Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e69; doi:10.1038/psp.2013.45

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PERSPECTIVE

Pharmacometrics: Opportunity for Reducing Disease Burden in the Developing World: The Case of Africa

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Pharmacometricians are virtually nonexistent in Africa and the developing world. The unrelenting burden of infectious diseases, which are often treated using medicines with narrow effectiveness and safety dose ranges, and the growing prevalence and recognition of non-communicable diseases represent significant threats for the patients, although affording an opportunity for advancing science. This article outlines the case for pharmacometricians to redirect their expertise to focus on the disease burden affecting the developing world.

CPT: Pharmacometrics & Systems Pharmacology (2013) **2**, e69; doi:10.1038/psp.2013.45; published online 28 August 2013

MOTIVATING EXAMPLE

Stavudine (2′-3′-didehydro-2′-3′-dideoxythymidine or d4T) received marketing authorization for the treatment of human immunodeficiency virus (HIV) infection in 1994 at a dose of 40 mg twice daily. After 7 years of clinical usage, the dose was reduced to 30 mg twice daily, following evidence from a systematic review of maintained benefit at this reduced dose with lower toxicity (www.who.int/hiv/art/ARTadultsaddendum.pdf). Despite a WHO press release in 2009, advising countries to phase out stavudine usage (http://www.who.int/mediacentre/news/releases/2009/world_aids_20091130/en/index.html), observations in Africa in 2013 indicate that the usage of this drug continues due to the large stockpiles in resource-constrained treatment centers. Guiding dose selection during drug development is an underused application of pharmacometrics in the developed world. The recommendation by Makinson *et al.*[1] to evaluate further dose reductions to 20 mg twice daily for virological efficacy vs. toxicity presents an opportunity.

PERSPECTIVES

Pharmacometrics is still an emerging discipline in the developed world but has nevertheless made substantial progress in becoming an integral part of modern drug discovery and development. In Africa, drug development science and infrastructure is being built with very little in the way of a legacy system. This represents an opportunity to bring modern methods into play. The pharmaceutical industry has a poor track record of getting the dose right at the time of product approval, with about 80% of drugs having a reduction in dose within 2–6.5 years after approval.[2] For adults, typically doses are too high because the dose-concentration–response relationship is poorly studied during drug development.

Clinical research and development of new treatments has traditionally been conducted in North America and Western Europe in sites that are familiar with the standards dictated by the major drug regulatory agencies. Therapies are optimized in these patient groups, with these data providing the main source of drug information for the developing world. Thus, genetically and perhaps physiologically different patients from Africa and the developing world receive therapies that have been optimized for a developed world target population and healthcare environment.

Therapies for most of the diseases that plague patients in the developing world, such as HIV, tuberculosis, malaria, and several neglected infectious diseases such as human African trypanosomiasis, Chagas disease, and leishmaniaisis, frequently involve the use of toxic compounds with serious adverse effects. In addition to dose and treatment duration, adverse events occur because of the need to use multiple drugs in combination to prevent the emergence of drug resistance or to treat comorbidities.

The rising prevalence of non-communicable diseases[3] in the developing world, on top of the infectious diseases burden, has created unprecedented therapeutic challenges. This dual burden of disease warrants the use of combinations of drugs rather than single agents. Drug development for combination drug therapy is a complicated field that the traditional drug discovery and clinical development models struggle with, even in the developed world. We argue that this demands pharmacometric methods for elucidating the clinical pharmacology rather than traditional basic studies using SHAM (Slope, Height, Area, Moments) PK analysis.

Pharmacometricians with their toolkits of robust mathematical and statistical techniques grounded in the pharmacological sciences are uniquely placed to concretely contribute to addressing some of these challenges. Various authors, e.g., Zhang *et al.*,[4] have listed the individual

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Received 2 May 2013; accepted 28 June 2013; advance online publication 28 August 2013. doi:10.1038/psp.2013.45

