



Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

Pediatric therapeutics and medicine administration in resource-poor settings: A review of barriers and an agenda for interdisciplinary approaches to improving outcomes[☆]

Sienna R. Craig^{a,*}, Lisa V. Adams^{a,b}, Stephen P. Spielberg^{c,d}, Benjamin Campbell^a

^a Dartmouth College, Hanover, NH, United States

^b Dartmouth Medical School, Hanover, NH, United States

^c Institute for Pediatric Innovation, Cambridge, MA, United States

^d Children's Mercy Hospital, Kansas City, MO, United States

ARTICLE INFO

Article history:

Available online xxx

Keywords:

Pediatric drug formulations
Pharmaceutical practice
Social use of medicines
Child health
Tuberculosis
Review

ABSTRACT

The lack of affordable, available pediatric drug formulations presents serious global health challenges. This article argues that successful pharmacotherapy for children demands an interdisciplinary approach. There is a need to develop new medicines to address acute and chronic illnesses of children, but also to produce formulations of essential medicines to optimize stability, bioavailability, palatability, cost, accurate dosing and adherence. This, in turn, requires an understanding of the social ecologies in which treatment occurs. Understanding health worker, caregiver and patient practices, limitations, and expectations with regard to medicines is crucial to guiding effective drug development and administration. Using literature on pediatric tuberculosis as a reference, this review highlights sociocultural, pharmacological, and structural barriers that impede the delivery of medicines to children. It serves as a basis for the development of an intensive survey of patient, caregiver, and health care worker understandings of, and preferences for, pediatric formulations in three East African countries.

© 2009 Elsevier Ltd. All rights reserved.

Introduction

It is estimated that 9.2 million children—most of them under five years of age—die annually (UNICEF, 2008). This astounding statistic is due, in part, to the lack of available, affordable pediatric drug formulations for many common infectious diseases. We define a 'pediatric drug formulation' as a dosage format which is suitable for accurately, safely, effectively, and adherently administering a medication to children of various ages. The World Health Organization (WHO) approximates that more than 50% of medicines prescribed for children, including many of those on the Model List of Essential

Medicines for Children, *do not actually exist* in dosage forms appropriate for children (WHO Press Release 1/21/09). Even when pediatric formulations exist, clinical availability varies. Consequently, health workers often dispense adult dosage forms with instructions on how to achieve desired pediatric doses. This may include instructing caregivers to break tablets, crush pills, open capsules and estimate dose, or use medicines formulated for intravenous injection as oral liquids. Use of medicines in such a manner can lead to inaccurate dosing and result in potentially reduced efficacy (due to under-dosing) and/or adverse effects (due to excessive doses). An unpublished 2006–2007 WHO survey notes that countries reported using adult formulations for the treatment of children with HIV/AIDS (53% of respondents), TB (52%) and malaria (41%). Thirteen countries described problems with dosing of pediatric medicines, while 14 identified problems caused by lack of pediatric dosage forms and high prices of those available (S. Hill, pers. comm.). Formulations of drugs are fundamentally important because they help to determine whether the dose will be successfully delivered to pediatric patients; however, information on how best to prepare and administer pediatric drug formulations—in *any cultural setting*—is often lacking (Nunn & Williams, 2005). This is a critical global health issue.

In this article, we use pediatric tuberculosis an example of such dynamics. The WHO estimates that worldwide one in three

[☆] This research was supported by a grant from the World Health Organization (WHO) as part of the Better Medicines for Children project. The findings, interpretations and conclusions expressed in this paper are entirely those of the authors and should not be attributed in any manner whatsoever to WHO. The authors thank Suzanne Hill, Jane Robertson, Kalle Hoppu, Robert Whitley, and the four anonymous reviewers for their helpful comments on drafts of this manuscript.

* Corresponding author. Department of Anthropology, Dartmouth College, 6047 Silsby Hall, Hanover, NH 03755, United States. Tel.: +1 603 646 9356; fax: +1 603 646 1140.

E-mail addresses: sienna.craig@dartmouth.edu (S.R. Craig), lisa.v.adams@dartmouth.edu (L.V. Adams), sspielberg@cmh.edu (S.P. Spielberg), benjamin.w.campbell@dartmouth.edu (B. Campbell).

people is infected with *tuberculosis bacillus*. About 8.5 million people develop TB annually and 1.8 million people die from the disease each year. Latest estimates put the number of smear-positive cases among children and adolescents at 1 million per year (Nelson & Wells, 2004; Newton, Brent, Anderson, Whittaker, & Kampmann, 2008). Currently, more than 90% of childhood TB cases occur in the developing world (Adams, 2004). In areas where HIV is also prevalent, a dangerous synergy ensues. In one Ethiopian study, TB mortality was reported as six times higher in HIV-infected children (Berggrem et al. in Adams, 2004: 689). Additionally, HIV infection has been associated with poorer TB treatment adherence in children, due to parent illness or death, as well as poorer treatment outcomes due to immune suppression (Adams, 2004).

Determining estimated TB burden in children poses particular challenges. It is difficult to establish a definitive pediatric TB diagnosis because children with TB are rarely sputum-smear positive. Furthermore, childhood TB—including clinical evaluation of new drugs—has consistently been a lower public health priority than adult TB (Adams, 2004; Burman, Cotton, Gibb, Walker, Vernon, & Donald, 2008; Nelson & Wells, 2004; Newton et al., 2008). Yet children are ‘sentinel’ cases: they represent recent transmission of TB into communities. Children are also at higher risk of progression to active disease than adults; this risk is greatest for infants and children under two years (Newton et al., 2008). In addition, children younger than five are more likely to develop severe forms of TB, and those who recover from primary TB disease remain sources of future active, infectious cases (Adams, 2004). The dearth of high quality (e.g. non counterfeit, expired or substandard) TB drugs at costs that are free or affordable, and that are administered through functioning health systems in pediatric dose forms hinders childhood TB control and treatment (Zucker & Rago, 2007). Fixed-dose combination pills have long been available for adults, but the ratios of medicines and doses are inappropriate for children; no fixed dose or even individual pediatric TB formulations are available. Furthermore, despite WHO recommendations for combination treatment of malaria and TB, no such products have been registered for use in children.

The need to reconcile appropriate pediatric formulations and issues of drug palatability with socioeconomic, cultural, and health systems realities with which the majority of the world’s children contend (and in which most pediatric TB cases occur) is urgent. Children cannot be treated as ‘little adults’ when it comes to producing and distributing essential drugs, including frontline TB pharmaceuticals (Braine, 2007; Burman et al., 2008). The creation of actionable, informed policies and interventions aimed at addressing pediatric health inequalities demands an interdisciplinary approach. Aside from pharmacological concerns about dosage, toxicity, stability, bioavailability, and palatability, as well as the economics of drug production and distribution, an array of sociocultural issues surface in the effort to create, market, distribute, and administer essential pediatric pharmaceuticals in resource-poor settings. We not only need more clinical evidence on the efficacy and safety of medicines for children; we also require more qualitative data from diverse social ecologies about patient, caregiver, and provider knowledge, behavior, beliefs, and attitudes with regard to medicine in general and biomedical pharmaceuticals in particular. This includes efforts to understand the socioeconomic parameters within which medicines are given: how childhood illnesses are classified and explained, how definitions of a ‘child’ on the one hand, and ‘taste’ on the other, vary cross-culturally, and how these factors, in turn, impact patient, caregiver, and provider expectations and practices. Furthermore, we need to know how caregivers and providers manage to administer medicines to children under less than ideal

circumstances today. We also need to know more about what their preferences are—or would be—for improved pediatric pharmaceuticals, in order to mitigate barriers to adherence in the future. The goal of this article, then, is not only to provide a comprehensive review of literature on pediatric therapeutics across the social and biomedical sciences, but also to articulate the need for an interdisciplinary research agenda which employs pharmacological, clinical, and anthropological perspectives in order to improve health outcomes among young people, particularly in resource-poor settings.

