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation*, UNICEF, Geneva, 2017, p. 3.
[3] Word Health Organization, *Pneumonia Fact Sheet*, WHO, September 2016.

fungi, and viruses. The most common cause of bacterial pneumonia in children is *Streptococcus pneumoniae*.[4]

UNICEF and WHO set out clear goals to end preventable child deaths by pneumonia in their Global Action Plan for Pneumonia and Diarrhoea (GAPPD) by 2025. It seeks to reduce the incidence of severe pneumonia among children under-five by 75%; reduce under-five child mortality from pneumonia to fewer than 3 per 1000 live births; and ensure 90% of cases have access to appropriate case management with antibiotics.[5]

Amoxicillin is a broad-spectrum penicillin antibiotic used to treat bacterial infections. It is especially effective to treat bacterial pneumonia in children, as well other illnesses, including bacterial infections in the abdomen, blood, ears, sinuses, skin, throat, and urinary tract, amongst others. Nutrition interventions also use amoxicillin to prevent infections when treating severe acute malnutrition (SAM). WHO recommends amoxicillin 250 mg, preferably in DT form, to replace cotrimoxazole as a more effective first-line treatment for pneumonia in children under-five years of age.[6] WHO recommends trained community health workers (CHWs) treat children under-five with pneumonia not showing danger signs (non-chest in-drawing) at community level,[7] using either 10 or 20 oral amoxicillin 250mg DT per treatment depending on the age reference (Table 1).

Table 1 Doses of Amoxicillin 250mg Dispersible Tablets for Children 2–59 Months of Age with Pneumonia

Tools	Category of Pneumonia	Age/Weight of Child	Dosage of Amoxicillin Dispersible Tablets (250 mg)
iCCM* tool for community health workers	Fast breathing pneumonia	2 months up to 12 months (4–<10 kg)	1 tablet twice a day x 5 days (10 tablets)
		12 months up to 5 years (10–19 kg)	2 tablets twice a day x 5 days (20 tablets)
IMCI† tool for professional health workers at health facilities	Fast breathing and chest in drawing pneumonia	2 months up to 12 months (4–<10 kg)	1 tablet twice a day x 5 days (10 tablets)
		12 months up to 3 years (10–<14 kg)	2 tablets twice a day x 5 days (20 tablets)
		3 years up to 5 years (14–19 kg)	3 tablets twice a day x 5 days (30 tablets)

Source: World Health Organization
Note*: Integrated Community Case Management (iCCM).
Note†: Integrated Management of Childhood Illness (IMCI), developed by UNICEF and WHO in 1995, reviewed in 2003 to include care for newborns under one week of age, renamed IMNCI in in many countries.

Integrated Community Case Management (iCCM) is a community-based management approach to treat diarrhoea, malaria, and pneumonia.[8] A review by the Child Health Epidemiology Reference Group (CHERG), estimated that a community-based approach to treating pneumonia could result in a 70% reduction in mortality in children under-five.[9]

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[4] Ibid.
[5] UNICEF, World Health Organization, *Ending Preventable Child Deaths from Pneumonia and Diarrhoea by 2025: The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD)*, UNICEF, New York, 2013, p. 7.
[6] World Health Organization, *Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities: Quick Reference Guide*, WHO, Geneva, 2014.
[7] World Health Organization, *Caring for Newborns and Children in the Community: A Training Course for Community Health Workers*, WHO, Geneva, 2011.
[8] Maternal and Child Survival Program, *Integrated Community Case Management (iCCM), MCSP*, Washington, 2018.
[9] Theodoratou, Evropi, et. al, *The Effect of Case Management on Childhood Pneumonia Mortality in Developing Countries*, International Journal of Epidemiology, Volume 39, Issue supplement 1, Oxford, March 2010, p. 155–171.