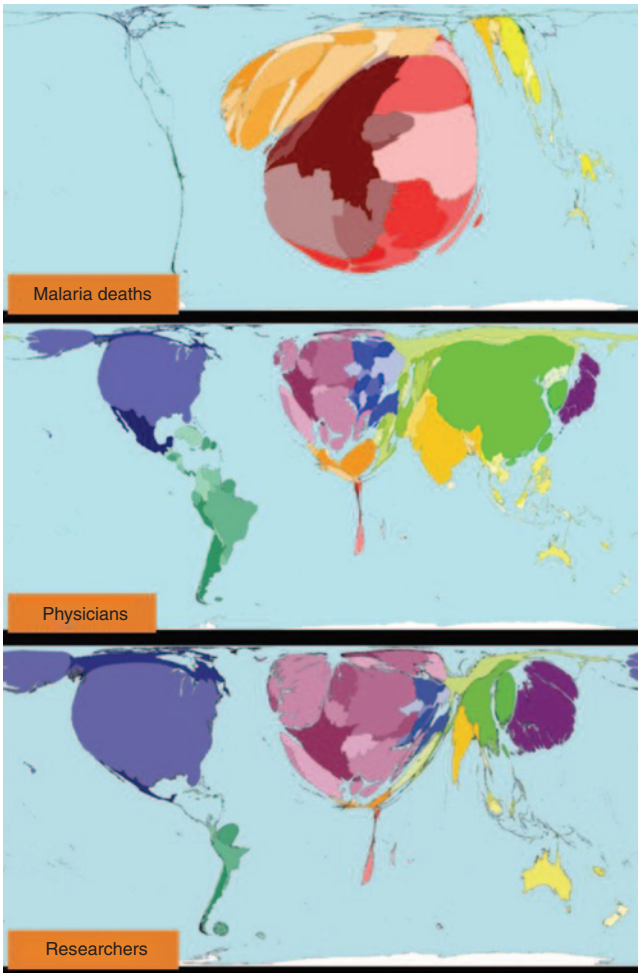

Figure 1 Africa has the highest disease burden (illustrated for malaria deaths) but the lowest number of healthcare workers (illustrated by number of physicians) and researchers (source: www.worldmapper.org).

techniques and analyses that fall under the broad remit of applying mathematical models to improve our knowledge of treatments before they are registered for clinical use. This includes the use of models to guide drug design, target screening, choice of drug formulation, preclinical testing, exposure-biomarker response, disease progression, healthcare outcome, patient behavior, and socio-economic impact. At the core is an understanding of the dose–concentration–response relationship. In this regard, some of the best examples have been in pediatrics where modeling and simulation methods have been shown to be valuable to understand how to predict doses in children and infants with minimal inconvenience for the children participating in the clinical trial.[5] In contrast to the situation with adults where initially approved dosage regimens are too high, children with tuberculosis, HIV, and malaria are frequently exposed to lower concentrations and potentially reduced efficacy of the anti-infectives than adult patients.[6–8] This can be attributed to the use of mg/kg doses in children based on adult doses. It is predictable from allometric theory that this will lead to underdosing in children.[5]

However, expanding beyond a narrow pharmacometrics focus, the emerging concept of "phase V" research of new clinical treatments (i.e., beyond phase IV regulatory obligations) as these become integrated into widespread public health practice provides a rich opportunity for understanding the behavior of therapeutic interventions under real-world conditions. This is a particularly relevant concept in infectious diseases where the original development programs leave a lot of questions unanswered, e.g., "*What's the right dose for resistance prevention at the population level in malaria in order to maximize the effective lifespan of treatments*?" or "*What are the appropriate regimens and doses in patients requiring combined treatments for HIV and TB*?" or "*What's the robustness of different HIV and TB regimens to resistance under field conditions with modest adherence*?" Addressing these questions in the developing world will also benefit the developed world.

Africa is the birthplace of genetic diversity. Studying this diversity in a comprehensive and integrated manner holds the promise of not only understanding local diseases but also benefiting global health when solutions from Africa are exported to the developed world. Studies into genetic diversity and implications for pharmacotherapy in Africa should be an immediate priority for population deployment of medicines. This is in contrast to the developed world's application at the individual patient level. Illustrative questions might include: "*Are dosing recommendations for efavirenz really appropriate in Africa given the higher frequency of null alleles for CYP2B6?*"[9] or "*Does NAT2 polymorphism explain some of the differences in response profile in early phase trials in tuberculosis in different countries*?" or *"Will point-of-care genetic tests lead to real patient benefit and cost-effective therapeutics*?"

Pharmacometricians and their skills are not located (or applied) where the diseases exist and this represents an unmet medical need. **Figure 1** dramatically illustrates the scale of this inequality. Africa has 24% of the global burden of disease (e.g., 90% of global malaria deaths occur in Africa), only 2 physicians per 10,000 people vs. 33 in Europe (http://www.who.int/gho/publications/world_health_statistics/2012/en/), and very little medical research to tackle the huge health problems its population faces. We conducted a keyword search in the Web of Science software and identified the number of authors who published modeling papers by country over the past 10 years. We noted that the output from the countries in the developing world is an order of magnitude lower than in the developed world; e.g., Switzerland, Sweden, and New Zealand had >20 authors/million population, whereas countries like Zimbabwe, South Africa, Brazil, and China had <2.5 authors/million population. The link between research results and changing medical practice is still tenuous[10] but the presence of researchers may itself have an impact on how health problems are approached.