Background and conceptual framework

This article addresses—through the lens of children’s medicines—key methodological issues raised by Nichter and Vuckovick (1994: 1509) in their “Agenda for an Anthropology of Pharmaceutical Practice.” Specifically, this review moves from a concern with patterns of curative resort that are illness-centered toward a framework that considers pediatric therapeutics and medicine administration from the perspective of the social and economic realities of prescription, to the interrelationship between practitioner, consumer, and patient expectations on the one hand, and pharmacology, drug production, and marketing on the other. We are concerned with the contexts in which medicines are selected, evaluated, used, and spoken about in developing countries (van der Geest & Whyte, 1988), and the pharmacologic and social ‘lives’ medicines take on in the process (Whyte, van der Geest, & Hardon, 2002). We argue that local and regional explanatory models (Kleinman, 1980) of childhood illnesses, conceptions of ethnophysiology (Nichter, 2008), and the social stigmas associated with particular diseases, including those that afflict young people, must be taken into account in the creation of pediatric drugs, since they bear on prevention and treatment strategies for diseases that impact infant and child survival. Interdisciplinary efforts to address the dearth of pediatric formulations for essential medicines must also stem from a human rights perspective which combines a recognition of the ‘rights of the child’ and an acknowledgment of the structural violence (Farmer, 2003: 40–50) underlying high rates of child mortality and morbidity, with a commitment to strengthening health systems and working with purveyors of local knowledge (both expert and lay) who are often at the frontline of diagnosing, treating, and striving to prevent childhood illness (Hurtig, Porter, & Ogden, 1999).

The authors of this article represent a suite of interests, knowledge, and perspectives that, in our experiences, have not interacted enough. For quite some time, medical anthropologists have conducted ethnography of, and worked alongside, health care workers, epidemiologists, basic scientists, and public health professionals (c.f. Hahn & Inhorn, 2008; Latour, 1988; Martin, 1995). In recent years, critical anthropological engagements with the global pharmaceutical industry have emerged (c.f. Petryna, Lakoff, & Kleinman, 2006). While an anthropology of pharmaceutical practice is well established, collaborative and/or critical engagement with pharmacologists around the issue of drug formulation and production itself has been rare. Likewise, even *within* the biomedical sciences, partnerships between physicians at the frontline of health care delivery and pharmacologists at the cutting edge of drug development is relatively uncommon. Yet, we argue, such scholarly and pragmatic alliances are essential in order to address issues of global health inequity. Nowhere does this alliance become more urgent than when considering the health of children worldwide.

Methodology

In preparation for research which aims to describe and analyze patient, caregiver, provider, and pharmacist preferences for optimal

formulations of pediatric pharmaceuticals in three East African countries,¹ we conducted a review of more than 200 studies in the social sciences, public health and epidemiology, and biomedical literatures, more than 100 of which are cited herein. The review was conducted using Pubmed, WebofScience, Ebscohost and Elsevier databases, and was catalogued using Refworks (www.refworks.com). Articles reviewed spanned three decades (1978–2008). Key search terms included: aesthetics/formulations of pharmaceuticals/medicine; adherence/compliance; child health; child medicines; childhood illness; cultural epidemiology; dosage; drug bioavailability; essential medicines; ethnophysiology; human immunodeficiency virus; HIV/TB co-infection; malaria; parent/caregiver/physician/health worker behavior/preferences; palatability; pediatric therapeutics; pharmacokinetics; pill burden; side effects; stigma; taste; tuberculosis. These examples are emblematic rather than exhaustive. Through this review we identified gaps in communication that seem to exist across key disciplines (such as anthropology, pharmacology, and epidemiology) and practices (such as drug production and prescription). Through our survey of the literatures, we identified five cross-cutting themes that, we argue, should inform future interdisciplinary research. Perhaps more importantly, these themes highlight the scientific and social realities—as well as the ethics and economics—in which the production, prescription, and administration of pediatric medicines are embedded. We address each of these cross-cutting themes, in turn. A summary of findings is presented in [Table 1](#).

Palatability and physical attributes of medicines

People often evaluate medications based on color, form, and taste. In a study among the Mende of Sierra Leone, [Bledsoe and Goubaud \(1985\)](#) found that people assessed the strength and effects of medications largely by evaluating their physical characteristics: the size of a pill indicated its power. In a study among drug sellers and consumers in rural Nigeria, respondents associated the color of medicines with their effects and purposes; they preferred yellow to blue for, in this case, age-specific packages of pediatric malaria medicines ([Brieger, Salami, & Oshiname, 2007](#)). Other studies have reported similar findings, and have noted that humoral reasoning—by which we mean associations between ‘hot’ and ‘cold’ foods, medicines, and illness etiologies that are articulated based on concepts such as blood, wind, bile, etc.—guide evaluation of medicines, including folk analyses of their uses and effects based on color, form, etc. ([Ferguson, 1988](#); [Haak, 1988](#); [Logan, 1973](#); [Nichter, 1987, 1996](#)). [Moerman \(2000\)](#) notes a similar pattern in preferences and cultural variation for placebos. These preferences affect how, when, and why medicines are used—in a word, adherence.

This raises the issue of what ‘child-size’ formulations should look and taste like, and how these preferences might vary cross-culturally. [Nunn and Williams \(2005\)](#) state that one of the biggest gaps in pediatric drug formulation development is understanding how to measure taste and, therefore, determine optimal palatability. [Matsui \(2007\)](#) presents a thorough discussion of palatability in pediatric medicine. The author notes that, while in adult studies, most participants judged taste alone to be the most important category, for children the issues tended to encompass not only taste, but also texture, smell, and aftertaste. Parents of children with HIV have reported difficulties administering anti-retroviral (ARV) medications due to the taste of these medications; of the ten potential interventions to address problems that parents have giving medications,

better tasting medications were rated as “very helpful” by 81% of caregivers of HIV-infected children ([Matsui, 2007](#)).

Matsui’s work addresses methods for measuring palatability, including a discussion of texture/consistency, which may be useful in the development of future study instruments. However, cultural norms influence what is thought of as ‘palatable’ as well as caregiver decision-making about what kinds of tastes to allow children. For example, [Odebiyi \(1989\)](#) states that children in Ile-Ife, Nigeria, normally have their sugar intake restricted so as to prevent them from developing a ‘sweet tongue.’ As suggested by another study, preferences for medicine formulations may vary by gender ([Hames, Seabrook, Matsui, Rieder, & Joubert, 2008](#)). In addition, taste and form preferences may vary within the course of a chronic illness; the example of long-term ARV therapy in HIV-infected children and youth is still unfolding, but raises this issue directly ([Yeung & Wong, 2005](#)).

Many palatability studies of pediatric medicines have been conducted ([Ameen, Pobiner, Giguere, & Carter, 2006](#); [Angelilli, Toscani, Matsui, & Rieder, 2000](#); [Dagan, Shvartzman, & Liss, 1994](#); [Holas, Chiu, Notario, & Kapral, 2005](#); [Moniot-Ville, Chelly, Consten, & Rosenbaum, 1998](#); [Nasrin, Larson, Sultana, & Khan, 2005](#)). The applicability of such findings is limited, however, since the majority have been conducted in predominantly North American settings. Some researchers advocate sweetening children’s medications with pantry and refrigeration items so they ‘go down easy’ and suggest the use of a variety of dosing gadgets and technologies ([Cabaleiro, 2003](#)). These suggestions are neither practical nor cost effective for many of the world’s children, including pediatric TB patients. Furthermore, many clinical studies account for ethnocultural variation in a limited fashion, and do not account for the socioeconomic circumstances in which taste develops, and in which diets are restricted and conform ([Bourdieu, 1984](#); [Scaglioni et al., 2008](#)).

Palatability studies tend to stress the perceived need to mask bitter tastes and aftertastes with sweetness ([Ishizaka et al., 2004](#)). The Swiss pharmaceutical company Novartis’s recent launch of a new cherry-flavored malaria drug for children has been developed based on this premise ([Callimachi, 2009](#)). However, the use of sweet ‘inert’ excipients raises a variety of issues. Excipients are not well regulated in most countries. Most excipients are well tolerated, but adverse effects are known for some excipients which play a critical role in liquid and chewable preparations—the most common formulation for infants and children ([Pawar & Kumar, 2002](#)). Non-validated excipients or use of foods in combination with medicines can lead to physical–chemical interactions which can degrade the active pharmaceutical product, decrease bioavailability or alter toxicity ([Schmiedlin-Ren et al., 1997](#)).

