Reducing avoidable medication-related harm: What will it take?

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ABSTRACT

Consumption of quality-assured medicines is expected to maintain or improve population health. Yet in a number of situations, what is realized is lower health benefits or magnified safety risks. Recognizing the public health implications of safety risks or medication-related harm, and that some types of harm are avoidable, the World Health Organization has initiated the third Global Patient Safety challenge on Medication Safety. Under the term “Medication Without Harm”, this Challenge aims to assess the scope and nature of avoidable medication-related harm, create a framework for intervention and develop national guidance and tools to support safer medication use. The global target under the Challenge is to reduce the level of severe avoidable medication-related harm by 50% over a five-year period or within the next five years. Given a higher morbidity and mortality due to medication-related harm in low-income countries, this paper evaluates what needs to be done in low-income countries in order to achieve the global target. The ideal solution advocated requires that health planners in each low-income country determine what fraction of safety risks or harm can be prevented; and the relationship between number or frequency of avoidable harm or safety risks and the resource costs of treatment or prevention. In the absence of such information, this paper discusses a number of prevention strategies that might help; arguing that the period over which avoidable medication-related harm can be reduced by 50% will depend on whether significant continuous investments in health-system strengthening are made prior to and within that period.

Introduction

Medicines are not usually approved, licensed or marketed for use in humans unless their health benefits and safety risks (medication-related harms or adverse health effects) have been assessed. For medicines that diffuse globally, this assessment will be conducted by each country’s drug regulatory authority (DRA). The aim is to balance immediate access to the health benefits provided by medicines and the possibility of safety risks or harm. And, in principle, each country could apply their own preferences for health benefits as opposed to concerns about safety risks. Meaning the benefit-risk trade-off employed by the DRA in Bhutan will be different from that used by the US Food and Drugs Agency (FDA), the European Medicines Agency (EMA) or DRAs in Canada and Uganda. Conditional in receiving regulatory approval or marketing authorization, and with some existing institutional structures and capacity to support supply, demands for and consumption of medicines will depend on the interplay of interlocking agency relationships that influencing prescribing choices, dispensing and consumption. Differences in the mix of medicinal products on a country’s market therefore reflect not only differences in how DRAs assess health benefits and safety risks but other issues related to medicine affordability, availability, accessibility, and acceptability. However, the sheer number of therapeutic molecules (some with multiple clinical indications), different formulations of these molecules and the growing number of therapeutic classes means some form of administrative restrictions of the mix of medicinal products recommended for treating illnesses in any given healthcare setting.

The recommended mix of medicinal products is often enshrined in essential medicines list (EMLs), formularies or standard treatment guidelines (STGs). EMLs and STGs are based on (1) a synthesis of a body of evidence from randomized controlled trials (RCTs and well-conducted non-RCTs, (2) expert committee reports or the collective opinions of group of national and international experts, and (3) real-life effectiveness data collected from routine clinical use or observational studies. The contents of each country’s EMLs, formularies and STGs can then be considered a reflection of societal preferences for the health benefits and safety risks for all currently available therapeutic molecules and medicinal products for treating prevalent illnesses indicated by each country’s epidemiologic profiles. EMLs and formularies can also be considered as medical purchasing guidelines specifying the (actual trademarked) medicinal products to be purchased contingent on the expression of price-sensitive choices to credibly negotiate price

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discounts based on a promise or guarantee to offer in return more than equi-proportionate incremental demand volumes or market shares. Given the mix of products available on each country’s market, appropriate medicines use will be the outcome of concordance between (1) professionally-determined clinical choices and (2) consumer-patient consumption. There are, unfortunately, a number of deviations from what we have just described and the sum of these deviations, some of which may lead to medication-related harms, could offset the aggregate health benefits of universal access to safe and efficacious medicines, which in turn means delayed or zero improvements in population health indicators.

