Improving access to and appropriate use of medicines for newborn and child health for primary health care:

Challenges in assuring the quality of pediatric amoxicillin and gentamicin injection

Child Health Task Force – May 17, 2022

USAID FROM THE AMERICAN PEOPLE

Promoting the Quality of Medicines Plus (PQM+)

USAID MEDICINES, TECHNOLOGIES, AND PHARMACEUTICAL SERVICES (MTaPS) PROGRAM
Improved Access. Improved Services. Better Health Outcomes.

USAID GLOBAL HEATH SUPPLY CHAIN PROGRAM
Procurement and Supply Management

CHILD HEALTH TASK FORCE

unicef for every child

Agenda

I. Introductions

II. Background & challenge

III. Consultative series on improving uptake of pediatric amoxicillin and gentamicin

IV. Quality of products is not guaranteed: evidence, root causes, and interventions

Introduction
Child Health Task Force

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Child Health Task Force (CHTF)
Newborn and Child Health Commodities subgroup

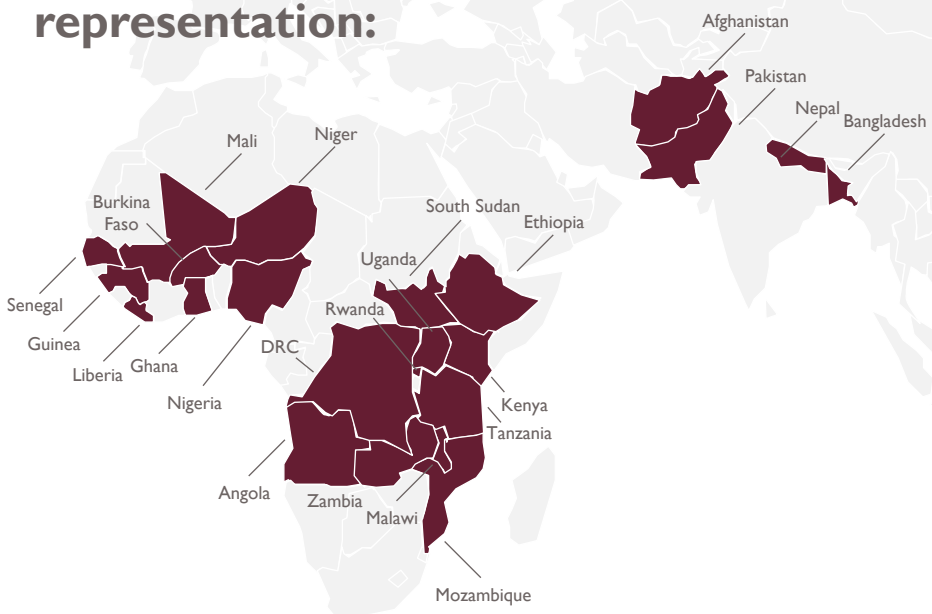
- A subgroup on newborn and child health commodities was created in 2019 within the Child Health Taskforce. Co-chaired by UNICEF and USAID.
- Goal: raise awareness and promote collective efforts to improve the way commodities for newborn and child health are prioritized, financed, and managed.
- This meeting is in line with some of the CHTF objectives:
  - To develop evidence-based strategies to improve access to and appropriate use of newborn and child health commodities
  - To share resources on recognized and emerging best practices and innovations, as well as practical experiences from implementation in country programs for management of child and newborn health commodities.

Introduction
Participants

Government and organizational representation:

- Relevant government entities including Ministries of Health, Regulatory authorities, Central Medical Stores, Maternal & Reproductive Health units, and others
- Global health institutions, including World Health Organization, UNICEF, USAID, The Bill and Melinda Gates Foundation, and others
- Non-governmental organizations, national and international implementing partners
- Academic institutions

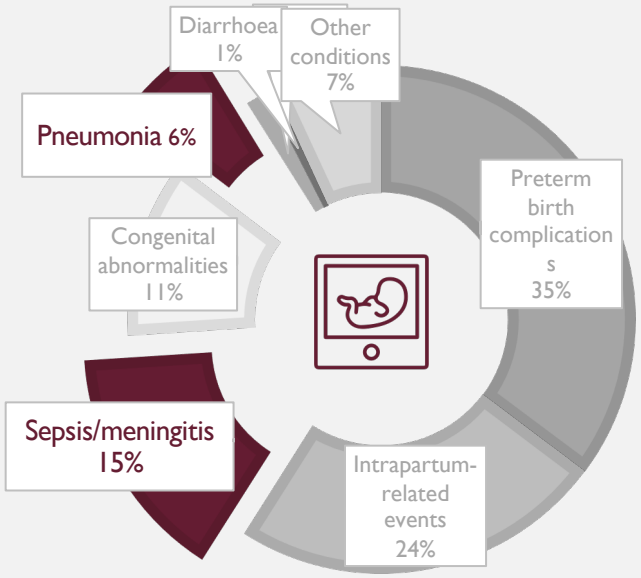
Country representation:



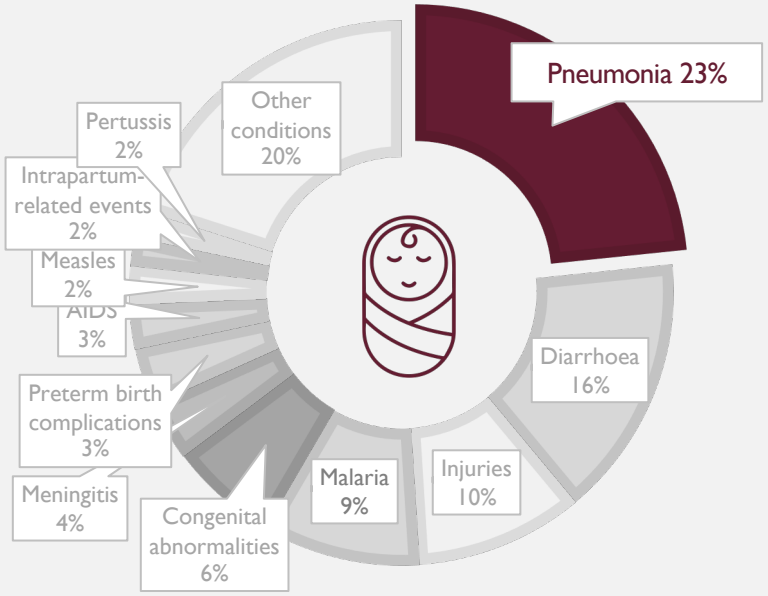
Global challenge
Children are still dying of preventable causes

- Almost half of under 5 deaths are in newborns due to infections, including sepsis/pneumonia, pre-term complications, and birth asphyxia
- Lower respiratory infections are the second leading cause of death among children under five years – 800,000 children a year
- Recent global changes in treatment of newborn and child health conditions still not widely adopted
    - Treatment with amoxicillin was recommended by WHO in 2014 for pneumonia and dispersible tablets were the preferred formulation
    - Oral amoxicillin with gentamicin injection recommended in 2015 for treatment of PSBI in newborns where referral is not feasible
    - In sick young infants with fast breathing as the only sign of illness:
        - under 7 days old refer and, if referral is not feasible, treat with oral amoxicillin
        - 7-59 days old treat with oral amoxicillin, referral not needed (IMCI 2019)
- 54 countries need accelerated action to meet the SDG target for under-five mortality
- **Access to and appropriate use of amoxicillin and gentamicin for newborn and child health through primary heath care remains a challenge.**

Causes of newborn mortality



Causes of child mortality



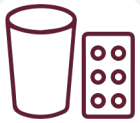
Addressing **key barriers** and **bottlenecks**

What is needed to further the advances already made and increase access to and appropriate use of pediatric amoxicillin and gentamicin?

Prioritized bottlenecks:

Quantification & Financing

Inaccurate quantification at all levels and/ or inadequate financing of pediatric amoxicillin and gentamicin formulations