These are known cases. However, for the vast majority of substances a caregiver might use to increase palatability and adherence, there are no data, but some concern. Furthermore, access to clean drinking water cannot be assumed in many areas. This is crucial in terms of developing new pediatric dosage forms. Malnutrition or high disease burden may further impact palatability. Finally, some studies revealed statistically significant differences between tastes and medication forms, but preference differences were minimal in other studies. This leads to a lack of clarity on what new formulations might work best in a variety of contexts. New data on the palatability of malaria medications for children—specifically the use of flavored dispersible tablets compared with crushed commercial tablets in several African countries—indicate promising directions for research ([Abdulla et al., 2008](#)).²

¹ The first of these countries will be Tanzania. The second and third countries remain to be named, and will be chosen in consultation with partners at the World Health Organization.

² See: <http://www.who.int/tcdr/svc/research/antimalarial-policy-access/projects> for a list of ongoing studies.

Table 1
Findings and recommendations.

Themes	Findings	Recommendations
Taste and palatability	Many cultural factors, including diet, gender and religious beliefs, can influence variations in taste preference. The applicability of most palatability studies to children in low resource settings is limited. Palatability studies stress the perceived need to mask bitter tastes with sweet excipients, which can raise issues of safety and bioavailability.	Obtain data, both qualitative and quantitative, on taste preferences; apply this information to development of children's medicines. Gather more comprehensive data on the socioeconomic circumstances in which taste develops. Identify substances a caregiver might use to modify children's therapies to increase palatability and adherence.
Definitions of the child	In a variety of settings, the categories 'child,' 'adolescent' or 'adult' do not easily or necessarily map onto age-weight calculations used to determine dosage for children's medicines. Universal dosage recommendations and practices are often based on social and medical convention, rather than scientific evidence or clinical realities.	Investigate how distinctions between 'children', 'adolescents', and 'adults' are made on the basis of socially constructed categories in different settings, and how this can influence pediatric therapeutics on the ground. Obtain more empirical data on how health providers and caregivers categorize children and how they determine who qualifies for what medical regime is needed.
Cultural epidemiology and ethnophysiology	Illness classification and lay epistemology informs care-seeking behavior, including uses and meanings of both biomedical pharmaceuticals and traditional therapies.	Investigate how children's diseases are classified and addressed in a variety of contexts, how pharmaceuticals circulate within these contexts, and what structural and cultural barriers limit or challenge the prescription and administration of drugs.
Patient/caregiver attitudes	Caregiver decisions are often made not on 'best practices' bases, but rather on cost and availability, as well as aesthetic and palatability.	Obtain more qualitative data from diverse social ecologies about patient, caregiver, and provider knowledge, behavior, beliefs, and attitudes regarding children's medicines. Specifically, look at folk dietetics, literacy levels, non-rational drug prescription, and role of pharmacists.
Illness stigma	Social stigma related to disease can affect how, why, or if people seek treatment and adhere to medicine regimes. Stigma can be associated with other patient characteristics that are potential sources of discrimination: gender, poverty, and co-infection are the most common. Data on illness stigma in relation to children is limited.	Obtain qualitative data on stigma with specific reference to children. Investigate generational stigma, gender, and the ways these two forces work together in pediatric contexts.
Pharmacologic criteria for improved pediatric therapeutics	Children have often been, but should not be, treated as 'little adults' when it comes to drug formulation. Sociocultural, economic, and pharmacologic parameters all influence access and adherence to medications.	Develop 'generalizable' technical platforms whose form and flavor can be adapted for local or regional preferences and that can be used to prepare multiple medications. Such 'optimal' formulas must meet a range of criteria if they are to prove practical in meeting needs of children around the world. These criteria include: heat stability; stability in high humidity conditions; ease of transportation and distribution; low cost; high quality free of potentially harmful excipients; good palatability and form to enhance adherence.

Dosage and definitions of the child

Many experts describe pediatric TB dosage regimes, and discuss the challenges in administering these medicines (Enarson, Enarson, & Gie, 2005; Hopewell, Pai, Maher, Uplekar, & Raviglione, 2006; Newton et al., 2008). They report that few randomized controlled trials have been done in children to establish optimum regimes; current treatment guidelines are largely inferred from adult data. Currently, WHO is working on a consensus for dose and dose-ratios for combination TB products for children, based on pharmacokinetic and pharmacodynamic data and modeling. However, issues surrounding duration of therapy (e.g. whether shorter courses produce comparable outcomes) are still not well enough understood. This has obvious implications for adherence and treatment costs. And, while the properties of TB drugs may be well understood, additional basic biomedical science and clinical data on dosing and side effects are also needed for other essential pediatric medicines.

Tuberculosis research provides both necessary data and an opportunity to critique how dosage is determined for many pediatric medicines. In clinical and research settings 'children' are defined based primarily on weight, secondarily on age, to determine dosage. However, the categories 'child', 'adolescent' or 'adult' do not easily or necessarily map onto age-weight calculations. From seminal anthropological works (Lévi-Strauss, 1949; Malinowski, 1930; Mead, 1961 [1928]; Morgan, 1870; Radcliffe-Brown, 1952; Turner, 1969; Van Gennep, 1960), we learn that definitions of the

'child' and experiences of adolescence are highly variable. Being a child relates to, but is not necessarily dictated by, weight or age in years. Rather, distinctions between 'children', 'adolescents', and 'adults' are made on the basis of socially constructed categories and can vary with respect to political-economic circumstances.

Even from the pharmacologic perspective, dosage recommendations for specific age bands often have little to do with physiology or pharmacologic maturation, but are often driven by cultural norms. While universal dosage recommendations for an infant or even a person under five may be possible, adolescence poses a variety of challenges across the world. Medical regulatory agencies in the US, Japan, and the European Union all operate on different assumptions when defining the 'adolescent' for clinical purposes. In Tanzania, children over the age of nine are routinely admitted to adult wards, and often given adult dosage forms. While age 12 is used as a defining age-group separator in pediatric therapeutics according to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E11), this designation is a *cultural convention* that emerges from Jewish law, rather than a designation based on physiology, pharmacology, or medicine.³ This convention has become standard practice; yet it has meant that about 20% of

³ The authors thank Dr. Hoppu Kalle (pers. comm. 2/09) for this insight.

children receive many medicines 'off-label' based on discrepancies between onset of puberty and age in years.

We are confronted with dissonance between how a 'child' is understood in pharmacologic and social terms. Pharmacokinetic studies can define developmental changes in drug clearance and action, and lead to official mg/kg dosing guidelines in accord with age and development indices. Yet this does not necessarily translate into how dosage is determined on the ground. In many settings, a person's exact age is sometimes unknown and other times departs from how age is calculated with respect to pharmacokinetics. Likewise, clinical and ethnographic experiences of the authors garnered in a range of international settings indicate that children over 9–12 months of age are infrequently weighed. This raises fundamental questions about dosing by rough 'age bands' versus mg/kg. For drugs with a 'broad therapeutic index' where dosing precision is not crucial to achieve efficacy and minimize dose-related toxicity, this dissonance remains minimal. In medicines with a 'narrow therapeutic index' – for example, when toxicity can occur just above therapeutic levels, and where falling below such levels can lead to failure of therapy and/or resistant organisms—this dissonance is crucial.

Furthermore, pharmacokinetic research reveals shifts in developmental pharmacology in clearance of drugs, both between neonatal and toddler periods, but, more significantly, at puberty. For example, children outside the neonatal period often exhibit drug clearance that is more rapid and requires greater mg/kg doses than for adults; at puberty, drug clearance by many pathways, renal and hepatic, decreases to adult levels. Yet the moment at which a person is an 'adult' in a pharmacologic sense does not necessarily correspond to when a person would be considered an 'adult' in many ethnocultural contexts. Gender should also be considered as a second-order variable affecting dosage, in this respect. From a pharmacologic perspective, dosing is based on pharmacokinetic/pharmacodynamic (PK/PD),⁴ efficacy, and safety studies. In the real socio-therapeutic world, dosing is based on cultural definitions of childhood as well as preference of formulations (which may change with maturity), physical ability to swallow pills, and the socioeconomic circumstances in which children and their caretakers find themselves—specifically, the opportunity costs and access issues that influence availability of, and adherence to, therapy.