Amoxicillin DT is one of the 13 life-saving commodities identified by the United Nations Commission on Life-saving Commodities for Women and Children (UNCoLSC). The UNCoLSC, established in 2010 as part of the UN's Every Woman and Every Child Programme, sought to support overlooked commodities that could effectively prevent premature death and disease in under-five children and women during pregnancy and childbirth; that are not supported by existing funding mechanisms; and that have the potential to benefit neglected communities with increased access through innovative product development and market-shaping scale-up.[10]

Despite available and affordable diagnostics and antibiotics, two thirds of pneumonia cases do not receive antibiotics as part of treatment regimens.[11] One major reason is that communities in resource-constrained settings have limited access to child-friendly formulations. In many instances, pharmaceutical presentations in many developing countries are predominantly for adults. CHWs have difficulty administering these presentations in appropriate dosages for children. They counter this and often proxy paediatric formulations by breaking and dividing adult formulations for children, compromising effectiveness. For instance, CHWs often cut, crush, and mix tablets into a liquid; or dilute capsules into unknown liquid concentrations, attempting to provide a paediatric dose to a child. Table 2 describes the different available amoxicillin formulations through UNICEF.

Table 2 Different Amoxicillin Product Formulations through UNICEF

Amoxicillin Products	Purpose
Amoxicillin Tablets	• Amoxicillin tablets are another conventional form, often available with scoring. • Scored tablets allow users to brake pharmaceutical tablets to adjust dosing per prescription. • Available in strengths of 250mg and 500mg.
Amoxicillin Oral Suspension	• Amoxicillin powder for oral suspension (OS) is at present the most commonly used paediatric formulation. • Available in a strength of 125mg/5ml. • CHWs administer it as a liquid to facilitate the treatment of children and those with difficulties swallowing tablets.
Amoxicillin DT	• Equivalent to amoxicillin OS, with each dose compacted into a tablet, dispersible in 5-10 ml of water. • Cheaper than its amoxicillin OS equivalent. • Offers cost-effective logistical and supply chain advantages in term of volume and weight. • Designed for patients with difficulties in swallowing. • Facilitates and simplifies CCM and dosage accuracy compared to Amoxicillin OS, which CHWs measure and mix manually. • Does not need refrigeration. • Combined with revised protocols and clear and easy treatment prescription and administration instructions, they provide the most cost-effective method to treat pneumonia in under-fives. • Available in strengths of 250mg and 500mg.

Source: UNICEF Supply Division

UNICEF supplies amoxicillin 250mg tablets in a dispersible form as a child-friendly paediatric dosage. They are blister packed to simplify dispensing and supply. Dispersible tablets remove the need for CHWs to crush tablets and they simplify treatment administration. By comparison, amoxicillin syrup and other oral solution (OS) formulations require refrigeration, reconstitution with clean water, and accurate measuring devises to administer correct dosages. In addition, liquid presentations are more expensive, heavier to transport, and require more space to store. Each amoxicillin DT, which is equivalent to amoxicillin powder for OS, is an accurately measured dose compacted into a tablet that quickly disperses in 5-10 ml of water or milk.

[10] The UN Commission on Life-saving Commodities, *Life-saving Commodities*, UNICEF, New York, 2018.
[11] UNICEF, WHO, *Ending Preventable Child Deaths from Pneumonia and Diarrhoea by 2025: The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD)*, p. 5.

Amoxicillin DT also has a comparatively lower volume and weight, and generates less waste, offering greater logistical and supply chain efficiency through to end-users in a community, without any cold chain requirements.