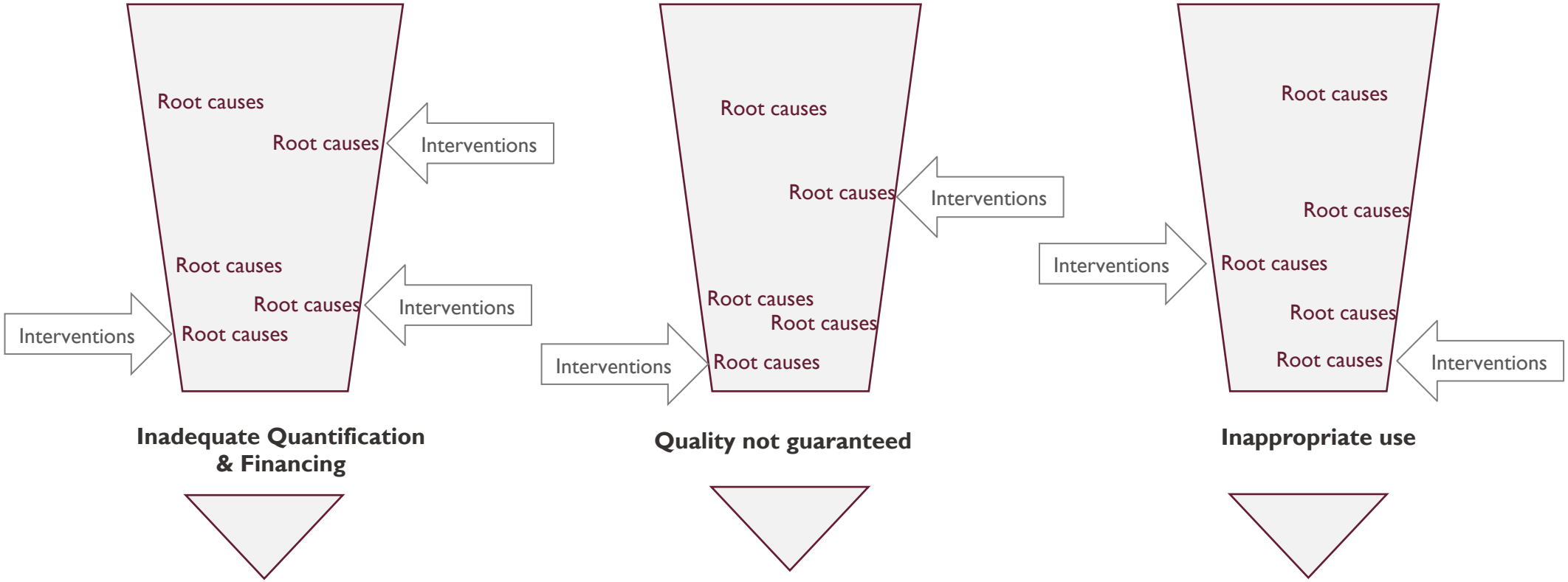
Quality

Quality of child health products not guaranteed

Appropriate Use

Inappropriate use of medicines for treatment of pneumonia and PSBI by providers and caregivers

Challenges impacting commodity access & appropriate use



Improving uptake of amoxicillin and gentamicin

Evidence and solution building process to review experience and evidence related to selected bottlenecks

Consultative process:

- Review of recent literature
- Call for evidence, experience and data.
- Surveys to priority countries
- Consultative meetings
  - Convene country stakeholders, donors, and implementing partners
  - Share evidence on prioritized bottlenecks in uptake of medicines for newborn and child health
  - Discuss root causes
  - Develop consensus on actionable, prioritized solutions
- Call-to-action paper
  - with defined roles for both countries and global partners

Schedule of consultative meetings:

Consultative Meeting #1: **Quantification & Financing**

– May 10th

Consultative Meeting #2: **Quality**

– May 17th

Consultative Meeting #3: **Appropriate Use**

– May 24th

#1

Background on Quality

Quality of newborn and child health products is not guaranteed

Access to safe, effective and quality medicines is a global priority and challenge

- In low- and middle-income countries, an estimated 10% of **medical products** are substandard or falsified[1].
- Based on WHO model using this data, up to 72,430 childhood pneumonia deaths can be attributed to the use of substandard/falsified medicines[1]
- As few as 30% of national regulatory authorities globally have the capacity to perform all core regulatory functions for medicines[2]
- 7% of African countries have MRA moderately developed capacity with more than 90% having minimal or no capacity[3]

What is **quality assurance**?

Quality assurance is the sum of all activities and responsibilities required to ensure that each medicine reaching a patient is **safe, effective, and of standard quality**