Cultural epidemiology and ethnophysiology of childhood illnesses

Among other topics, medical anthropologists examine the pluralistic nature of health care systems. Many scholars have pointed out that diversity *within* health care systems has not obviated the need for conceptual frameworks applicable *across* cultures and changing social settings (Janzen, 1978; Kleinman, 1980; Leslie, 1977, 1980). Two key frameworks to emerge from the discipline are cultural epidemiology and ethnophysiology. Cultural epidemiology arose from efforts to apply an integrated formulation of anthropological and epidemiological principles to health-related research; it is concerned with rates of disorders as well as categories of illness-related experiences, meaning, and behavior, and how these experiences impact disease control, treatment and prevention (Atre, Kudale, Morankar, Rangan, & Weiss, 2004; Weiss, 2001). Ethnophysiology refers to the study of how bodily processes are understood in different communities and how such knowledge influences perceptions of health, illness, medicines, physical

development or decline, and diet (Nichter, 2008). Both cultural epidemiology and more conventional public health/infectious disease perspectives are concerned with issues of climate and seasonality (with respect to disease transmission, diagnosis, and control) and with socioeconomic and cultural barriers to treatment. The difference between these perspectives, however, is in how 'culture' is positioned within policy discussions and interventions. Ethnophysiology and cultural epidemiology encourage us to think anthropologically, rather than in strict biophysical terms, about disease processes.

The ethnographic record is replete with examples of afflictions that are viewed as 'milestone' illnesses for children and adolescents, and that are taken as part of 'normal' child development (c.f. Nichter, 1996). Illness categories and etiologies change as individuals move through the life cycle, and can vary by gender. Take the association of hematuria in adolescent boys with a type of 'male menstruation,' which is a 'normal' part of development and puberty. This can lead to delays in treatment for schistosomiasis and other diseases that manifest with the particular symptom of blood in the urine (Amazigo, Silva, Kaufman, & Obikeze, 1997; Bello & Idiong, 1982; Huang & Manderson, 1992; Hunter, 2003; Kloos, 1995).

Other approaches to childhood illness provide frameworks for negotiating responsibility and causality for child death in the face of structural factors that contribute to high mortality and morbidity rates (Amuyunzu, 1998; Castle, 1994; Dettwyler, 1994; Schepher-Hughes, 1993). This can include childhood illnesses that are regarded as supernaturally caused, that can only be diagnosed by a traditional healer or elder kin after a child has died, and that apportion responsibility for children's health or demise within the context of a society's worldview. Local illness terminology for loose, watery stools and fevers, as well as physiological and spiritual attributions of causality for these illnesses, and the home management of these conditions, provide further examples (Ellis et al., 2007; Makundi, Malebo, Mhame, Kitua, & Warsame, 2006; Nsungwa-Sabiiti et al., 2004). These examples, in turn, reflect some of the leading causes of child mortality and morbidity worldwide, as understood from a biomedical and public health perspective: namely, diarrhea and malaria. Illness classification and lay epistemology informs care-seeking behavior, including uses and meanings of both biomedical pharmaceuticals and traditional therapies. Illness classifications also emerge from social and power relations, including efforts to 'translate' indigenous illness concepts into biomedical terms. Recent work on the recognition, perception, and treatment practices for severe malaria (Warsame et al., 2007) and the relationship between *degedege* and malaria (Langwick, 2007; Nsimba & Kayombo, 2008), both in rural Tanzania, provide apt illustrations of these dynamics. While many biomedical practitioners and public health workers equate *degedege* with malaria and view a parent/caregiver's decision to withhold malaria treatment from a child who has been diagnosed with *degedege* as problematic, others see these two disease categories as distinct: arising from different causal factors and requiring distinct therapies.

With reference to TB and related respiratory illnesses, Nichter (1994) identifies what he calls the "TB/'weak lungs' complex." Sometimes 'weak lungs' is interpreted as TB. In most cases, TB is understood to emerge from a person who suffers from weak lungs, itself resulting from factors that weaken or shock the body, modes of etiology involving pathogens, contagion and heredity, as well as illnesses or injuries which can transform into TB. This complex is not only promulgated by those who lack scientific training; many primary health workers and physicians might embrace *both* a pathogen-based explanation of TB *and* a view that predisposition to 'weak lungs' can lead to active TB. From this perspective, factors that place one at risk for TB include hunger, exposure to the

⁴ We define PK/PD as the relationship between dose, exposure (e.g. serum concentrations, and effect).

elements especially during changes of climate, overwork and excessive habits such as smoking, drinking, and sex. These associations are echoed in other studies (Atre et al., 2004; Bond & Nyblade, 2006; Liefvooghe, Michiels, Habib, Moran, & De Muynck, 1995; Liefvooghe, Baliddawa, Kipruto, Vermeire, & De Muynck, 1997; Promtussananon & Peltzer, 2005).

Notably, few of these perspectives on TB etiology account for children directly; indeed, TB is often linked to prototypically 'adult' behavior. This provides us with a cautionary tale: we must consider how *possible categories* of childhood illness are defined cross-culturally, and how this, then, impacts the course of an illness, from diagnosis to treatment adherence. Diverse and sometimes contradictory diagnostic practices—at the confluence of biomedicine, ethnophysiology, and traditional medicine—impact how medicines are used, and what medicines are considered appropriate for children.

Perceptions and expectations of medications among caregivers and providers

The literature reveals significant differences in caregiver reports of adherence to drug regimes and physician judgments about adherence rates. Some reasons for this difference emerge directly from ethnophysiological concerns related to diet and the possibilities within a given cultural context for defining, diagnosing, and treating childhood illnesses. Other concerns are tied to duration of treatment and associated 'pill burden', a term which refers to the number and kinds of dose forms a person must take on a regular basis (Alperstein, Morgan, Mills, & Daniels, 1998). Pill burden is an issue in all contemporary societies, but it is particularly salient in co-infected HIV/TB populations (Albano, Giacomet, de Marco, Bruzzese, Starace, & Guarino, 2007). In addition, when accounting for discord between providers, caregivers, and patient expectations, we must never forget that medicines, as material things, are not only tokens of healing and hope but they are also valuable (and sometimes unaffordable) commodities; biomedical pharmaceuticals are symbols of modernity and social change, in both positive and negative senses (van der Geest, Whyte, & Hardon, 1996; Whyte et al., 2002). With reference to pediatric TB, unless free, fixed-dose pills become the global norm, caregivers will likely continue to make triage decisions about which medicines to give to children. These decisions are often made not on 'best practices' bases, but rather on cost and availability, as well as aesthetic and palatability (Nichter 2008: 88).

To explore this dynamic of perceptions and expectations of medicines with reference to caregivers, let us return to the 'weak lungs'/TB dynamic. Nichter (1994) observed that mothers of children who took medications for primary complex TB, classified in this local Filipino context as 'weak lungs', expected that this medication would also cure other respiratory problems. In some cases, children treated with INH (isoniazid, locally termed 'vitamins for the lungs') were not taken to see health care providers when they were suffering from pneumonia until they were extremely ill. This treatment delay was directly associated with mothers' expectations that INH would cure the illness—an expectation that was not addressed by health staff at the time that TB medications were provided (Nichter, 2008: 657). Warsame et al. (2007) report on similar dynamics, with reference to malaria.

Local conceptions of what constitutes good or nutritious food, and what substances are viewed as potentially medicinal (as opposed to harmful)—what Nichter (2008) terms 'folk dietetics'—can also influence caregiver and patient uses and expectations of medicines. In either resource-poor or resource-rich settings, caregivers may deem biomedical pharmaceuticals too 'strong' for children, with too many 'side effects' that could impact child development, or with iatrogenic effects (Etkin, 1992). As Odebiyi

(1989) points out, dietary proscriptions and prescriptions for treatment reflect healers' and caregivers' concept of various childhood diseases and are often influenced by religious beliefs. As in other parts of the world (Kaiser, Martinez, Harwood, Garcia, & Kabra, 1999; Nichter, 1987), Yoruba healers often recommended hot and cold foods as part of therapy, depending on a child's condition and orientation in relation to certain spiritual figures or forces.

The relationship between mothers' education, particularly literacy levels, and health behavior, including health-related communication skills are also crucial to consider (LeVine, LeVine, Rowe, & Schnell-Anzola, 2004; Schnell-Anzola, Rowe, & LeVine, 2005; levers, Brown, Drotar, Caplan, Pishevar, & Lambert, 1999). In a study of Venezuelan mothers, Schnell-Anzola et al. (2005) showed that academic literacy skills women learned in school and retained in adulthood predicted their health-related communication abilities above and beyond the amount of schooling they received. This included not only communicating health messages to children in their care, but also navigating the health care systems on behalf of their charges. Indeed, the universal surrogate of overall child health outcomes is maternal literacy and education.