Recognition of the various medication-related harms to patients’ health is the impetus behind the World Health Organization (WHO) third Global Patient Safety Challenge on Medication Safety. Prior to the Challenge on Medication Safety, and in response to growing concerns about patient safety in healthcare delivery, WHO in partnership with the World Alliance for Patient Safety initiated two Global Patient Safety Challenges: “Cleaner Care Is Safer” to reduce healthcare-associated infections and “Safer Surgery Saves Lives” to address the issue of patient harm in surgery. The third global challenge, under the term “Medication Without Harm”, aims to assess the scope and nature of avoidable medication-related harm, create a framework for intervention and develop national guidance and tools to support safer medication use. Worldwide the cost of medication errors alone is estimated to be US$42 million annually (0.7% of global healthcare expenditures). Disability-adjusted life years (DALYs) due to medication-related harm experienced by patients in low-income countries is twice that experienced by patients in high-income countries. Yet only a few countries have national agencies with a clear mandate and equipped to protect patient safety. Training and education programmes on patient safety are equally few. For these reasons, the Global Patient Safety Challenge on Medication Safety has set a target of reducing the level of severe, avoidable harm related to medications by 50% over a five-year period, globally. The emphasis of the Challenge on Medication Safety appears to be “high-risk situations” of polypharmacy, transitions in care and medicine consumption by young children, the elderly and hospitalized patients.2,3 The higher morbidity and mortality attributable to medication-related harm in low-income countries, however, suggests efforts to reduce avoidable harm must be skewed towards what happens in these countries. Such a skewed focus makes more sense when one considers that health systems in low-income countries are either basic, non-functional or non-existent (in the case of war-torn or post-conflict countries).

The aim of this paper therefore is to make a contribution to the “Medication Without Harm” challenge by evaluating what needs to be done in low-income countries, in order to achieve the set global target over the specified time horizon. The paper focuses mainly on the micro-level, complex interactions within country’s pharmaceutical systems that ultimately has implications for the safety of medicines used in routine clinical practice, the potential harm they present and what fraction of the harm can be prevented without losing the health benefits offered by these medicines. However, the paper also considers macro-level issues of providing a global public good in safety evaluations over products’ lifecycle – and the implications this ultimately has for medication safety in low-income countries. In this paper, the word drug is synonymous with medicines and pharmaceutical drugs. We will proceed as follows. The section “Differentiating what is avoidable and unavoidable” describes the aetiology of medication-related harm in order to distinguish what can be avoided from what is unavoidable harm. The sections “What will it take to reduce avoidable harm?” and “Prevention” presents and discusses theory and evidence indicating the kind of interventions this paper believes will be needed in low-income countries. The section “Concluding Comments” completes the paper by providing general thoughts on the way forward – arguing that the period over which avoidable medication-related harm can be reduced by 50% will depend, at least, on whether significant continuous investments in health-system strengthening are made prior to and within that period.

Differentiating what is avoidable and unavoidable

To have an idea of what it will take to reduce avoidable medication-related harm, we need to first understand the aetiology of safety risks, medication-related harm, or adverse drug events (ADEs). Second, we need to determine what is unavoidable and avoidable; and third, we need to make an important distinction between quality-assured medicines and medicines of questionable quality.

We start by assuming consumer-patients are insured, have financial access to healthcare and hence affordability constraints do not negatively affect their compliance with recommended course of treatment. The health benefits or safety risks of any medicinal product may be either uniform across an eligible patient population or differ across individuals of that patient population; some above uniform average, some below that average. Demand for the medicine and the quantity consumed under appropriate use should then reflect the combined effect of following the recommended dosing regimen or treatment protocol and restricting medicine use to just the eligible patient population. Hence, in this paper, appropriate, rational or responsible use of medicines is defined as the outcome of adherence to the recommended treatment protocol specified in products’ marketing authorization or licenses, local or international (essential) medicine lists, formularies and clinical guidelines. Appropriate medicine use means there is appropriate prescribing, appropriate transcribing of clinical orders and information; appropriate dispensing and appropriate consumption by the consumer-patient. Put differently, appropriate use of medicine maintains the clinical and economic value of medicine in routine practice. Conversely, inappropriate medicine use, synonymous with “medication errors”, is defined as deviations from recommended treatment protocols due to failures in the process of prescribing, transcribing, dispensing and consumption. Inappropriate use of medicine distorts the clinical and economic value of medicines and this may or may not lead to patient harm. Fig. 1, adapted from Morimoto et al.,6 shows the relationship between safety risks, medication-related harms or ADEs and medication errors. We will make use of these definitions and distinctions throughout this paper.