Are safe, efficacious, and have the correct identity

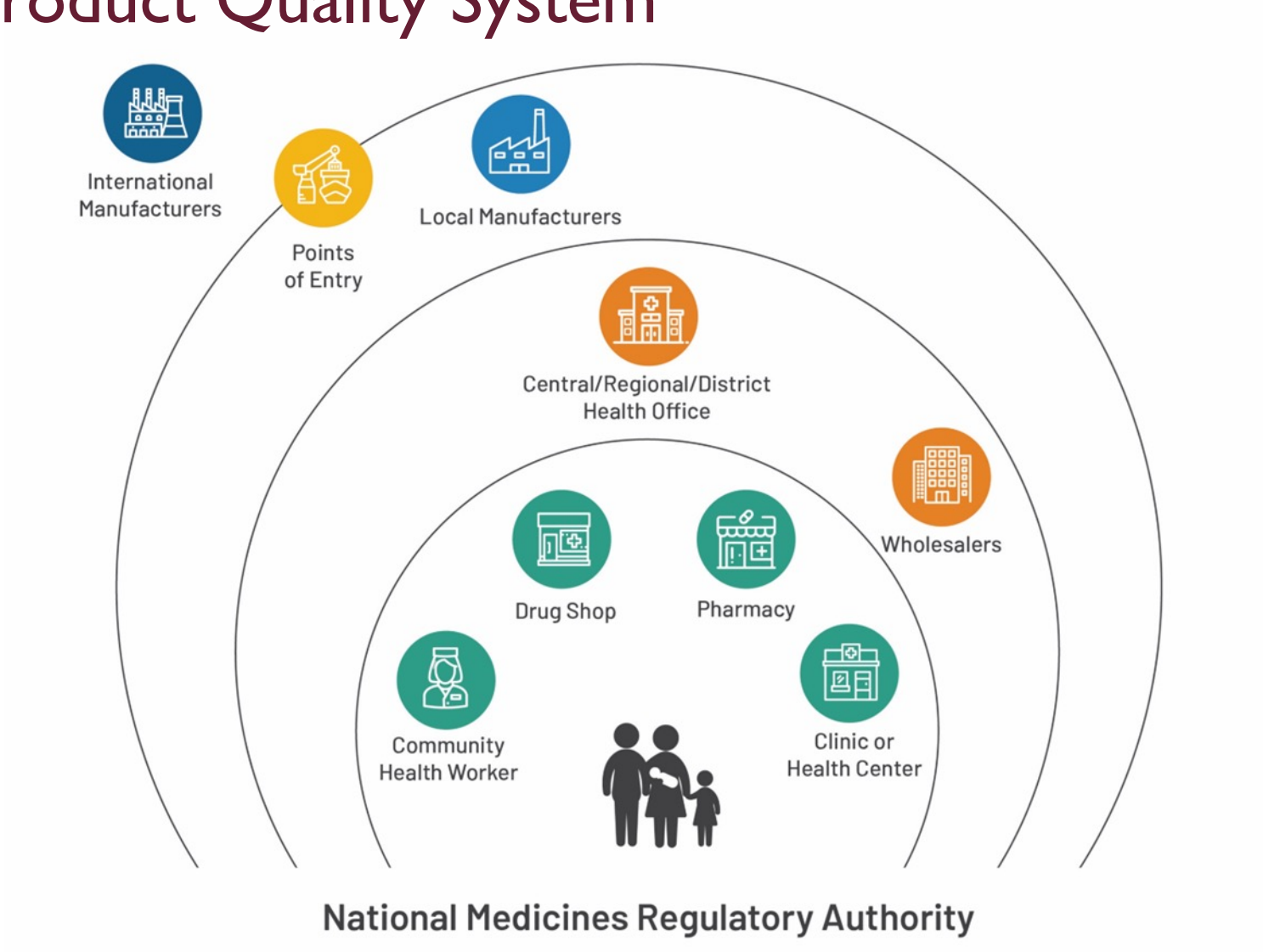
Deliver the same performance as described in the label

Perform consistently over their shelf life

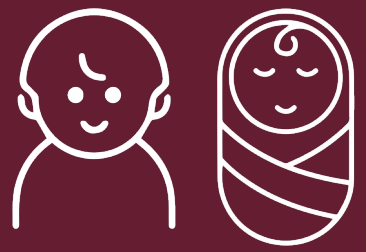
Are made in a manner that ensures quality

Quality guarantee

Medical Product Quality System



Gentamicin injection - Characteristics



Newborn and Children

Gentamicin

Injection

10 mg/mL in 2 mL vial

40 mg/mL in 2 mL vial

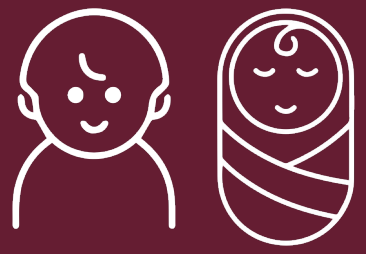
Gentamicin injection must be manufactured in a sterile environment[4]

The system (vial and rubber stopper) must preserve sterility during the shelf life of the product[4].