Inappropriate (or 'non-rational') drug prescription is a global phenomenon. Satisfying patient prescription expectations is often reported by practitioners across the world, as a way to build or preserve the doctor-patient relationship. Providers sometimes prescribe because they think it is what patients want, even if patient/caregiver expectations for receiving drugs remain lower. This dynamic is particularly salient when caregivers interact with providers on behalf of children (Bagner, Fernandez, & Eyberg, 2004; Stivers, Mangione-Smith, Elliott, McDonald, & Heritage, 2003). Mangione-Smith, McGlynn, Elliott, Krogstad, and Brook (1999) note such patterns of over-prescription related to the use of pediatric antimicrobials. With reference to HIV, discrepancies between caregiver reports and physician judgment on child adherence to ARV therapy can be severe (Albano et al., 2007).

Despite the existence of firmly established TB control programs, anti-TB drugs are sometimes prescribed by physicians outside the framework of directly-observed therapy (DOT), even for other respiratory conditions (Ottmani, Scherpbier, Chaulet, Pio, Van Beneden, & Raviglione, 2004). Despite the relative success of DOT in adult populations, they are not as relevant for children. Often, the person doing the 'observing' is a parent or caregiver. In some instances, children receive clinic-based DOT for the first two months of TB treatment, but this is not a pervasive policy. Some argue that children are often 'orphaned' from participating in a treatment modality that works well in adults. Immunocompromised children with TB present even more complications (Albertini, 2005; Al-Dossary, Ong, Correa, & Starke, 2002; Duarte, Amado, Lucas, & Sapage, 2007; Reid et al., 2006). These circumstances remind us, again, that children's lives, including their social and medical lives, are different than that of adults, and require different strategies.

The role pharmacists play in the context of health systems must also be considered. Nichter (1994: 656) notes that pharmacists commonly offer INH preparations to clients who request 'vitamins', given the colloquial use of the term to refer to TB medications as 'vitamins for the lungs.' This or similar behavior can, of course, lead to misdiagnosis, improper medicine sharing, drug resistance, and other adverse effects. Other scholars (Das & Das, 2006) have shown that pharmacists are playing increasingly important roles in diagnosing diseases and prescribing medications, particularly in circumstances driven by market-based medicine and a fee-for-service model of care. The role of pharmacists, both as sources of knowledge and social power, and as possible avenues through which to disseminate health education messages and gather information on 'end user' preferences—including decisions caregivers make for children—cannot be underestimated.

Stigma and social suitability of medicines

It is crucial to consider the roles medicines play in the construction and negotiation of specific *illness* identities (Nichter & Vuckovic, 1994: 1515). The ways illnesses are viewed socially bears directly on how, why, or if people seek treatment and adhere to medicine regimes. This may include social affinities or aversions to specific forms of medicines (e.g. pills or injections). Assessing the 'social suitability' of medicines is particularly salient in cases where forms of treatment can 'out' patients or their families as being carriers of socially stigmatized diseases. As Goffman (1963) reminds us, stigma can be enacted or internalized, or both.

The literature reveals a paucity of stigma studies with specific reference to children. And, despite many general articles on TB stigma, fewer TB stigma studies exist when compared with literature on HIV/AIDS stigma. Studies reveal that TB is often referred to a 'dirty disease.' Upon learning that one is a carrier of TB or that one has active TB, a common response is shock, a sense that one felt 'clean' or healthy, or denial of the presence of the disease (Johansson, Diwan, Huong, & Ahlberg, 1996). This is reflected in ethnophysiological conceptions of the affliction. Nichter (1994) reveals that TB is a 'bad mark' on the family, that it brings shame, and that many affected by the disease try to keep their medicines a secret. Furthermore, part of the point of associating TB with 'weak lungs' is that this vernacular description carries less social stigma than the more clinical, and not entirely interchangeable term, tuberculosis. Related to this, Nichter (1994: 652) notes that physicians reported they told some sputum or X-ray positive patients (but not coughing up blood) that they had 'weak lungs'. The most common explanation offered for their use of the term was 'to reduce social stigma.' In this study, children with 'weak lungs' were viewed as the least worrisome and least contagious type of possibly TB afflicted person.

Atre et al. (2004) report on generational stigma; it is posited that if the mother has TB, then transmission to her child is possible, either in utero or after birth (2004: 1234). Yet there may be significant variation in the ways TB stigma manifests within the family, and outward to the community. Sometimes stigma emerges in the population's desire for privacy in how sputum is collected, test results reported and medicine distributed (Nichter, 1994: 658). TB stigma can be *enacted* and/or *internalized* (Macq, Solis, & Martinez, 2006). Determinants of TB stigma are often beliefs about transmission and less frequently a product of health care provider attitude (Auer, Sarol, Tanner, & Weiss, 2000) or health care organization (Atre et al., 2004; Johansson, Long, Diwan, & Winkvist, 2000). TB stigma is often associated with other patient characteristics that are potential sources of discrimination: gender (Ahsan et al., 2004; Atre et al., 2004; Johansson et al., 2000; Long, Johansson, Diwan, & Winkvist, 2001), poverty (Johansson et al., 2000) and co-infection with HIV (Liefoghe et al., 1997) are reported most frequently.

To elaborate, Atre et al. (2004) note a gender differential with reference to TB stigma. In this Indian study, women were more vulnerable to worse outcomes with TB; they and their children were more vulnerable to generational stigma. The social fact of gendered TB stigma can have adverse effects on children, given the primary role many women play in addressing childhood illness and in maintaining the household. Yet we do not know enough about generational stigma, gender, and the ways these two forces work together in pediatric contexts. Future research might address: 1. whether gender affects how TB is viewed among, and how treatment is sought for, children; 2. whether a child's gender in any way determines whether s/he is seen as vulnerable to contracting TB or able to adhere to a treatment regime; and 3. how this impacts access and adherence to medications. These circumstances also

provide impetus for the development of a fixed-dose pediatric formula that is both palatable and easy to administer.

Finally, Bond and Nyblade (2006) speak about unfolding TB-HIV stigma in high HIV prevalence settings. Theirs is one of the few studies that addresses children directly. TB, the most common and serious of HIV's opportunistic infections in Sub-Saharan Africa, has become progressively stigmatized. As part of this study, pediatric TB patients drew poignant pictures of themselves eating separately from the rest of the household. Bond and Nyblade argue that TB patients are put under considerable pressure to reveal their status, but to do so in the context of high HIV prevalence and the strong association with HIV can undermine their integrity. This is a daunting portrait. The issue of stigma is especially significant for pediatric populations, since the ethnographic record indicates TB can be conceived of as a disease that results from improper social behavior (such as excessive smoking, drinking, sexual promiscuity, etc.) and is therefore not often or directly associated with children. Stigma, combined with the difficulty in diagnosing pediatric TB, may be placing more children at risk of TB morbidity and mortality.

Conclusions

Since 2006, a number of steps have been taken by WHO and the World Health Assembly (WHA) to address these issues (Braine, 2007; Couper & Kaplan, 2007). In May 2007, WHA identified the improved access to essential medicines for children as a prerequisite to achieving health outcomes set out in the United Nations Millennium Development Goals (MDGs) (Zucker & Rago, 2007). This was identified through resolution WHA60.20. Launched in December 2007 and spearheaded by WHO, the '*make medicines child size*' campaign aims to improve availability and access to safe, child-specific medicines, with a focus on resource-poor settings.⁵ The recognition within WHO and related agencies of the need to develop and make available essential medicines formulated for children further confirms the changing nature of childhood diseases within a global health context. Arguably, the management of chronic illnesses such as HIV and TB are just as critical as having appropriately formulated medications to address acute childhood diseases, such as diarrhea and respiratory tract infections, for which medications currently exist and new regimes are being developed. A notable new development here is the use of zinc to control and treat diarrheal disease in children (see Nichter, Acuin, & Vargas, 2008). These transitions in global health priorities further acknowledges the need to address essential children's medicines in appropriate formulations from regulatory, health systems, human rights, cultural epidemiological, and pharmacological perspectives. We must continue to investigate how children's diseases are classified and addressed in a variety of contexts, how pharmaceuticals circulate within these contexts, and what structural and cultural barriers limit or challenge the prescription and administration of drugs. Without this, the existence of an essential medicines list for children, and regulatory structures to enforce the safety and efficacy of such drugs, will fall short of meeting the MDGs.

