

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

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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Division



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.

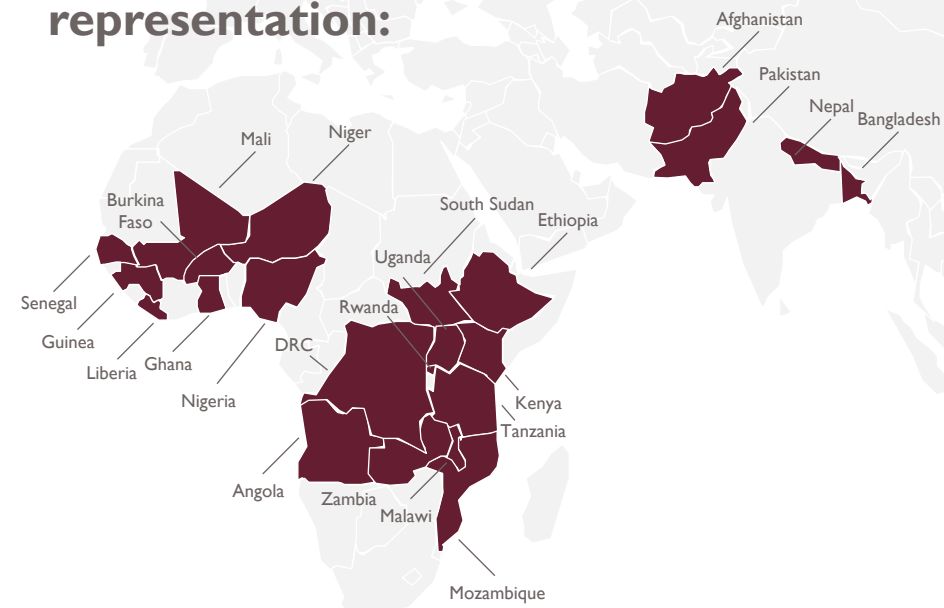
Introduction

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:

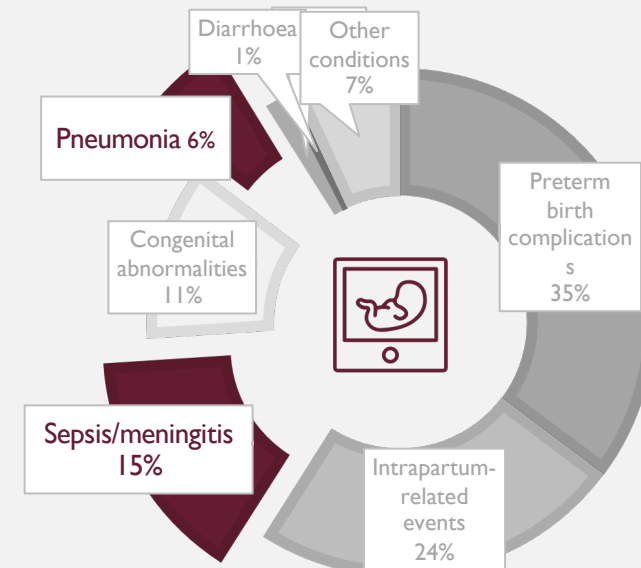


Global challenge

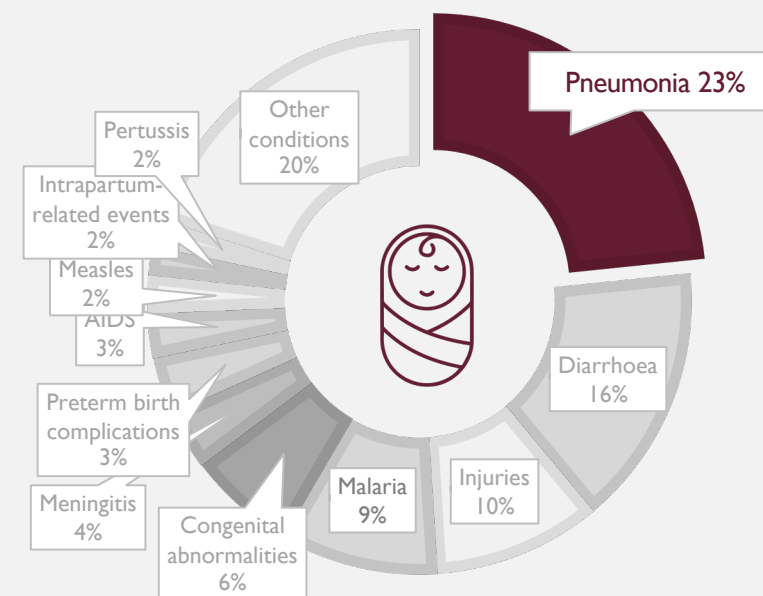
Children are still dying of preventable causes