Gentamicin injection does not need to be maintained in the cold chain, but should be stored **below 25°C**; it should not be refrigerated or frozen[4]

A custom-marked syringe (e.g., a 1-mL syringe with 0.2 increment markings) is most relevant for gentamicin administration to newborns[4]

Amoxicillin dispersible tablets - Characteristics



Newborn and Children

Amoxicillin

Dispersible tablets
125 mg ; 250 mg

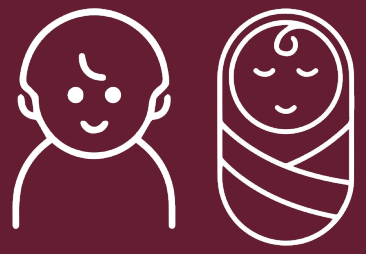
- Environmental controls for humidity and temperature during manufacturing process are essential
- API form is critical for this presentation
- Manufacturing requires a dedicated production line[4]

- Evaluation of taste masking and taste acceptability of the formulation should be conducted during product development to ensure acceptance of the product by children[4].

- Amoxicillin DT must be packaged in blisters (aluminum/PVC) or strips (aluminum) as dispersible tablets are water sensitive.
- Amoxicillin dispersible tablets should completely disintegrate within three minutes when put in a small amount (5–10 mL) of liquid (clean water or milk)[4].

- Storage condition below 30˚C[4].

Other pediatric formulations of amoxicillin (syrup/suspension) - Characteristics



Newborn and Children

Amoxicillin for Oral Suspension

125 mg / 5 ml
250 mg / 5 ml

- Manufacturing requires a dedicated production line to prevent cross contamination
- Amoxicillin trihydrate is the most stable solid form, however, is still sensitive to temperature and humidity.

- Qualitative and quantitative composition: when reconstituted, every 5 ml of oral suspension contains amoxicillin trihydrate B.P. equivalent to 250 mg amoxicillin.
- After reconstitution, the required amount of suspension should be placed directly on the child's tongue for swallowing. These preparations should then be taken immediately

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- Shelf life: Reconstituted suspension: 14 days (very short shelf life)

- Special precautions for storage: do not store above 25°C.
- Reconstituted suspensions: at 2°C - 8°C in a refrigerator.

Data on Quality: WHO 10-Country Survey[6]

Samples collected from 10 Countries

Burkina Faso, Kenya, Madagascar, Nepal, Nigeria, Tajikistan, Tanzania, Uganda, Viet Nam, Zimbabwe

Twelve samples (41%) produced by 11 manufacturers did not comply either in the assay or the gentamicin composition test, or in pH value.

29 batches of gentamicin injection tested (BP monograph) from 23 manufacturers.

No failures were found for any of the amoxicillin DT samples.

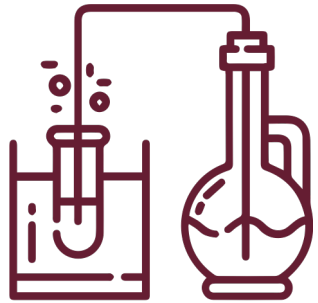
Ten samples of amoxicillin DT (each from a different batch) from 8 manufacturers tested (USP monograph)

#2

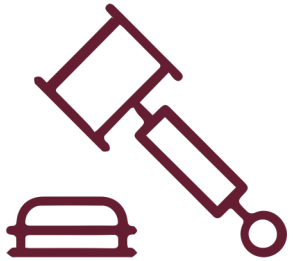
Root causes: risks to quality throughout the product life cycle