Let us remember the larger context: nearly two billion people are estimated to have inadequate or no access to life-saving medicines (Ahmad, 2002; Ruxin, Paluzzi, Wilson, Tozan, Kruk, & Teklehaimanot, 2005). The reasons for this colossal health and human rights failure are complex: ineffective health systems, including human resource and infrastructure deficiencies; international trade agreements which favor consolidation of power and resources in the hands of those who have historically had more social and economic capital, including the global pharmaceutical

⁵ <http://www.who.int/childmedicines/targets/en/index.html>.

industry; weak national governance; lack of political will; inadequate donor assistance; lack of donor–recipient coordination on the ground; and a variety of sociocultural constraints that disproportionately prevent women, children, ethnic minorities and other marginalized groups from gaining access to medicines (Farmer, 2003; Ruxin et al., 2005).

The development of new pediatric formulations that are easy to administer and palatable must be coupled with continued human and financial resources devoted not only to ensuring access to such medicines, but also to health education, community-based illness management, and efforts to reduce stigma around specific diseases. And, in shaping pediatric formulations, the effects of pill burden should be seriously considered and further ethnographically examined. TB chemoprophylaxis and treatment is a case in point. Differences in adherence rates to three-month versus six- to nine-month chemoprophylaxis regimens in both developed and developing countries were significant across the literature reviewed, with the three-month regimes garnering consistently higher levels of adherence. In communities where pediatric TB often co-occurs with HIV infection, and where ARVs regimes are available, the pill burden issue becomes even more critical. From a basic science perspective, clinical research and interventions are moving toward specific etiology-based diagnoses, away from disease phenotype and symptomatology. To this end, enhanced diagnostic precision through molecular and other approaches may lead to dramatic changes in health care systems over time, particularly as these methodologies and associated technologies are made available to more of the global community. Global health equity issues should challenge basic scientists, social scientists, and health care providers to think about the clinical and cultural changes that will result from enhanced diagnostic precision, and to consider how these shifts will affect practitioner–patient–caregiver communication across the world, and how such technologies will be received and made sense of in a variety of localities. There is a role for ethnophysiology and cultural epidemiology here, in terms of how they elucidate, with great degrees of accuracy, depth, and consistency—if not ‘standardization’ per se—the relationship between types of individuals, specific etiologies, and illness experiences, including those of children.

Finally, we must remember that health systems are at once a product of, and producers of, cultural meanings (Nichter & Vuckovic, 1994: 1510). These meanings—as well as the socioeconomic and political circumstances in which children live—vary considerably. However, many of the issues outlined here with reference to resource-poor settings today are echoed in the histories, clinical practices, and uses of biomedicine in resource-rich settings: from issues surrounding definitions of the child, to rationales underlying drug prescription, manufacture and demand, to concerns about the ‘strength’ of pharmaceuticals and their impacts on children. To this end, further comparisons across moments in medical history and geography may generate fruitful discussion toward developing intelligent, pragmatic solutions to meeting the medical needs of children.

This article has presented evidence from wide-ranging scholarship to set an agenda for an interdisciplinary approach to research and interventions aimed at improving pediatric medicines and health outcomes. Such an agenda must involve both qualitative and quantitative methodologies and take into account the cultural and socioeconomics of drug production, prescription, and use. Underlying this agenda is the fundamental need to think comprehensively and creatively about the needs of children and their caregivers. Understanding the socioeconomic and cultural determinants of medicine use is critical to informing the types of pediatric drug formulations that may help to optimize successful therapy—at least within the framework of biomedical intervention.

Differences in preferences may suggest that development of a ‘common platform’ as a starting point for the chemistry of formulations, which can then be readily adapted to various formats and preferences, might be most advantageous. As we develop new technologies for drug delivery and formulations, we must not only endeavor to understand the contexts in which medicines are used, but also put this information to work in novel ways. Otherwise, we run many risks, including repercussions from the naïve assumption that adult information can be applied to children or that knowledge produced in one context can simply be applied to another.

References

- Abdulla, S., Sagara, I., Borremann, S., D’Alessandro, U., González, R., Hamel, M., et al. (2008). Efficacy and safety of artemether–lumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, single-blind, multicentre trial. *Lancet*, 372, 1819–1827.
- Adams, L. V. (2004). Childhood tuberculosis in the developing world. *Pediatric Annals*, 33, 685.
- Ahmad, K. (2002). Access denied to essential medicines in developing world. *Lancet Infectious Diseases*, 2, 711.
- Ahsan, G., Ahmed, J., Singhasivanon, P., Kaewkungwal, J., Okanurak, K., Suwannapong, N., et al. (2004). Gender difference in treatment seeking behaviors of tuberculosis cases in rural communities of Bangladesh. *Southeast Asian Journal of Tropical Medicine and Public Health*, 35, 126–135.
- Albano, F., Giacomet, V., de Marco, G., Bruzzese, E., Starace, F., & Guarino, A. (2007). Adherence to antiretroviral therapy in children: a comparative evaluation of caregiver reports and physician judgment. *AIDS Care*, 19, 764–766.
- Albertini, M. (2005). Treatment of tuberculosis in children. *Archives of Pediatrics*, 12(Suppl 2), S110–S116.
- Al-Dossary, F. S., Ong, L. T., Correa, A. G., & Starke, J. R. (2002). Treatment of childhood tuberculosis with a six month directly observed regimen of only two weeks of daily therapy. *Pediatrics Infectious Diseases Journal*, 21, 91–97.
- Alperstein, G., Morgan, K. R., Mills, K., & Daniels, L. (1998). Compliance with anti-tuberculosis preventive therapy among 6-year-old children. *Australian and New Zealand Journal of Public Health*, 22, 210–213.
- Amazigo, U., Silva, N., Kaufman, J., & Obikeze, D. (1997). Sexual activity and contraceptive knowledge and use among in-school adolescents in Nigeria. *International Family Planning Perspectives*, 23, 28–33.
- Ameen, V. Z., Pobiner, B. F., Giguere, G. C., & Carter, E. G. (2006). Ranitidine (zantac) syrup versus ranitidine effervescent tablets in children: a single-center taste preference study. *Paediatric Drugs*, 8, 265–270.
- Amuyunzu, M. (1998). Willing the spirits to reveal themselves: rural Kenyan mothers’ responsibility to restore their children’s health. *Medical Anthropology Quarterly*, 12, 490–502.
- Angelilli, M. L., Toscani, M., Matsui, D. M., & Rieder, M. J. (2000). Palatability of oral antibiotics among children in an urban primary care center. *Archives of Pediatrics & Adolescent Medicine*, 154, 267–270.
- Atre, S. R., Kudale, A. M., Morankar, S. N., Rangan, S. G., & Weiss, M. G. (2004). Cultural concepts of tuberculosis and gender among the general population without tuberculosis in rural Maharashtra, India. *Tropical Medicine & International Health*, 9, 1228–1238.
- Auer, C., Sarol, J., Tanner, M., & Weiss, M. (2000). Health seeking and perceived causes of tuberculosis among patients in Manila, Philippines. *Tropical Medicine & International Health*, 5, 648–656.
- Bagner, D. M., Fernandez, M. A., & Eyberg, S. M. (2004). Parent–child interaction therapy and chronic illness: a case study. *Journal of Clinical Psychology in Medical Settings*, 11, 1–6.
- Bello, C. S., & Idiong, D. U. (1982). Schistosoma urethritis: Pseudo-gonorrhoeal disease in northern Nigeria. *Tropical Doctor*, 12, 141.
- Bledsoe, C. H., & Goubaud, M. F. (1985). The reinterpretation of western pharmaceuticals among the Mende of Sierra Leone. *Social Science & Medicine*, 21, 275–282.
- Bond, V., & Nyblade, L. (2006). The importance of addressing the unfolding TB-HIV stigma in high HIV prevalence settings. *Journal of Community & Applied Social Psychology*, 16, 452–461.
- Bourdieu, P. (1984). *Distinction: A social critique of the judgment of taste*. Cambridge: Harvard University Press.
- Braine, T. (2007). WHO to launch first essential medicines list for children. *Bulletin of the World Health Organization*, 85, 249–250.
- Brieger, W. R., Salami, K. K., & Oshiname, F. O. (2007). Perceptions of drug color among drug sellers and consumers in rural southwestern Nigeria. *Research in Social and Administrative Pharmacy*, 3, 303–319.
- Burman, W. J., Cotton, M. F., Gibb, D. M., Walker, S., Vernon, A. A., & Donald, P. R. (2008). Ensuring the involvement of children in the evaluation of new tuberculosis treatment regimens. *PLoS Medicine*, 5(8), 1–5.
- Cabaleiro, J. (2003). Flavoring meds for children and adults so it goes down easy!. *Home Health Nurse*, 21, 295–298.
- Callimachi, R. (2009). *Cherry-flavored malaria drug launched for kids*. Associated Press.