Quality-assured medicines

Appropriate use of medicines

With appropriate medicine use, one may observe incidence of type-A ADRs that are known from RCTs and non-RCT studies that evaluated the medicine in question. The incidence of unexplained or unexpected type-B ADRs will be either rare or previously unreported, tending to occur in patients who have been exposed to the drug for periods longer than the time frame over which the RCTs or non-RCTs supporting regulatory approval of these medicines were conducted. Examples of type B ADRs include immunologic reactions stemming from hypersensitivity and idiosyncratic patient-specific side effects of unknown origin.7,8 When ADRs occur, they can be treated by (1) discontinuing drug therapy if there are alternatives to the medicine, for example, one could switch to substitute molecules in a given therapeutic class (assuming no cross-sensitivity) or from other therapeutic classes; or (2) clinical management of ADRs, especially if there are no alternatives available. This model of clinical events accommodates consumption of multiple medications by patients suffering from coexisting illnesses. This will not described as polypharmacy since the use of multiple medicines is necessary for the disease comorbidities afflicting a patient; and appropriate medicines use, by definition, requires due consideration of drug-drug interactions and contraindications. One will also expect consumption of multiple medications in cases where ADRs associated with a medicine can be countered by co-administration with another medicine. An example is the use of injectable flumazenil to reverse over-
Inappropriate use of medicines

In situations of inappropriate use, quantities of medicines consumed by a patient population at any point in time will reflect the combined effects of deviations from recommended treatment protocols or regimens and/or usage in ineligible patient populations or what might be considered understudied populations if the drug is used in an off-license manner. We could either have underuse (e.g. therapeutic failure from using quantities below the recommended levels), overuse (drug intoxication and drug dependence from quantities above recommended levels) or misuse (using medicines to treat ineligible patient populations). In the case of under-use, health benefits will be lower than expected although resource costs consumed will also be lower. In the case of overuse, expected health benefits in aggregate will exceed that which will be attained from appropriate use but this increasingly will be worth less the resource costs. In other words, the cost-effectiveness of a medicine will decline with overuse, will not be maximized with underuse and in the case of ineligible patient populations, it might result in pure wasteful healthcare expenditures (with zero health benefits to consumer-patients).

As shown in Fig. 1, inappropriate medicine use (medication error) may result in pADEs, which could either be (1) new previously unreported harm or (2) it could be known safety risk with unexpected or unknown severity and duration (due to exaggerated pharmacologic actions, for example). Fig. 1 together with Table 1 (which shows criteria for “medicine appropriateness” presented in Lund et al. and criteria for determining ADE preventability as presented in Duchame and Boothby) presupposes a close link between (in)appropriate use of medicines and preventability of ADEs. But what distinguishes ADRs from preventable ADEs (pADEs) is not just appropriateness of medicines but also whether prevention requires forewarning the health benefits gained from a drug. Preventable ADEs, in contrast to ADRs, are associated with inappropriate use of medicines and they can be avoided without losing the health benefits gained from restricted or unrestricted use of a drug. This distinction accommodates cases where a formerly unavoidable ADR associated with a drug transforms into a pADE, i.e., subsequent use of that drug is appropriate only if usage is restricted to patients for whom the drug is not contraindicated.

Whether inappropriate medicine use in any low-income country results in too many or too few pADEs is an empirical question. Yet we know pADEs can be prevented by correcting inappropriate, irresponsible or irrational usage. Prevention efforts must however recognize that inappropriate medicine use stems from (1) inappropriate professionally-determined clinical choices and/or (2) inappropriate consumer-patient consumption. Inappropriate professionally-determined clinical choices, especially the absence of standardization through EMLs, formularies and STGs, is such that we will observe a lot more variation in medicine prescribing and use profiles to the point that it is more difficult to tell whether patients have been treated with the best-proven medicines and the best possible clinical outcome has been
achieved. In such situations, it will also be more difficult to assign causality of ADRs/pADEs to specific medicinal products. Inappropriate use in particular aggravates the harms associated polypharmacy, i.e., the routine use of four or more medications which may have in part evolved out uncertainty in clinical diagnosis due to the unavailability of reliable diagnostic and laboratory tests. Studies, mostly in older people, have reported that inappropriate prescribing is a predictor of subsequent pADE risk independent of the number of medications and other confounders – although the magnitude of this risk (odds ratio) depends on the criteria used to assess the inappropriateness of medicine use.\(^\text{11}\) But even when clinical choices have been standardized and/or validated, it is known that one in four medication errors are due orthographic (look-like) similarity and phonological (sound-alike) similarity between branded and unbranded medicinal products. The odds ratio of reporting medication error is an increasing function of similarity, and every measure of similarity is known to be significant predictor of medication error.\(^\text{14}\)