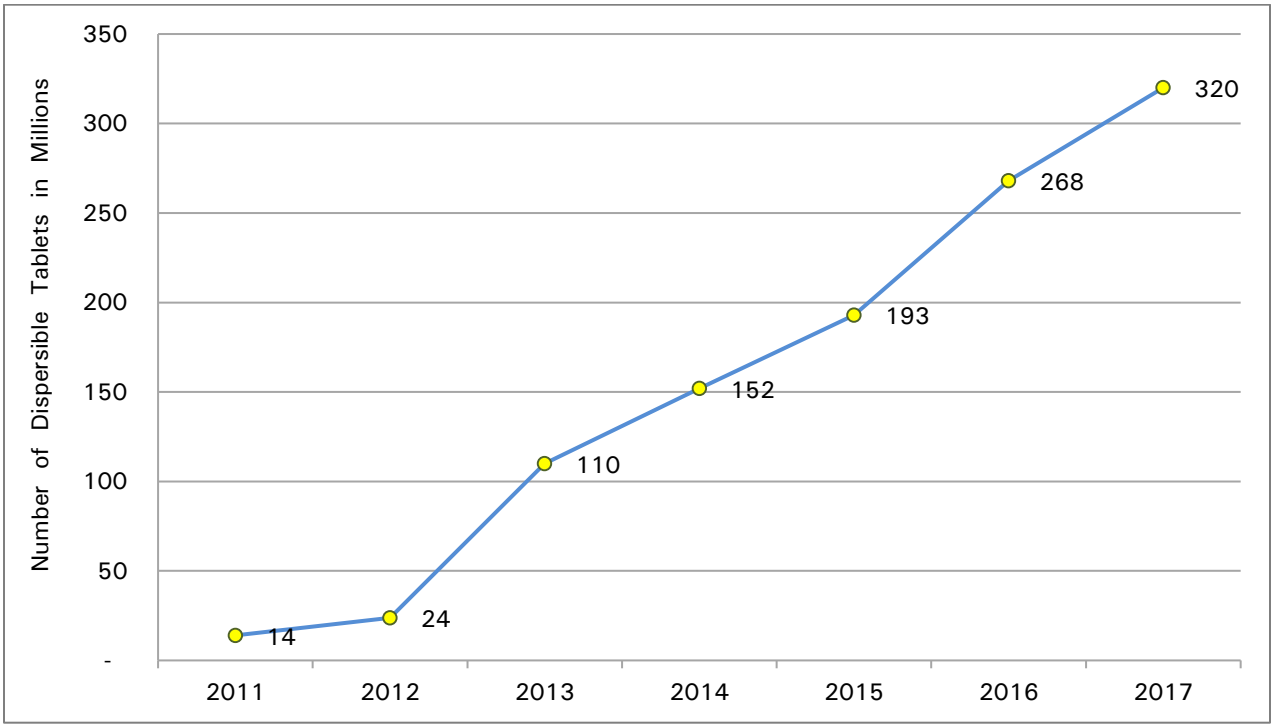
3. Current Market Situation

3.1 Demand

The market for amoxicillin 250mg DT is steadily increasing as more countries change their treatment protocols to align with WHO's revised childhood pneumonia treatment guidelines using 250mg amoxicillin DT. UNICEF, independently and through partnerships, continues to shape global and local delivery markets, including improving quality assurance and supply of heretofore limited amoxicillin DT use and availability in resource-limited settings by communities. Whereas amoxicillin DT for paediatric dosages (125mg and 250mg) is currently more established in Asia than other regions, in Africa, the market for paediatric amoxicillin is more established for amoxicillin OS than DT.[12]

To stimulate the market, UNICEF has supplied amoxicillin 250mg DT to several countries since 2011. From 2013, UNICEF has observed an exponential increase in demand for amoxicillin DT (and associated procurement) to reach approximately 320 million tablets in 2017, representing an average increase of approximately 60 million tables a year (Figure 1).

Figure 1 UNICEF 250mg Amoxicillin Dispersible Tablet Procurement 2011-2017



Source: UNICEF Supply Division

Except for very small quantities of other presentations, procurement through UNICEF has in the most part been of amoxicillin 250mg scored DT in multi-dispensing blister strips of 10x10. Blister strips are also available of 1x10 as individual patient packs to treat children under one year of age, and 2x10 for children over one year.