- 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 health care remains a challenge.**

Causes of newborn mortality



Causes of child mortality



Addressing key barriers and bottlenecks

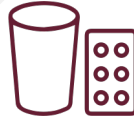
What is needed to further the advances already made and increase access to and appropriate use of pediatric amoxicillin and gentamicin?

Prioritized bottlenecks:



Quantification & Financing

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



Quality

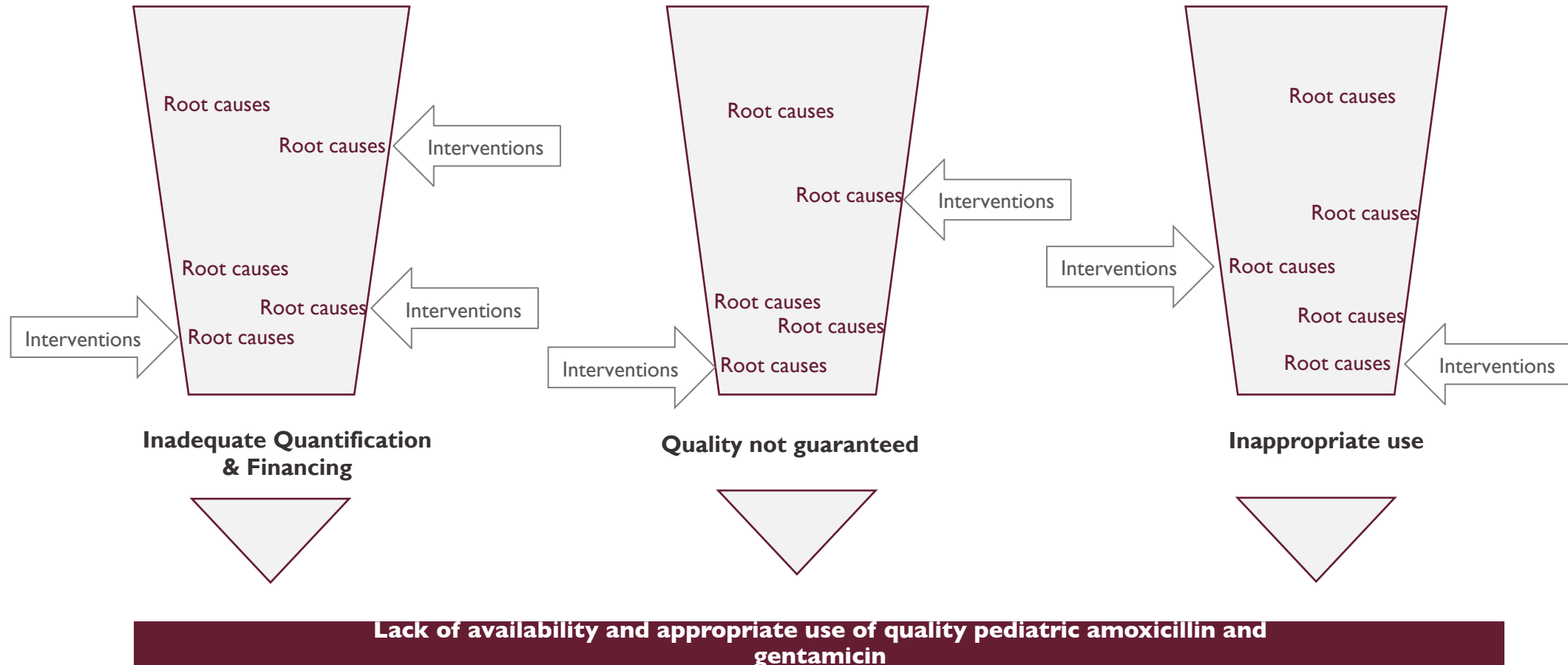
Quality of child health products not guaranteed



