GLOBAL HEALTH COMMENTARY

Review of the Quality of Pediatric Medications in Developing Countries

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ABSTRACT: The quality of essential medicines for pediatric populations in developing countries is largely unknown. This review examines quality studies (2000–2011) of medicines on the WHO Essential Medicine List for Children, the quality of a subset of pediatric formulations, and the association of these poor quality medicines with adverse clinical outcomes. We searched Embase, Medline, BIOSIS, and IPA using MeSH subject terms for quality measures, medicine formulations, and substandard medicines and combined these with 267 medicines, and 91 low-income and lower-middle-income countries. Seventy articles met our inclusion criteria examining the quality of 75 medicines from 28 countries. Content and dissolution tests were utilized most often. Results indicate that antibacterials, antifungals, and antiretrovirals were consistently of good quality. Quality tests on pediatric formulations were performed on 55 of 75 of the medicines studied and followed the general trend of quality results. Three studies were included that examined clinical consequences of substandard medicines—two cases of diethylene glycol poisoning and one case of substandard malaria drugs. We conclude that there is a need for more quality studies of pediatric formulations of essential medicines in developing countries and their clinical consequences. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:1419–1433, 2013

Keywords: drug quality; drug effects; drug interactions; drug resistance; formulation; LMIC; global health

BACKGROUND

The World Health Organization's (WHO) Model List of Essential Medicines for Children (EMLC) was published in its latest version on March, 2011.[1] The list is intended to guide therapeutic treatment for priority conditions for children up to 12 years of age. There are 207 core and 70 supplementary medicines, including 21 with age and weight restrictions. The explanatory notes on page 1 of the EMLC state "an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality"; therefore, the regulatory agencies within each country are expected to provide pharmacovigilence and an adequate drug surveillance system to protect its residents from substandard and/or counterfeit drugs. Although this is a realistic expectation for high-income countries, low-income countries (LICs), and lower-middle-income countries (LMICs) may not have adequate systems;[2] pharmacovigilence capacity in Africa has grown to 23 countries by 2010 but most are reported as understaffed and underresourced.[3]

Within the total distribution of causes of death in 2008 for children under 5 years, HIV/AIDS, diarrhea, malaria, pneumonia, and "other diseases" accounted for 70% of deaths in LICs and 61% of deaths in LMICs.[4] All of these conditions can be treated with essential medicines. Although there have been reviews of disease-specific medicines such as antimicrobials and antimalarials,[5,6] there has been no known

Additional Supporting Information may be found in the online version of this article.Supporting Information

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review of the quality of all medicines on the EMLC. In addition, little data exists on the quality of pediatric formulations, such as suspensions and syrups. It is also presently unknown to what extent there may be adverse clinical effects associated with the use of substandard or counterfeit medicines for children under the age of 12 years.

Objective

The objectives of this study are (1) to identify and summarize studies published in the last 11 years providing measurements of the quality of essential medicines for children listed on the EMLC, (2) to identify and summarize studies examining the quality of pediatric formulations of medicines on the EMLC (whether the specific pediatric formulation is listed or not), (3) to identify and summarize studies examining the association of poor quality medicines with adverse clinical outcomes, and (4) to identify whether poor quality medicines can be associated with a particular level of the distribution chain.

We define quality testing as: (1) physical measurements such as uniformity of mass and weight, friability, hardness, and appearance; (2) chemical tests that measure the content and active ingredient, which may include stability testing to simulate storage in tropical conditions; and (3) *in vitro* disintegration and dissolution tests that simulate the bioavailability of medicine for therapeutic purposes in the patient.

Methodology

Literature searches were conducted in Medline, Embase, BIOSIS, and IPA for the period of 2000–2011 inclusive. A three-subject search strategy was used—country, medicine, and quality. Each of the 91 countries names listed as low-income and lower-middle-income on the World Bank list of economies (18 July, 2011) and the terms "developing countries," "low-income countries" were combined with each of the names of 267 medicines listed on the EMLC, and MeSH terms utilized for quality measures and formulation type—"quality control"; "prescription drugs"; "drug quality"; "drug contamination"; "therapeutic equivalency"; "drugs, generic"; "drug equivalence"; "tablets"; or "dosage forms"; "drug uniformity"; "chemistry, pharmaceutical"; "solubility"; "friability"; "hardness test"; "capsules"; "syrup"; "suspension"; "substandard"; "tablets, enteric-coated"; "technology, pharmaceutical"; "disintegration test"; "pharmacopoeias as topic"; "drug disintegration"; "biological availability"; "drug label"; "contamination"; "counterfeit"; "*in vitro* equivalence test"; and "*in vitro* dissolution test."

The inclusion criteria for this review were: English language, primary research with quality testing (as specified above), medicine, and dosage is included on EMLC, and medicines were sampled in countries of interest. We included a study if it sampled medicines in both developing and developed countries, and results were reported separately.

The following information was extracted from each study: author, year of publication, medicines sampled with dosage and form, study type (mostly defining sampling method), distribution level of sample (i.e., pharmacies, wholesalers, etc.), country of sample(s), testing methods, general results or comments (includes combined failure rates as noted), specific testing results (recorded failure rates—all percentages are of the specific formulation of medicine unless otherwise noted), adverse clinical effects, counterfeit or substandard drug characteristics, any manufacture information mentioned (country and name), and a brief note on study limitations. We also recorded any findings regarding the use of label identification and manufacturer verification methods to identify counterfeit materials. We grouped distribution levels where the sampling of medicines occurred as: (a) manufacturer, government supply, and medical stores; (b) wholesaler or importer; (c) hospitals, health and treatment centers; (d) NGO's, private clinics and private pharmacies; (e) pharmacies—licensed and unlicensed—drug sellers and drug shops; and (f) street vendors and the illegal market.

We report on the characteristics of the included studies, the quality test results by medicine category and specific pediatric formulations, adverse clinical effects, and quality at levels of the distribution chain. The extracted detail of each study is included as supporting information.

RESULTS

Seventy articles met our inclusion criteria. The flowchart for article selection is shown in Figure 1 below.

Characteristics of Included Studies

The characteristics of the included studies are shown in Table 1. The number of studies has been increasing by year. The included studies sampled medicines from a total of 28 countries; 13 low-income and 15 lower-middle-income, the majority of which were in Africa. Although there was a variety of testing methodology utilized in the included studies, content (92.6%, 65/70) and dissolution (54.3%, 38/70) tests were the most common.

Quality Testing Results by Medicine Category

The 70 included studies examined 75 of the 267 (28.1%) medicines listed on the EMLC. Many studies tested quality with small sample sizes ($n \leq 10$).[7–29] Of the 262 individual medicine tests, 56.5% (148/262) had sample sizes of $\leq$10. Very few medicine tests