Despite higher effectiveness compared to existing, often more expensive, alternatives antibiotics, the use of amoxicillin DT as a first-line treatment for pneumonia in countries with

[12] The UN Commission on Life-saving Commodities, *Amoxicillin Product Profile*, UNICEF, New York, 2018.

a high-burden caseload remains limited. To date, few governments have adopted WHO's recommendations to incorporate amoxicillin DT into their country's national treatment guidelines and List of Essential Medicines (EML).[13] The EML comprises a list of essential medicines that should be available in all functioning health systems. For those countries that have included amoxicillin DT, they often do not have sufficient funds to finance procurement. In addition, amoxicillin DT often competes with cotrimoxazole, used to treat opportunistic infections in HIV positive patients, often funded by the Global Fund (formerly the Global Fund to Fight AIDS, Tuberculosis, and Malaria) in low- and middle-income countries. Some countries, perhaps for convenience, retain cotrimoxazole as their first-line treatment for childhood pneumonia, even though evidence shows it contributes to growing antibiotic resistance.[14] As many governments have funding constraints, they choose to utilize resources from the Global Fund for cotrimoxazole to treat childhood pneumonia, instead of rolling out amoxicillin DT, which requires self-financing (in the absence of large global funders for amoxicillin DT).

UNICEF has predominantly procured amoxicillin DT (93%) on behalf of UNICEF country programmes, utilising various short-term funding, and ad hoc donor funds; i.e. demand for this product is not yet mostly financed by country governments. Even though UNICEF currently anticipates this trend to continue in the short- to mid-term, UNICEF seeks to transfer financing of amoxicillin DT procurement to governments to ensure treatment of pneumonia is sustainable and embedded in government programmes. In 2016, the interagency emergency group recommended replacing amoxicillin 250mg conventional tablets with amoxicillin 250mg DT, to increase existing demand. However, UNICEF cannot accurately project long-term country demand as most governments in countries where pneumonia burden is high do not yet drive demand. Nevertheless, based on the historical demand for amoxicillin DT through UNICEF procurement (Figure 1), UNICEF anticipates the increasing trend in demand to continue in the short- to medium- term.

3.2 Supply

In 2015, with the support of UNCoLSC, UNICEF and WHO launched an Expression of Interest (EoI) for manufacturers to submit amoxicillin 250mg DT to WHO's Expert Review Panel (ERP). The ERP is an independent advisory body of technical experts, coordinated by WHO, that assess the quality risks of pharmaceutical products that do not yet meet all stringent quality requirements.[15] Amoxicillin DT manufacturers needed to demonstrate, and establish, product efficacy, and conduct bioequivalence (BE) studies (a means to show for all intents and purposes that products are the same) using GlaxoSmithKline's Amoxil® powder for OS as a comparator product for amoxicillin DT generics.

Based on the outcome of the EoI and submissions to the ERP, in 2017, UNICEF tendered for amoxicillin DT to increase the availability of quality assured supply for countries implementing WHO's protocol for childhood pneumonia. Based on the bids received, UNICEF identified four suppliers as compliant with UNICEF specifications, and awarded them LTAs to supply amoxicillin DT (Table 3).

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[13] World Health Organization, *WHO Model List of Essential Medicines*, WHO, Geneva, March 2017 (amended August 2017), p. 49.
[14] Marwa, Karol J., et al., *Resistance to Cotrimoxazole and Other Antimicrobials Among Isolates from HIV/AIDS and non-HIV/AIDS Patients at Bugando Medical Centre, Mwanza, Tanzania*, Hindawi Publishing, London, January 2015.
[15] World Health Organization, *Expert Review Panel*, WHO, Geneva, February 2016.