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 falsified¹.
- Based on WHO model using this data, up to 72,430 childhood pneumonia deaths can be attributed to the use of substandard/falsified medicines¹
- As few as 30% of national regulatory authorities globally have the capacity to perform all core regulatory functions for medicines²
- 7% of African countries have MRA moderately developed capacity with more than 90% having minimal or no capacity³



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

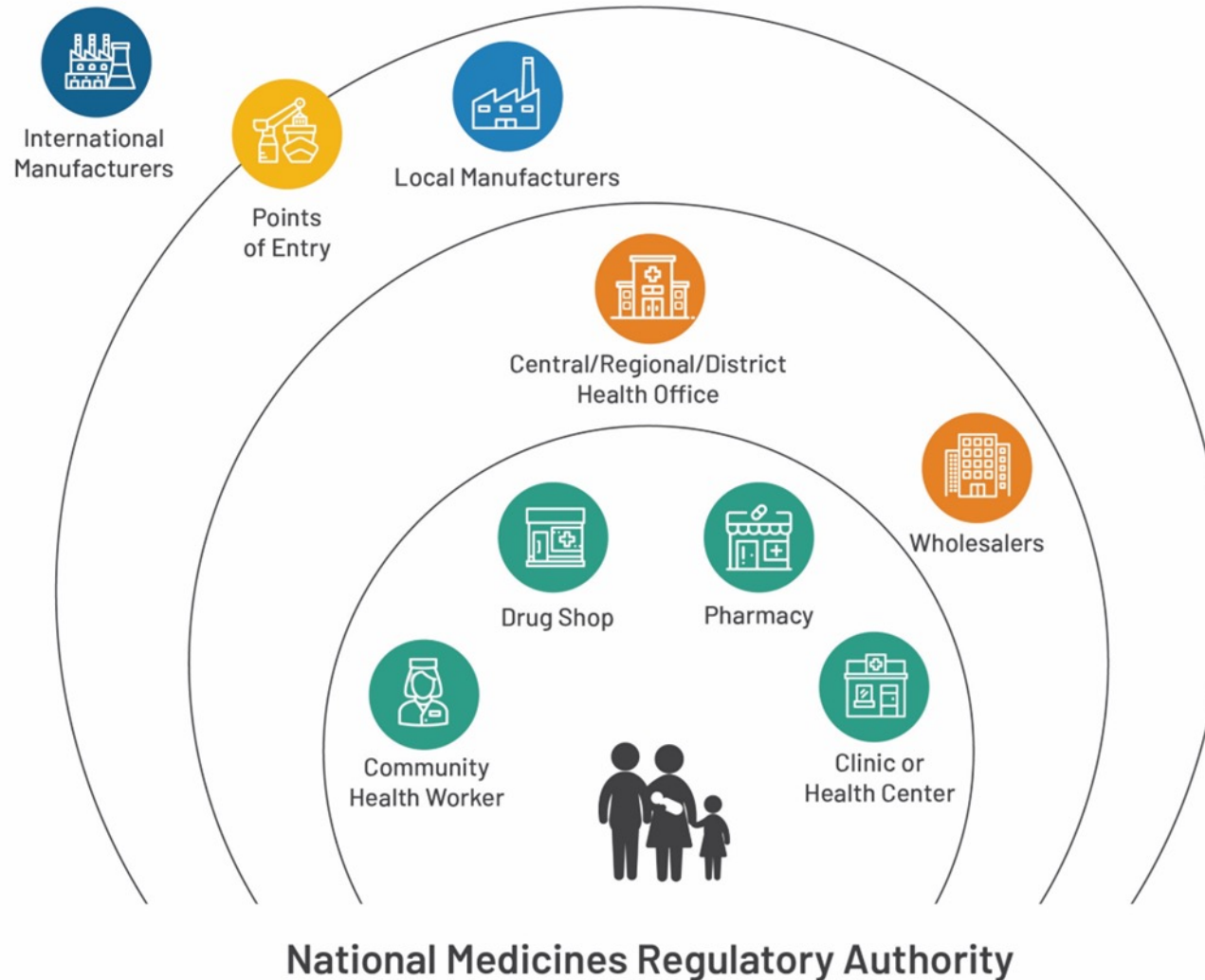


Are made in a manner that ensures quality

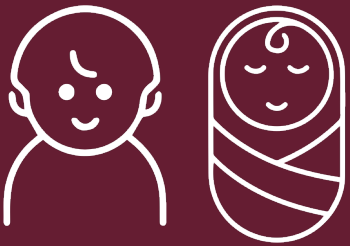


Quality guarantee

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

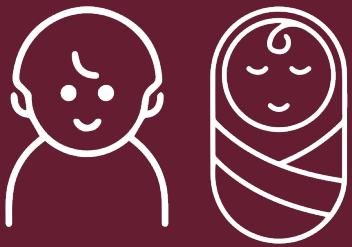
Gentamicin injection must be manufactured in a sterile environment⁴

The system (vial and rubber stopper) must preserve sterility during the shelf life of the product⁴.