The application of pharmacometrics just isn't happening on a large enough scale in Africa. A concerted collaborative effort among basic and clinical researchers in academia and the industry both within Africa and outside the continent is needed to fully exploit the opportunity that this presents and realize value for the patient. **Table 1** illustrates programs and

Table 1 Examples and proposals to increase pharmacometrics research in Africa to improve patient care

Perceived gap	Examples, comments, and proposals
Skills training, hands-on experience and certification	Training courses and workshops using a teaching format similar to the Uppsala Pharmacometrics Summer School (http://www.farmbio.uu.se/research/researchgroups/pharmacometrics/upss/) but located in Africa to increase access for local scientists. The concept of training the trainers should be implemented from the outset to promote sustainability of the efforts.
	Post-graduate training programs e.g., a masters in pharmacometrics. A curriculum has been proposed by Holford and Karlsson.[11] These will need contextualization to Africa healthcare needs and should use a combination of available and affordable state-of-the-art distance learning pedagogy as popularized by Coursera (https://www.coursera.org/) and traditional classroom teaching.
	Sabbaticals for African scientists in Academia, Industry, or with Pharmacometrics Consulting Groups for hands-on training. Sabbaticals in Africa for scientists from the developed world.
	The organizers of pharmacometric meetings such as the Population Approach Group Europe (www.page-meeting.org), American Conference on Pharmacometrics (www.go-acop.org) and World Conference on Pharmacometrics (www.go-wcop.org) should encourage attendance from the developing world scientists at their meetings via targeted funding mechanisms or themed sections.
High-quality data	Availability of good pharmacology data in patients will require parallel efforts to increase capabilities and capacity in clinical research, including phase V research.
	Retrospective PKPD data from completed clinical investigations represent an untapped rich resource for meta-modeling projects e.g., PKPDia Consortium and WWARN (http://www.wwarn.org/partnerships/data). This would complement prospective data collected from routine clinical use and postmarketing clinical trials.
	The emphasis on high quality data should always be maintained to avoid incorrect expectations that sophisticated pharmacometrics methodologies can rescue poor data.
Infrastructure and environment	Co-location of a critical mass of quantitative scientists (modelers/pharmacokineticists/statisticians) together with bioanalytics and clinical experts in the regions where the diseases exist such as the University of Cape Town (http://www.clinpharm.uct.ac.za) and Thailand groups (http://www.tropmedres.ac/departments-units/pharmacology).
	Develop an accessible network of peers and mentors for scientific collaboration.
	Provide access to high speed computing clusters with relevant software for data analysis and simulation.
Advocacy and translation to benefit healthcare	Advocacy efforts should highlight the impact of pharmacometrics research for patient benefit in diseases prevalent in the developing world. This should be directed at the scientific peer-reviewed literature and as motivation to agencies such as WHO that publish treatment guidelines.
	Funding agencies should recognize the high benefit vs. smaller relative investment inherent in pharmacometrics research vs. the laboratory-based sciences.
	This should ultimately translate into national and local treatment guidelines, algorithms and standard of care.

efforts that are either needed or currently underway. Our view is one of optimism that these applications can be achieved in the developing world, and especially on the continent of Africa.

Pharmacometrics has the convenient advantage of being relatively inexpensive; this allows its successful implementation in resource-limited settings such as in Africa. All that is required to perform advanced analyses is computational power and software licenses (or internet access to a computational hub with these resources). This is a minimal cost if compared, e.g., with the price of setting up a "wetlab" laboratory with state-of-the-art equipment. Africa is the home to many high-quality academic institutions as acknowledged in university performance tables (e.g., http://www.timeshighereducation.co.uk/world-university-rankings/2012–13/world-ranking); however, talented students in the biological sciences are often forced to move to the developed countries to access more sophisticated equipment, essential for their research. This cause of the scientific brain drain might not affect pharmacometricians to the same extent, because their infrastructure can be affordably setup locally. Indeed, this represents an argument for outsourcing developed world pharmacometric problems to Africa where human resource costs are typically lower, while providing the additional advantage of developing the skills needed for studying African specific problems. Currently, the biggest hurdle for the development of pharmacometrics in Africa is the lack of a local network of centers of excellence fostering an African community. The formation of such a network would not only consolidate the individual efforts and further the advancement of research but also help to increase awareness among clinicians and policy makers, advocating a wider application of pharmacometrics to address the health challenges affecting the continent. The development of these skills would also put local universities in a stronger position to attract research funds, thus allowing African scientists to focus their contribution on tackling African health emergencies.

These efforts within the developing world should continue, while philanthropic research organizations, academia, and the pharmaceutical industry continue their search for safe and effective drugs.

CONCLUSION

The global pharmacometrics community is invited to explore Africa and the developing world as a venue for collaborations, scientific capability, and capacity building efforts. One particular focus would be to define target concentrations that are optimal for the target effect with an acceptable safety profile for the toxic drugs that continue to be used for the neglected diseases prevalent in the developing world, such as stavudine. Developing pharmacometrics will be mutually beneficial in improving the ability to conduct, access, verify, and

advocate for using the best science to develop relevant local solutions to global healthcare problems.

Acknowledgment. The authors acknowledge the advice and input from Michael Looby, Thomas Bouillon, Kathleen Sprangers, and Stephen Moore from Novartis Pharma.

Conflict of Interest. The authors declared no conflict of interest.

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