Table 3 UNICEF 2017 Amoxicillin 250mg DT LTA Awards

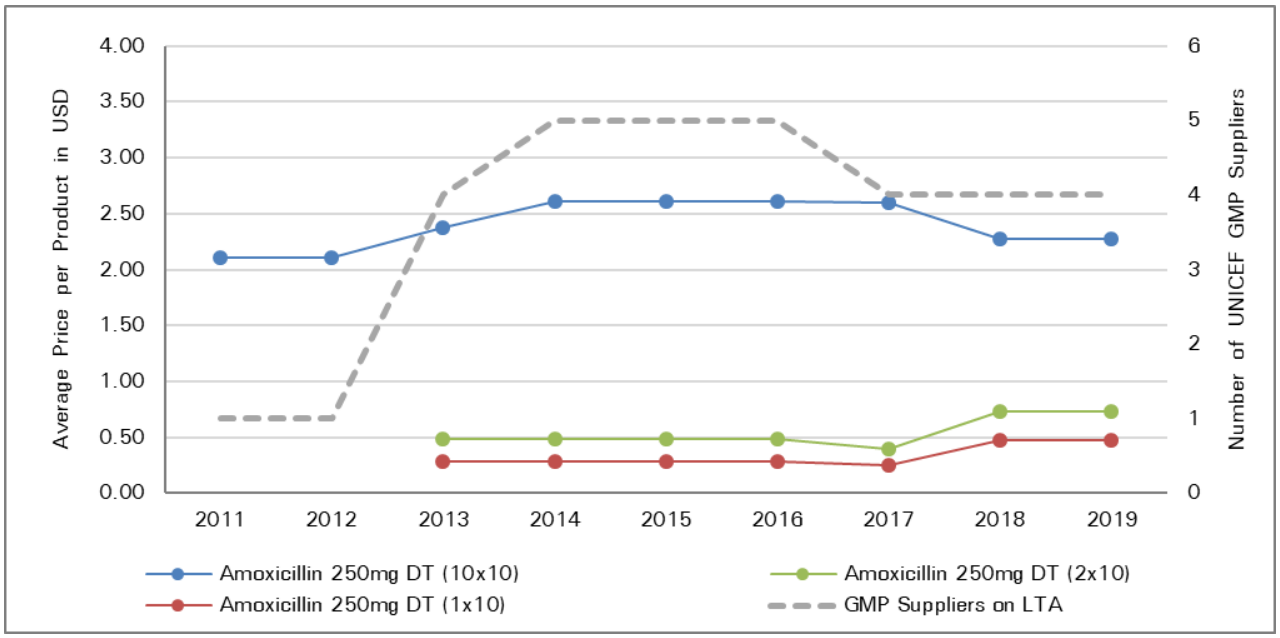
Supplier	LTA Duration	Start	End	Product
Medreich, India	2 years	8-Nov-17	7-Nov-19	Amoxicillin 250mg DT / Pac-10
				Amoxicillin 250mg DT / Pac-20
				Amoxicillin 250mg DT / Pac-100
Micro Labs, India	2 years	8-Nov-17	7-Nov-19	Amoxicillin 250mg DT / Pac-10
				Amoxicillin 250mg DT / Pac-20
				Amoxicillin 250mg DT / Pac-100
Remedica, Cyprus	2 years	8-Nov-17	7-Nov-19	Amoxicillin 250mg DT / Pac-10
				Amoxicillin 250mg DT / Pac-20
				Amoxicillin 250mg DT / Pac-100
Sandoz, Denmark	2 years	8-Nov-17	7-Nov-19	Amoxicillin 250mg DT / Pac-10
				Amoxicillin 250mg DT / Pac-20
				Amoxicillin 250mg DT / Pac-100

Source: UNICEF Supply Division

3.3 Pricing

Figure 1 describes the average price trend per amoxicillin 250mg products UNICEF has procured since 2011. UNICEF increased the number of good manufacturing practice (GMP) approved suppliers to increase product availability to meet growing demand. Price increases reflect UNICEF including European suppliers, which have higher prices as production costs are higher, compared to India (Figure 2).