Risks to quality throughout the product life cycle

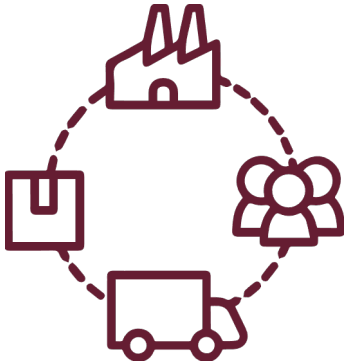
Manufacturing



Regulation



Supply Chain



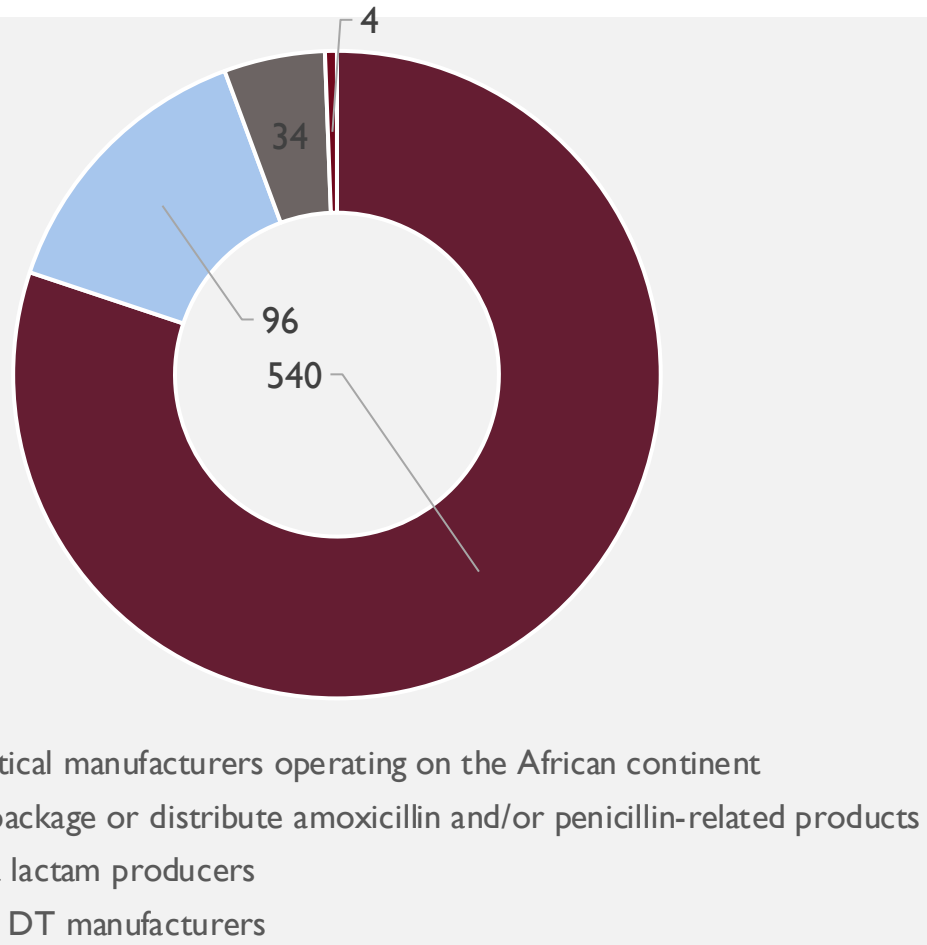
Quality

Manufacturing

Status of amoxicillin DT manufacturers in Africa: Results of PQM+ Assessment[9]

Only 34 manufacturers (6%) on the African continent produce amoxicillin or penicillin

- 4 companies currently manufacturing amoxicillin dispersible tablets
- 6 firms with plans to develop it
- 3 manufacturers who expressed interest in future production.



[9] USAID-PQM+. 2022. Survey of Manufacturers of Amoxicillin and Beta-Lactam Products in Africa. March 2022.

Root causes
of quality issues in the manufacture of amoxicillin pediatric and gentamicin injection

Gaps in generic formulation, research, and development of amoxicillin DT

Manufacture of poor quality MNCH medicines- low capacity to follow GMP.

Small profit margin: elevated costs prevent local manufacturers in LMIC from investing in the production of quality assured medicines.

- Rising costs of API
- Require dedicated production line: can increase costs.
- Reluctance to invest in quality: no guarantee of volume; perceived low demand

Difficulties in sourcing **Active Pharmaceutical Ingredient (API)**

Lengthy registration process perceived as a deterrent. Registration of MNCH medicines takes on average about six months in Asia but can take from one to nearly four years in African countries[7].

Regulation

Regulation

GMP inspection

The MRA conducts inspections to verify compliance with the standards that a medicines manufacturer must meet in their production processes.

Marketing Authorization

The MRA authorizes the marketing or free distribution of a medical product in the respective country after evaluation of its safety, efficacy, and quality.

Post-marketing surveillance (PMS)

The MRA uses PMS to survey the quality of medical products available to the population and if problems are identified, takes the necessary actions

Quality Assurance

Data on Good Manufacturing Practices Inspection: USAID-MTaPS study[7]

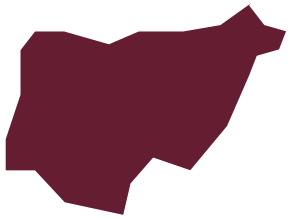
7/9	7/9 countries lacked clear national legal provisions for recognition of GMP certification and inspections by other NRAs or the WHO prequalification program.
2/9	Only 2/9 countries recognized and relied fully on the GMP certificate from the country of manufacture.
3/9	3/9 considered WHO inspection reports or GMP inspection certificates issued by reference members without full recognition.