- Castle, S. E. (1994). (Re)negotiation of illness diagnoses and responsibility for child death in rural Mali. *Medical Anthropology Quarterly*, 8, 314–335.
- Couper, M. R., & Kaplan, S. (2007). *Promoting safety of medicines for children*. Geneva: OMS. 64 p. tab.
- Dagan, R., Shvartzman, P., & Liss, Z. (1994). Variation in acceptance of common oral antibiotic suspensions. *Pediatric Infectious Disease Journal*, 13, 686–690.
- Das, V., & Das, R. (2006). Pharmaceuticals in urban ecologies: The register of the local. In A. Petryna, A. Lakoff, & A. Kleinman (Eds.), *Global pharmaceuticals: Ethics, markets, practices* (pp. 171–205). Durham: Duke University Press.
- Dettwyler, K. (1994). *Dancing skeletons: Life and death in West Africa*. Prospect Heights, Illinois: Waveland.
- Duarte, R., Amado, J., Lucas, H., & Sapage, J. M. (2007). Portuguese Society of Pulmonology. [Treatment of latent tuberculosis infection: Update of guidelines, 2006]. *Revista Portuguesa de Pneumologia*, 13, 397–418.
- Ellis, A. A., Winch, P., Daou, Z., Gilroy, K. E., & Swedberg, E. (2007). Home management of childhood diarrhoea in southern Mali: implications for the introduction of zinc treatment. *Social Science & Medicine*, 64, 701–712.
- Enarson, P. M., Enarson, D. A., & Gie, R. (2005). Management of tuberculosis in children in low-income countries. *International Journal of Tuberculosis and Lung Disease*, 9, 1299–1304.
- Etkin, N. L. (1992). "Side effects": cultural constructions and reinterpretations of western pharmaceuticals. *Medical Anthropology Quarterly*, 6, 99–113.
- Farmer, P. (2003). *Pathologies of power: Health, human rights, and the new war on the poor*. Berkeley: University of California Press.
- Ferguson, A. (1988). Commercial pharmaceutical medicine and medicalization: A case study from El Salvador. In S. Van Der Geest, & S. R. Whyte (Eds.), *The context of medicines in developing countries* (pp. 19–47). Springer Publisher.
- Goffman, E. (1963). *Stigma: Notes on the management of spoiled identity*. Upper Saddle River, NJ: Prentice-Hall.
- Haak, H. (1988). Pharmaceuticals in two Brazilian villages: lay practices and perceptions. *Social Science & Medicine*, 27, 1415–1427.
- Hahn, R., & Inhorn, M. (2008). *Anthropology and public health: Bridging differences in culture and society*. Oxford: Oxford University Press.
- Hames, H., Seabrook, J. A., Matsui, D., Rieder, M. J., & Joubert, G. I. (2008). A palatability study of a flavored dexamethasone preparation versus prednisolone liquid in children. *Canadian Journal of Clinical Pharmacology*, 15, 95–98.
- Holas, C., Chiu, Y. L., Notario, G., & Kapral, D. (2005). A pooled analysis of seven randomized crossover studies of the palatability of cefdinir oral suspension versus amoxicillin/clavulanate potassium, cefprozil, azithromycin, and amoxicillin in children aged 4 to 8 years. *Clinical Therapy*, 27, 1950–1960.
- Hopewell, P. C., Pai, M., Maher, D., Uplekar, M., & Raviglione, M. C. (2006). International standards for tuberculosis care. *The Lancet Infectious Diseases*, 6, 710–725.
- Huang, Y., & Manderson, L. (1992). Schistosomiasis and the social patterning of infection. *Acta Tropica*, 51, 175.
- Hunter, J. M. (2003). Inherited burden of disease: agricultural dams and the persistence of bloody urine (schistosomiasis hematobium) in the upper east region of Ghana, 1959–1997. *Social Science & Medicine*, 56, 219–234.
- Hurtig, A. K., Porter, J. D., & Ogden, J. A. (1999). Tuberculosis control and directly observed therapy from the public health/human rights perspective. *International Journal of Tuberculosis and Lung Disease*, 3, 553–560.
- Ievers, C. E., Brown, R. T., Drotar, D., Caplan, D., Pishevar, B. S., & Lambert, R. G. (1999). Knowledge of physician prescriptions and adherence to treatment among children with cystic fibrosis and their mothers. *Journal of Developmental and Behavioral Pediatrics. Special Issue: Pediatric Pain: New directions from a Developmental Perspective, Part II*, 20, 335–343.
- Ishizaka, T., Miyahara, Y., Mukai, J., Asaka, K., Nakai, Y., Tsuji, E., et al. (2004). Bitterness evaluation of medicines for pediatric use by a taste sensor. *Chemical & Pharmaceutical Bulletin (Tokyo)*, 52, 943–948.
- Janzen, J. M. (1978). *The quest for therapy: Medical pluralism in lower Zaire*. Berkeley: University of California Press.
- Johansson, E., Diwan, V. K., Huong, N. D., & Ahlberg, B. M. (1996). Staff and patient attitudes to tuberculosis and compliance with treatment: an exploratory study in a district in Vietnam. *Tubercle and Lung Disease*, 77, 178–183.
- Johansson, E., Long, N. H., Diwan, V. K., & Winkvist, A. (2000). Gender and tuberculosis control: perspectives on health seeking behaviour among men and women in Vietnam. *Health Policy*, 52, 33–51.
- Kaiser, L., Martinez, N., Harwood, J., Garcia, L., & Kabra, S. K. (1999). Child feeding strategies in low-income latino households: focus group observations. *Journal of the American Dietetic Association*, 99, 601–603.
- Kleinman, A. (1980). *Patients and healers in the context of culture*. Berkeley: University of California Press.
- Kloos, H. (1995). Human behavior, health education and schistosomiasis control: a review. *Social Science & Medicine*, 40, 1497–1511.
- Langwick, S. (2007). Devils, parasites, and fierce needles: healing and the politics of translation in southern Tanzania. *Science, Technology, & Human Values*, 32, 88–117.
- Latour, B. (1988). *Science in action: How to follow scientists and engineers through society*. Cambridge, MA: Harvard University Press.
- Leslie, C. (1977). Pluralism and integration in the Indian and Chinese medical systems. In D. Landy (Ed.), *Culture, disease, and healing: Studies in medical anthropology* (pp. 511). New York: Macmillan Press.
- Leslie, C. (1980). Medical pluralism in world perspective. *Social Science & Medicine [Medical Anthropology]*, 14B, 191.
- Lévi-Strauss, C. (1949). *The elementary structures of kinship*. Boston: Beacon Press.
- LeVine, R. A., LeVine, S. E., Rowe, M. L., & Schnell-Anzola, B. (2004). Maternal literacy and health behavior: a Nepalese case study. *Social Science & Medicine*, 58, 863–877.
- Liefoghe, R., Baliddawa, J. B., Kipruto, E. M., Vermeire, C., & De Munynck, A. O. (1997). From their own perspective. A Kenyan community's perception of tuberculosis. *Tropical Medicine & International Health*, 2, 809.
- Liefoghe, R., Michiels, N., Habib, S., Moran, M. B., & De Muynck, A. (1995). Perception and social consequences of tuberculosis: a focus group study of tuberculosis patients in Sialkot, Pakistan. *Social Science & Medicine*, 41, 1685–1692.
- Logan, M. (1973). Humoral medicine in Guatemala and peasant acceptance of modern medicine. *Human Organization*, 32, 385.
- Long, N. H., Johansson, E., Diwan, V. K., & Winkvist, A. (2001). Fear and social isolation as consequences of tuberculosis in Vietnam: a gender analysis. *Health Policy*, 58, 69–81.
- Macq, J., Solis, A., & Martinez, G. (2006). Assessing the stigma of tuberculosis. *Psychology, Health & Medicine*, 11, 346–352.
- Makundi, E., Malebo, H., Mhame, P., Kitua, A., & Warsame, M. (2006). Role of traditional healers in the management of severe malaria among children below five years of age: the case of Kilosa and Handeni Districts, Tanzania. *Malaria Journal*, 5, 1–9.
- Malinowski, B. (1930). *Parenthood, the basis of social structure*. New York: Macaulay Company.
- Mangione-Smith, R., McGlynn, E. A., Elliott, M. N., Krogstad, P., & Brook, R. H. (1999). The relationship between perceived parental expectations and pediatrician antimicrobial prescribing behavior. *Pediatrics*, 103, 711–718.
- Martin, E. (1995). *Flexible bodies: The role of immunity in American culture from the days of polio to the age of AIDS*. Boston: Beacon Press.
- Matsui, D. (2007). Assessing the palatability of medications in children. *Paediatric and Perinatal Drug Therapy*, 8, 55.
- Mead, M. (1961). *Coming of age in Samoa*. New York: HarperCollins Publishers Inc.
- Moerman, D. E. (2000). Cultural variations in the placebo effect: ulcers, anxiety, and blood pressure. *Medical Anthropology Quarterly*, 14, 51–72.
- Moniot-Ville, N., Chelly, M., Consten, L., & Rosenbaum, M. (1998). The acceptability, efficacy and safety of a new paediatric oral suspension of roxithromycin in respiratory tract infections. *The Journal of International Medical Research*, 26, 144–151.
- Morgan, L. H. (1870). *Systems of consanguinity and affinity of the human family*. Lincoln, Nebraska: University of Nebraska Press.
- Nasrin, D., Larson, C. P., Sultana, S., & Khan, T. U. (2005). Acceptability of and adherence to dispersible zinc tablet in the treatment of acute childhood diarrhoea. *Journal of Health, Population, and Nutrition*, 23, 215–221.
- Nelson, L. J., & Wells, C. D. (2004). Global epidemiology of childhood tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 8, 636.
- Newton, S. M., Brent, A. J., Anderson, S., Whittaker, E., & Kampmann, B. (2008). Paediatric tuberculosis. *The Lancet Infectious Diseases*, 8, 498–510.
- Nichter, M. (1987). Cultural dimensions of hot, cold and sema in Sinhalese health culture. *Social Science & Medicine*, 25, 377–387.
- Nichter, M. (1994). Illness semantics and international health: the weak lungs/TB complex in the Philippines. *Social Science & Medicine*, 38, 649–663.
- Nichter, M. (1996). Social science lessons from diarrhea research and their application for ARI. In M. Nichter, & M. I. Nichter (Eds.), *Anthropology and international health: Asian case studies* (pp. 135). Amsterdam: Gordon and Breach.
- Nichter, M. (2008). Global health: Why Cultural perceptions, social representations, and biopolitics matter. *Tucson*. The University of Arizona Press.
- Nichter, M., Acuin, C., & Vargas, A. (2008). *Introducing zinc in a diarrhoeal disease control programme: Guide to conducting formative research*. World Health Organization.
- Nichter, M., & Vuckovic, N. (1994). Agenda for an anthropology of pharmaceutical practice. *Social Science & Medicine*, 39, 1509–1525.
- Nsimba, S., & Kayombo, E. J. (2008). Sociocultural barriers and malaria health care in Tanzania. *Evaluation and the Health Professions*, 31, 318–322.
- Nsungwa-Sabiiti, J., Källander, K., Nsabagasani, X., Namusisi, K., Pariyo, Johansson, A., et al. (2004). Local fever illness classifications: implications for home management of malaria strategies. *Tropical Medicine & International Health*, 9, 1191–1199.
- Nunn, T., & Williams, J. (2005). Formulation of medicines for children. *British Journal of Clinical Pharmacology*, 59, 674–676.
- Odebiyi, A. I. (1989). Food taboos in maternal and child health: the views of traditional healers in Ile-ife, Nigeria. *Social Science & Medicine*, 28, 985–996.
- Ottmani, S., Scherpbier, R., Chaleet, P., Pio, A., Van Beneden, C., & Raviglione, M. (2004). *Respiratory care in primary care services: A survey in 9 countries*. World Health Organization.
- Pawar, S., & Kumar, A. (2002). Issues in the formulation of drugs for oral use in children: role of excipients. *Paediatric Drugs*, 4, 371–379.
- Petryna, A., Lakoff, A., & Kleinman, A. (2006). *Global pharmaceuticals: Ethics, markets, practices*. Durham, NC: Duke University Press.
- Promptunanon, S., & Peltzer, K. (2005). Perceptions of tuberculosis: attributions of cause, suggested means of risk reduction, and preferred treatment in the Limpopo province, South Africa. *Journal of Health Population, and Nutrition*, 23, 74.
- Radcliffe-Brown, A. (1952). *Structure and function in primitive society*. London: Routledge.
- Reid, A., Scano, F., Getahun, H., Williams, B., Dye, C., Nunn, P., et al. (2006). Towards universal access to HIV prevention, treatment, care, and support: the role of tuberculosis/HIV collaboration. *Lancet*, 6.
- Ruxin, J., Paluzzi, J. E., Wilson, P. A., Tozan, Y., Kruk, M., & Teklehaimanot, A. (2005). Emerging consensus in HIV/AIDS, malaria, tuberculosis, and access to essential medicines. *Lancet*, 365, 618–621.

