

# Collaborative partnerships as a solution for poor access to essential antimicrobial medicines: what can we learn from the chlorhexidine gel example?

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**To cite:** Tack B, Ravinetto R, Allegaert K. Collaborative partnerships as a solution for poor access to essential antimicrobial medicines: what can we learn from the chlorhexidine gel example? *BMJ Paediatrics Open* 2022;**6**:e001661. doi:10.1136/bmjpo-2022-001661

Received 31 August 2022  
Accepted 26 September 2022



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## ANTIMICROBIALS IN LOW-INCOME AND MIDDLE-INCOME COUNTRIES

Low-income and middle-income countries (LMICs) have the highest infectious disease burden, antimicrobial resistance levels and associated deaths,<sup>1</sup> but access to antimicrobials is limited, and the prevalence of substandard and falsified antibiotics is high.<sup>2</sup> This causes the use of no, ineffective or unnecessary broad-spectrum antimicrobials, leading to poor outcomes, under-5 mortality and resistance.<sup>1</sup> Access to preventative antimicrobials, for example, antiseptics, is essential, but supported by few international efforts.<sup>1</sup> Daily umbilical antiseptics with chlorhexidine digluconate can save 7/1000 newborns in contexts with harmful umbilical cord care practices.<sup>3</sup> Here, we discuss opportunities and challenges of access initiatives, based on the experience of a public–private partnership to improve access to chlorhexidine for umbilical cord care.<sup>4</sup>

## A PUBLIC–PRIVATE PARTNERSHIP IN WESTERN KENYA

In 2011–2012, the WHO and UN Commissions on Life-saving Commodities for Women and Children integrated chlorhexidine in the Essential Medicines Model List and called manufacturers to engage in production. GlaxoSmithKline (GSK) committed to improving access to chlorhexidine gel. They developed a simple manufacturing process, easily transferrable to local manufacturers and obtained in 2016 a positive opinion by a stringent regulatory authority (SRA), that is, the European Medicines Agency. This was hoped to facilitate local registration processes; however, in some cases these still took up to 2 years. The US Pharmacopeia supported local stakeholders to achieve quality-assured production,

sustainable supply and efficient resource use. In Kenya, local manufacturers successfully scaled up production and supply to Western counties, allowing GSK to stop its own manufacturing in 2021.<sup>4</sup>

Meanwhile, in 2016, the Ministry of Health had integrated chlorhexidine gel in the national essential medicines list and therapeutic guidelines, which helped to secure demand and adequate use, and incentivised manufacturers to engage in production. The international non-governmental organisation (NGO) Save the Children supported local stakeholders for implementing national recommendations, running advocacy and sensitisation campaigns, training healthcare workers (including on adverse event recognition), integrating chlorhexidine gel in mother and child healthcare, and documenting its use. Formal and informal exchanges with healthcare workers, users and the community, provided important insights on acceptability, implementation barriers and corrective measures. Importantly, acceptability considerations had determined the choice of a gel formulation, since easier to apply than a liquid solution and applicable with the fingertip without a cloth or cotton. The packaging was adapted to low-resource settings: single-dose sachets discourage multiple use and pictorial instructions fit illiterate users. (Re)training remains critical, as severe eye injury happened when chlorhexidine was mistaken for eye-drops/ointment.<sup>4</sup>

## LESSONS LEARNT

### From local to global needs

The Kenyan experience confirms that global partnerships can improve antimicrobial access in low-resource settings. It illustrates that multistakeholder and multisectoral



participation, integrated national strategies and capacity building are the cornerstones of global partnerships and affirms the power of these partnerships to improve sustained availability and acceptability of antimicrobials.<sup>1</sup> This local experience should inspire new private–public partnerships, for example, for improving access to other medicines and diagnostics, and improving their use. It can also serve to benchmark the access strategies applied by different pharmaceutical companies,<sup>1</sup> and it should be seen as a successful pilot for expanding such access initiatives to the national, regional and global level. However, availability is only a first step: affordability to users and appropriate use must also be ensured in the long term.