Figure 2 Amoxicillin 250mg DT Average Price per Product 2011-2019



Source: UNICEF Supply Division

UNICEF's indicative price per treatment course for a child under-one year of age is USD 0.22, and USD 0.44 for a child over one year age. [16,17] The different packaging options available through UNICEF have different price and cost implications, and choices to select the appropriate option depend on what best suits end-users, their context, and environment (Table 4).

[16] The UN Commission on Life-saving Commodities, *Amoxicillin*, UNICEF, New York, 2018.
[17] UNICEF, *Supply Catalogue Data, Pharmaceuticals, Anti-infectives, Beta-lactams*, UNICEF, Copenhagen, 2017.

Table 4 Simple Comparison of Amoxicillin 250mg DT Packaging Options

250mg Amoxicillin DT	USD Price / Treatment	Cost of Logistics	Ease of Dispensing	Patient Compliance
Multi-dispensing Blister Pack 10x10	0.22	Less expensive	Re-packing needed	More challenging
Patient Pack 1x10	0.27	More expensive	Easier	Better
Patient Pack 2x10	0.43	More expensive	Easier	Better

Source: UNICEF Supply Division

Product details are accessible via UNICEF's Supply Catalogue. UNICEF's Supply Catalogue contains the specifications of over 2,000 commodities that respond to the needs of children and their families. It assists UNICEF country offices and partners identify the most appropriate supplies for country programmes, and assists country offices with their supply planning, delivery, and monitoring.

4. Amoxicillin Adherence Aids

Until recently, only medically qualified personnel could prescribe antibiotics. The approach using iCCM allows low-skilled CHWs to administer amoxicillin DT to patients at home. To ensure CHWs do not administer inappropriate dosages to children and engage in any practices to proxy paediatric formulations, UNICEF and partners are currently researching how to provide CHWs clear and easy instructions to dispense and administer treatment. UNICEF is currently trialling how amoxicillin DT product packaging and instruction designs can match the new recommended treatment courses and re-packaged options to simplify child antibiotic administration at point of care (Table 3), and are subject to review. See more here: Amoxicillin adherence aids.[18]

5. Issues and Challenges

Several market challenges exist to scaling-up global access to quality amoxicillin DT. UNICEF summarises some of these technical and market challenges below (Figure 3).