- Scaglioni, S., Salvioni, M., & Galimberti, C. (2008). Influence of parental attitudes in the development of children eating behaviour. *The British Journal of Nutrition*, 99(Suppl 1), S22–S25.
- Scheper-Hughes, N. (1993). *Death without weeping: The violence of everyday life in Brazil*. Berkeley, California: University of California Press.
- Schmiedlin-Ren, P., Edwards, D. J., Fitzsimmons, M. E., He, K., Lown, K. S., Woster, P. M., et al. (1997). Mechanisms of enhanced oral availability of CYP3A4 substrates by grapefruit constituents. *Drug Metabolism and Disposition*, 25, 1228–1233.
- Schnell-Anzola, B., Rowe, M. L., & LeVine, R. A. (2005). Literacy as a pathway between schooling and health-related communication skills: a study of Venezuelan mothers. *International Journal of Educational Development*, 25, 19–37.
- Stivers, T., Mangione-Smith, R., Elliott, M. N., McDonald, L., & Heritage, J. (2003). Why do physicians think parents expect antibiotics? What parents report vs what physicians believe. *The Journal of Family Practice*, 52, 140–148.
- Turner, V. (1969). *The ritual process: Structure and anti-structure*. Chicago: Aldine Publishing Co.
- UNICEF. (2008). Child survival and development. http://www.unicef.org/media/media_45485.html.
- Van der Geest, S., & Whyte, S. R. (1988). *The context of medicines in developing countries*. Dordrecht: Kluwer Academic Publications.
- Van der Geest, S., Whyte, S. R., & Hardon, A. (1996). The anthropology of pharmaceuticals: a biographical approach. *Annual Review of Anthropology*, 25, 153.
- Van Gennep, A. (1960). *The rites of passage*. Chicago: University of Chicago Press.
- Weiss, M. G. (2001). Cultural epidemiology: an introduction and overview. *Anthropology & Medicine*, 8, 5–29.
- Warsame, M., Kimbute, O., Machinda, Z., Ruddy, P., Melkisedick, M., & Peto, T. (2007). Recognition, perceptions, and treatment practices for severe malaria in rural Tanzania: implications for accessing rectal artesunate as a pre-referral. *PLoS ONE*, 1, 1–11.
- Whyte, S., van der Geest, S., & Hardon, A. (2002). *Social lives of medicine*. Cambridge: Cambridge University Press.
- World Health Organization. (2009). *Press release 1/21/09*.
- Yeung, V. W., & Wong, I. C. K. (2005). When do children convert from liquid anti-retroviral to solid formulations? *Pharmacy World & Science: PWS*, 27, 399–402.
- Zucker, H., & Rago, L. (2007). Access to essential medicines for children: the world health organization's global response. *Clinical Pharmacology and Therapeutics*, 82(5), 503–505.