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 frozen⁴

A custom-marked syringe (e.g., a 1-mL syringe with 0.2 increment markings) is most relevant for gentamicin administration to newborns⁴

Amoxicillin dispersible tablets - Characteristics



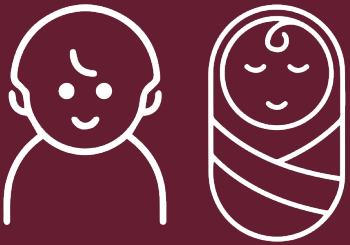
Newborn and Children

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 line⁴
-
- Evaluation of taste masking and taste acceptability of the formulation should be conducted during product development to ensure acceptance of the product by children⁴.
-
- 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°C⁴.

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
-
- 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 Survey⁶



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)

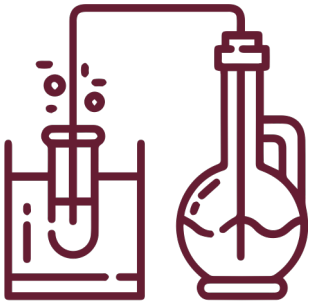


#2

Root causes: risks to quality throughout the product life cycle

Risks to **quality** throughout the product life cycle

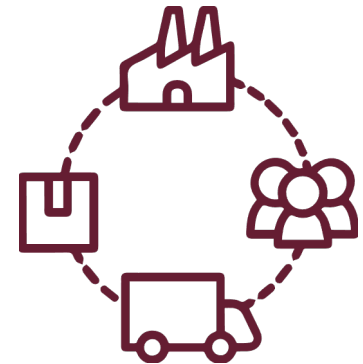
Manufacturing



Regulation

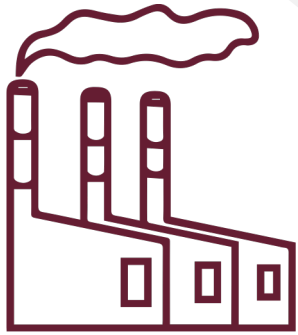


Supply Chain



Quality

Manufacturing

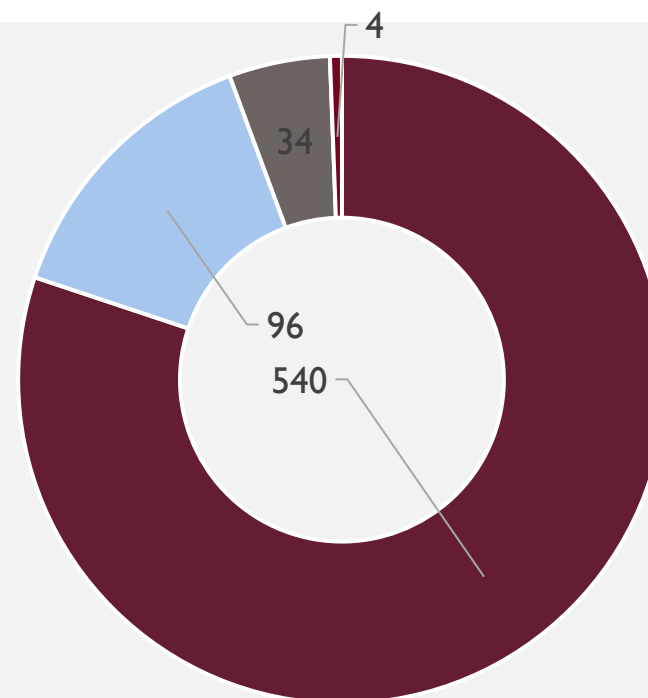


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Status of amoxicillin DT manufacturers in Africa: Results of PQM+ Assessment⁹

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.



- Pharmaceutical manufacturers operating on the African continent
- Import, repackage or distribute amoxicillin and/or penicillin-related products
- Actual beta lactam producers
- Amoxicillin DT manufacturers

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 countries⁷.