Registration status of amoxicillin DT in some Asian and African countries

A survey conducted by USAID-MTaPS in 9 countries (two in Asia, and seven in Africa) to examine registration of MNCH medical products produced the following results[7]:

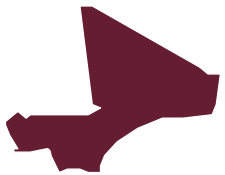
- Only 4 countries had a listing of registered medicines available to public
- 6 countries had a registered form of amoxicillin 125mg DT
- 6 countries had a registered product for amoxicillin 250mg DT
- 7 countries had a registered product for amoxicillin DT (either 125mg or 250mg DT)
- 2 countries had a registered product for gentamicin 20mg injection
- 7 countries had a registered product for gentamicin 80mg injection

Unregistered products on the market: Results from post-marketing surveillance supported by PQM+



Nigeria

- 8% (12/150) of pediatric amoxicillin products on the market did not have Marketing Authorization.
- 8% (14/176) of Gentamicin injection products on the market were not registered[10].



Mali

- 15 lots of amoxicillin DT samples collected were not registered[11]

[10] USAID – PQM+. Post-Marketing Surveillance in Nigeria. Technical Report, 2018

Data on Quality: Post-Marketing Surveillance in Nigeria 2018

Number of failed and passed tests in PMS-Nigeria 2018

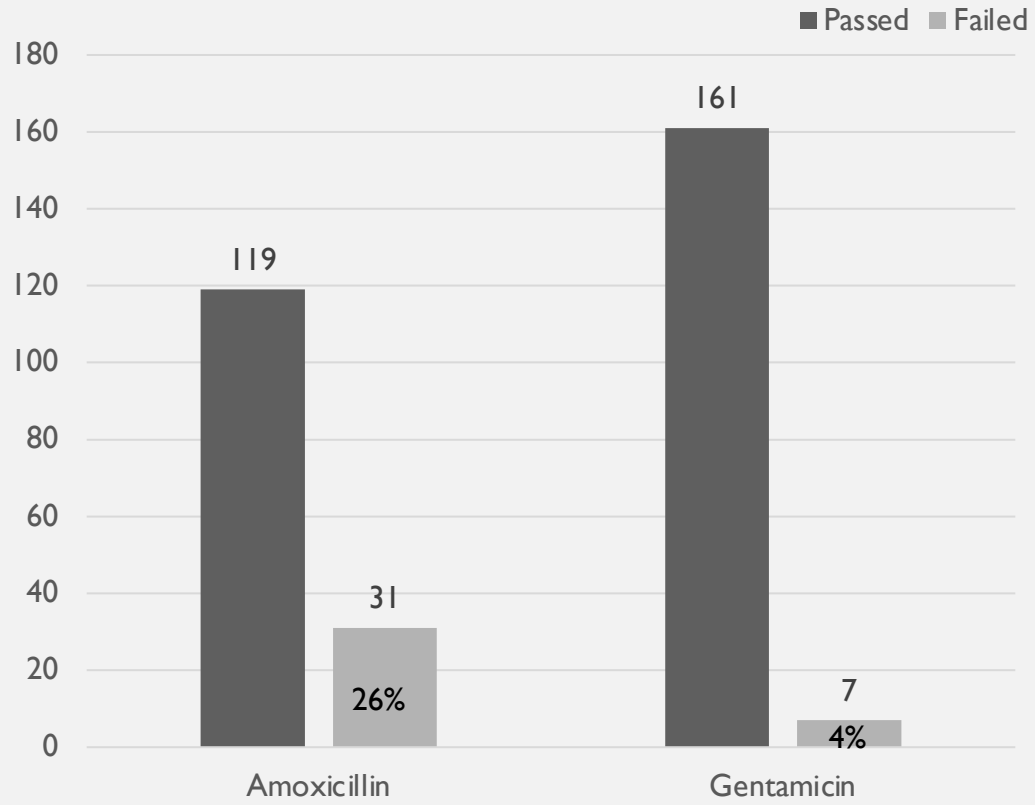
Nigeria

Samples collected from six geopolitical zones in Nigeria

- Federal Capital Territory, Borno state, Kano, Anambra, Rivers state and Lagos.

150 samples of amoxicillin DT and amoxicillin suspension tested: **26% Failed**[10]

177 Samples of gentamicin injection (40 mg & 80 mg) tested. **4% Failed**[10]



[10] USAID – PQM+. Post-Marketing Surveillance in Nigeria. Technical Report, 2018

Data: assessment report on post marketing surveillance capability of eight countries[8]

2/8	2/8 countries (Ethiopia, Nigeria) have a **PMS Guideline**
0	No data obtained from 7 countries to **verify their regulatory actions taken** > Only Ethiopia has provided recall letters on substandard medicines.
3/8	**Inclusion of amoxicillin or gentamicin:** > 3/8 countries included one; 1 country- both