### Regulatory harmonisation

Registration is an essential requirement for availability at country level, but pharmaceutical companies often do not file antimicrobials for registration in LMICs.<sup>1</sup> This is likely due to reluctance to engage in burdensome registration processes with relatively small and unclear financial return, related to small market sizes, poor pharmaceutical budgets and unpredictable demand—resulting from high out-of-pocket expenditures, absence of or non-compliance with guidelines and lack of microbiological surveillance data.<sup>1</sup> Major importers, including UN agencies and international NGOs, prioritise products with WHO prequalification or approval by SRAs (to be replaced in the long-term by ‘WHO-listed authority’ (WLA)).<sup>5</sup> Alignment and collaboration between WHO, SRA (WLAs) and national regulatory authorities (NRAs) are essential to facilitate transparent and efficient registration processes and postmarketing surveillance, both at national and supranational level. A good example is represented by the WHO Collaborative Procedure for Accelerated Registration.<sup>5</sup> Furthermore, regional harmonised regulatory systems enable streamlining the registration process. In particular, the East African Community Medicines Regulation Harmonisation (EAC MRH) Programme will likely facilitate similar access initiatives, expanded at a regional level.<sup>6</sup>

### Technology transfer

In sub-Saharan Africa, up to 90% of medicines are imported, which is associated to common stockouts and shortages.<sup>1</sup> Technology transfer is a powerful strategy for sustainable access to medicines, but not frequently implemented for antimicrobials.<sup>1</sup> While most low-income countries face major challenges to set up local production, for example, lack of adequate infrastructure and expertise, an LMIC, such as Kenya, member of EAC MRH, is an excellent candidate for technology transfers in general—and for chlorhexidine gel in particular,<sup>4 6</sup> and could become a supplier for neighbouring countries.

DeAngelis *et al* did not comment explicitly on chlorhexidine quality and microbiological safety. However, technology transfer should be accompanied by regulatory strengthening. Therefore, NRAs should be included in any future access collaborative partnerships, whether

national or supranational, to ensure sustained compliance with WHO Good Manufacturing Practices and with adequate quality specifications,<sup>5 7</sup> for example, correct chlorhexidine concentration,<sup>8</sup> or water of adequate quality to avoid contamination with Gram-negative bacteria.<sup>9</sup> The latter is particularly important for chlorhexidine. Despite debate about sterility needs for antiseptics,<sup>9</sup> chlorhexidine gel is used for neonates with immature immunity and applied to non-intact skin<sup>10</sup>; furthermore, *Burkholderia cepacia* complex, a major cause of waterborne bacterial contamination of antiseptics, has innate resistance to chlorhexidine.<sup>11</sup>

### From access and acceptability to monitoring and evaluation

The user-friendliness of formulations is too often neglected in paediatric medicine. Many oral formulations are not age-appropriate<sup>12</sup> and sales of age-appropriate oral antibiotics are limited.<sup>13</sup> In some LMICs, packaging and dosing devices are insufficiently regulated; we observed elsewhere, during ongoing research, the absence of dosing devices for liquid oral formulations and absence of instructions for reconstitution. Global partnerships aiming to improve access to paediatric antimicrobials should act on the whole product lifecycle, including these neglected aspects.

Monitoring and reevaluation are essential steps of the product lifecycle. The collaboration with Kenyan health authorities, non-governmental actors, prescribers or end-users and manufacturers facilitated the adoption and procurement of chlorhexidine gel, but few data on rollout, pricing policy, uptake, monitoring and reevaluation were shared. For instance, it is suggested that pictorial, self-explanatory packaging and training of healthcare workers and users are important for adequate use and safety, but DeAngelis *et al* did not report on the packaging adaptation, on sustainability of training and pharmacovigilance, on collaboration with the NRA, and neither on the ongoing reevaluation of chlorhexidine. Rational antiseptic use is critical to prevent acquired resistance, the more because chlorhexidine resistance already caused outbreaks and healthcare-associated infections.<sup>14</sup> New insights suggest very limited gains compared with clean, dry cord care and WHO now reserves chlorhexidine for settings with harmful traditional cord practices.<sup>3</sup>

In conclusion, global partnerships can improve local access to essential medicines including antimicrobials. However, they should include local stakeholders including the NRA as equal partners; explicitly plan measures for affordability to users and plan thoughtful exit strategies allowing sustainability of monitoring, reevaluation and pharmacovigilance. Furthermore, positive local experience should be expanded at national and global level, in a sustained effort to contribute to universal health coverage.

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**Acknowledgements** We thank Prof. Dr. Jan Jacobs for his contribution to the section on microbiological quality of antiseptics.

**Contributors** BT and KA conceptualised the editorial. BT wrote the original draft and KA and RR reviewed and edited it. KA supervised the editorial.

**Funding** BT has a scholarship from Research foundation Flanders (FWO, 1153220 and 1153222N).

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Commissioned; externally peer reviewed.

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