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 study⁷

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.

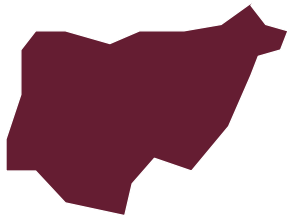
Registration status of amoxicillin DT in some Asian and African countries

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 results⁷:

- 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



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 registered¹⁰.



Mali

- 15 lots of amoxicillin DT samples collected were not registered¹¹

Data on Quality: Post-Marketing Surveillance in Nigeria 2018

Number of failed and passed test in PMS-Nigeria 2018



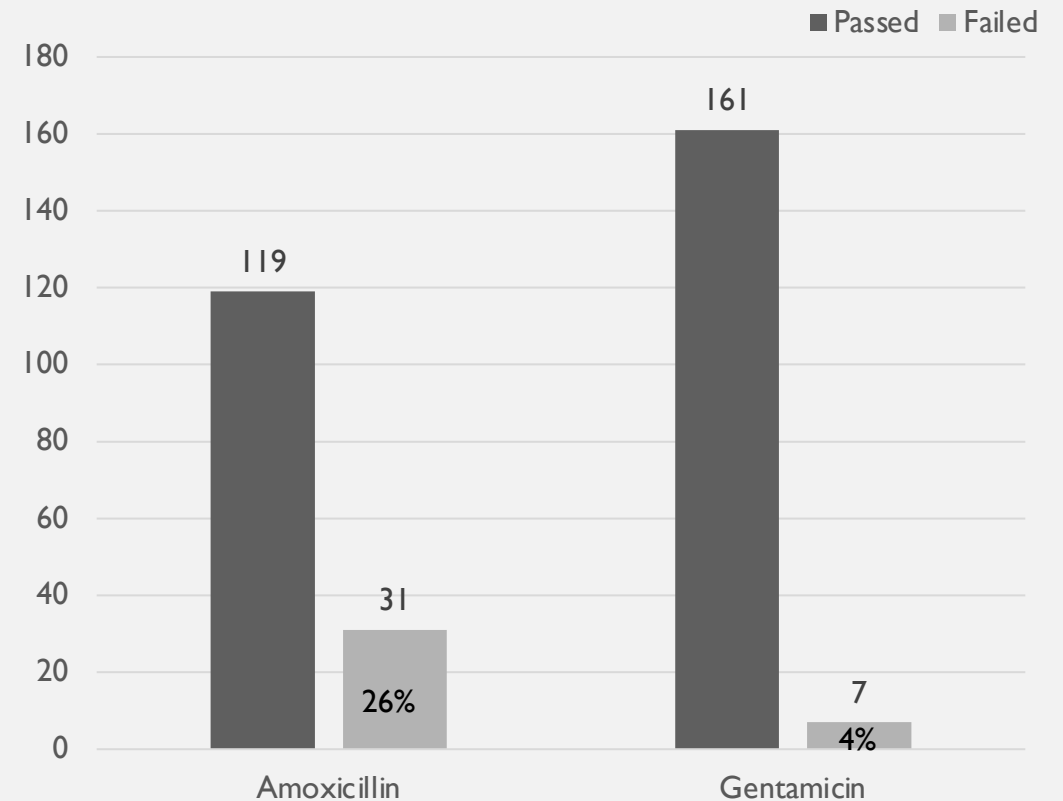
Nigeria

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



Data: assessment report on post marketing surveillance capability of eight countries⁸

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

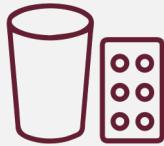
Unregistered products on the market

- 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

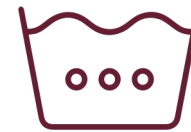


Specifications for procurement processes may not include necessary characteristics to assure quality (e.g., blister packs for amoxicillin DT)

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?

www.mentimeter.com
Code: XXXXXX



#3

Potential Interventions

Potential Interventions and Recommendations

Manufacturing Secure demand

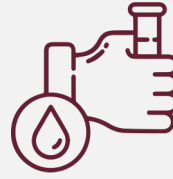
- Long-term agreements or other types of volume guarantees for manufacturers of quality-assured products to incentivize investment in quality
- Examine taxes and tariffs for API import
- Present the business case to manufacturers

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

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