Regulatory root causes of poor quality

Regulation

Little or no GMP inspections conducted

- Lack reliance practices
- Limited skilled/trained human resource capacity

Unregistered products on the market

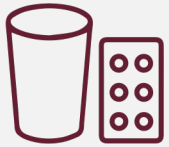
- Registration fees considered high
- Lengthy timeline for registration
- Backlog of dossiers for registration and priority not given to registration of MNCH medicines

Deficiencies in the Post Marketing Surveillance / PV program

- The main challenge common to all countries is getting funding. PMS is a capital-intensive activity
- MNCH medicines often not included in PMS
- Lack a risk-based PMS approach
- Lack a fully functional lab to conduct testing
- Lack of regulatory enforcement measures (recall, withdrawal)
- Limited human resource capacity

WHO Prequalification

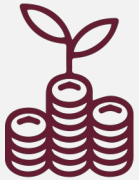
Expression of interest for amoxicillin DT but not gentamicin



No prequalified amoxicillin dispersible tablet products yet

- Active Pharmaceutical Ingredient (API)
- Palatability and bioequivalence studies

High costs of bioequivalence (BE) studies which are required for oral products



Return on investment for manufacturers

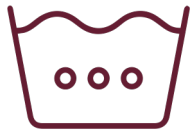
Supply chain

Selection, Procurement, Storage and Distribution

Specifications for procurement processes may not include necessary characteristics to assure quality (e.g., blister packs for amoxicillin DT)

Lack of coordination among procurement agencies, regulators and programs

Gentamicin and amoxicillin DT do not require cold storage, but still require appropriate storage conditions as do all essential medicines



Special caution with ruptures in blisters of amoxicillin dispersible tablets, as dispersible tablets are water sensitive.

Related to use: suspensions should be refrigerated after preparation

Are there other root causes of poor quality?

What are the most critical root causes?

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#3

Potential Interventions

Potential Interventions and Recommendations

Manufacturing
Secure demand

- Long-term agreements or other types of volume guarantees for manufacturers of quality-assured products to incentivize investment in quality
- Examine taxes and tariffs for API import
- Present the business case to manufacturers

Regulatory
Efficiencies

- Standardized and streamlined registration requirements and assessment processes for priority medicines
- Regional regulatory harmonization and reliance in regulatory functions, such as market authorization and inspections to optimize resources.
- Establish risk-based approaches to regulatory functions, such as GMP inspection and post-marketing surveillance

Procurement
Buy quality-assured medicines

- Advocate for the cost-benefit of quality
- Prioritize quality over cost in evaluating bids
- Ensure technical specifications for procurement cover all quality considerations
- Ensure coordination among regulators, procurement agencies and programs to make sure needs are understood

What are priority interventions and solutions to improve quality of pediatric amoxicillin and gentamicin?

Breakout group discussions

References

1. WHO. A study on the public health and socioeconomic impact of substandard and falsified medical products. 2017.
2. WHO. Access to medicines and vaccines. Seventy-second world health assembly. 2019.
3. Ncube BM, Dube A, Ward K. Establishment of the African Medicines Agency: progress, challenges and regulatory readiness. J Pharm Policy Pract. 2021.
4. USAID. Manual for Procurement and Supply of Quality-Assured Maternal, Newborn and Child Health Commodities. Global Health Supply Chain Program. 2019.
5. WHO. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 44. 46th report. WHO Technical Report Series, No. 970. 2012.
6. WHO- Survey of the quality of medicines identified by the United Nations Commission on Life-Saving Commodities for Women and Children. 2015
7. USAID-MTaPS. Improving Access to Maternal, Newborn, and Child Health Medical Products in Low- and Middle-Income Countries: Considerations for Effective Registration Systems. March 2021
8. Assessment Report on Post-Marketing Surveillance Capability of Eight Maternal, Neonatal, and Child Health PQM+ Countries. November 2020
9. USAID-PQM+. Survey of Manufacturers of Amoxicillin and Beta-Lactam Products in Africa. March 2022.
10. USAID – PQM+. Post-Marketing Surveillance in Nigeria. Technical Report, 2018
11. USAID – PQM+. Post-marketing surveillance exercise in Mali 2021.
12. Bartlett, Trends in international development assistance to combat pneumonia, From 2007- 2018, of the total $7.1B spent on pneumonia, only about $285M was spent on pneumonia diagnostics and treatment, combined. 2020.
13. Data on tenders for amoxicillin DT were collected from national procurement agencies across three countries, 2016 – 2020.
14. UNICEF Supply Division. Amoxicillin Dispersible Tablets: Market and Supply Update. May 2018.