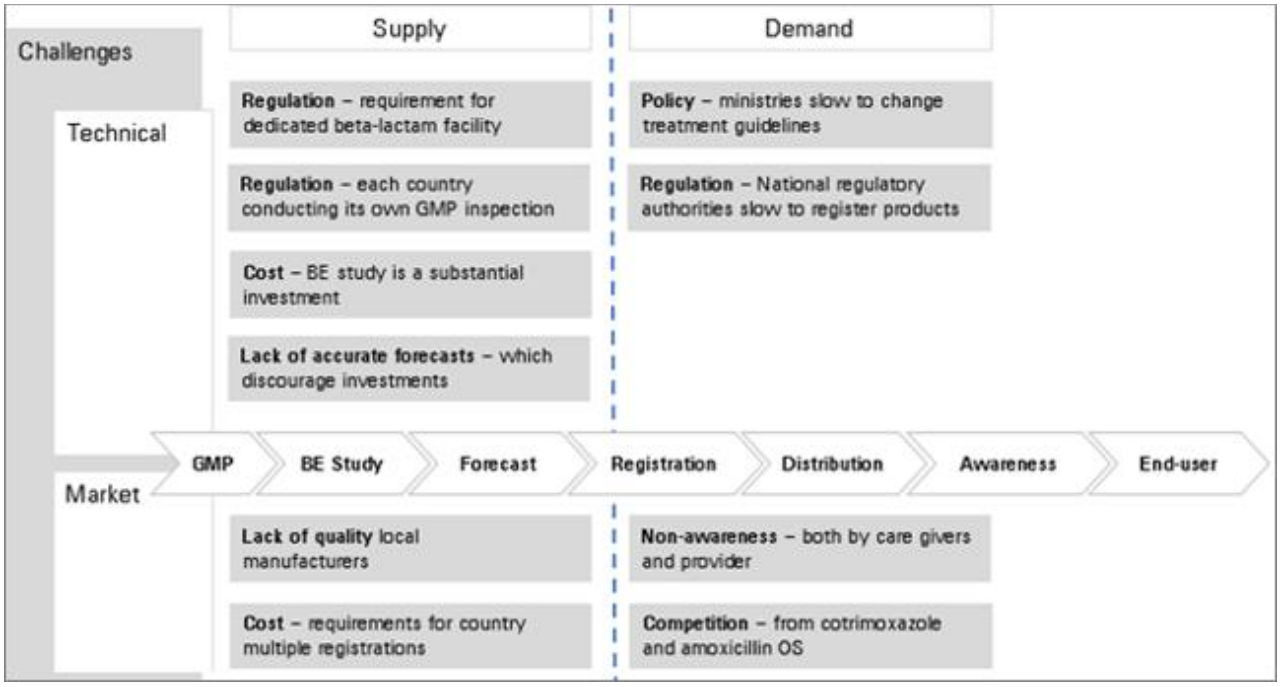
On the supply side, manufacturers must have dedicated beta-lactam manufacturing facilities to avoid beta-lactam contamination of other products, to comply with WHO Good Manufacturing Practice (GMP) guidelines, and which has cost and investment implications. Amoxicillin belongs to a class of antibiotics called beta-lactams, which can cause anaphylaxis (a serious allergic reaction) in approximately 0.01% of exposed patients.[19]

Amoxicillin DT is a class III drug (having high solubility, low permeability) and a low bioavailability, hence why amoxicillin generics require BE studies demonstrating equal efficacy to originator products. BE studies are expensive, and per WHO guidance could cost between USD 60,000 and USD 100,000. Should a BE study fail, manufacturers can repeat the process, which would incur the same cost. These costs prevent local manufacturers in low-income countries from investing in the production of quality assured amoxicillin DT.

New and growing manufacturers require capital to finance operations and product development. With improved financing, suppliers can develop products, improve pricing, offer better commercial terms, and enhance performance benefitting communities. While UNICEF does not finance suppliers' operations, to assist new and growing manufacturers, UNICEF developed a non-exhaustive, interactive list of different options in a database format that could provide different forms of financing, technical expertise, services, and support for new and growing manufacturers in programme countries, accessible here.[20]

[18] UNICEF, *Amoxicillin Adherence Aids*, UNICEF, Copenhagen, November 2017.
[19] Bhattacharya Sanjib, *The Facts About Penicillin Allergy: A Review*, Journal of Advanced Pharmaceutical Technology & Research, Gwalior, November 2010, p. 11-17.
[20] UNICEF, *Sources of Financing for New and Growing Manufacturers*, UNICEF, Copenhagen, January 2015.

Figure 3 Some Barriers to access of Amoxicillin DT



Source: UNICEF Supply Division

6. Steps Forward

- UNICEF will continue to advocate that countries include amoxicillin DT into their national EMLs, adopt WHO treatment guidelines, and register amoxicillin DT in country programmes.
- UNICEF will continue to engage approved amoxicillin DT manufacturers to ensure consistent amoxicillin 250mg DT manufacturing capacity and supply availability to address any gap between demand and supply.
- UNICEF will continue to support the development of more appropriate pneumonia diagnostic aid devices and improvements in product packaging for use in resource-limited settings to improve the accuracy of pneumonia diagnosis and treatment delivery respectively.
- UNICEF will continue to work with suppliers to secure a healthy and competitive market to sustain the increasing demand for amoxicillin DT.

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