Inappropriate consumer-patient consumption, on the other hand, is often associated with a divergence between patients and healthcare practitioners’ beliefs about the health benefits and safety risks of medicines. Etkin et al.\(^\text{15}\) for instance describes how indigenization of medical knowledge in Nigeria fuels both appropriate and inappropriate use of medicines. Similarly van de Geest\(^\text{16}\) documents the production of popular medical knowledge in marketplaces in Cameroon that is odds with existing medical knowledge and no more than a variable jumble of ideas, notions and perceptions. Given the imperfect stock of information patients have, we might observe inappropriate use including intentional non-compliance. From the perspective of patients, intentional non-compliance is a rational choice based on what they know, their perceptions and beliefs of the health benefits and safety risks of a medicine.\(^\text{17}\) In such situations, therapeutic failure is mostly likely although the incidence of known or unknown ADEs cannot be ruled out. The point here is: patients’ beliefs are a hidden determinant of therapeutic success\(^\text{18}\) – and for every primary disease requiring pharmaceutical interventions, there might be a behavioural co-morbidities or hazards that may or may not encourage appropriate use of medicines. The common practice style of biomedicine fails to recognize the unmet non-medical needs of patients that require showing empathy, compassion and an understanding of patients’ circumstances. A shift towards biopsychosocial models of health is needed.\(^\text{18}\)

Medicines of questionable quality

We identify three broad types of medicines of questionable or compromised quality – the use of such medicines is, by definition, inappropriate or a medication error in that 100% adherence to the recommended dosing regimen or treatment protocols provides either zero or suboptimal health benefits with the possibility of a wider range of pADEs. The first group is substandard medicines that contain positive amounts of the therapeutic molecule (active ingredient) but this amount is below what is in the corresponding quality-assured medicine. Substandard quality may be the result of deterioration due to poor storage conditions, for example. Generally, substandard medicines refer to not just defective or contaminated products that may contain incorrect or correct amounts of the active therapeutic molecules but also other substances with harmful health effects. The second group is counterfeit medicines that, for fraudulent reasons, contain zero amounts of the therapeutic molecule (active ingredient) and have more or less the standard amount of non-active ingredients or excipients. The third group is falsified medicines that contain zero amount of the therapeutic molecule or usual excipients but contain substances that are harmful. Across these groups, there is some kind of mimicry where a product that should have zero demand has some positive demands simply because it looks like the true, authentic quality-assured medicine. Variation in supply prices of substandard, counterfeits or falsified medicines can therefore be thought of variations in quality discounts. This is contrary to what we will expect from price competition, i.e., keeping quality constant, variation in supply prices reflect differences in production costs and differences in purchasers’ demand elasticities.

Consider first substandard medicines. The stream of reduced or partial health benefits gained from these medicines depend on how far the deviations are relative to what is in a quality-assured medicine. This is the reason why quality discounts are not justifiable since it is difficult to tell ex ante whether the quality-discount is worth the deviations from minimum standards of quality. That is to say, these deviations could be such that the value of positive health benefits (after taking into account safety risks) is not worth the lower costs of supplying that substandard medicine. In the case of counterfeits or falsified substandard medicines, appropriate use will be associated with zero health benefits (corresponding to the zero amounts of the active ingredient) but depending on whatever dangerous substances these medicines contain, we will have pADEs that are completely unrelated to the active therapeutic molecule. The source and the extent to which the quality of these medicines have been compromised as well as the chances of these quality distortions remaining undetected is hence critical. Chances are that consumer welfare will be zero at all demand quantities but welfare cost is increased by mimicry and the elevated likelihood these ADEs will cost is increased by mimicry and the elevated likelihood these ADEs will still be wrongly attributed to quality-assured medicines. To make things worse, falsified or counterfeit medicines extend the range and types of pADEs healthcare practitioners and society at large should be concerned about. The paracetamol tragedy in 1990 in Nigeria, in which 109 children died from defective paracetamol-containing products with ethylene glycol as an excipient, instead of propylene glycol, comes to mind.\(^\text{19}\) Over that period, paracetamol deaths (due mostly to kidney

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The close link between ADE preventability and appropriate medicine use.</th>
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<tbody>
<tr>
<td>Assessing appropriateness of medicine use</td>
<td>Assessing ADE preventability</td>
</tr>
<tr>
<td>Are there significant drug-drug interactions?</td>
<td>Was the medicine involved not considered appropriate for the clinical indication?</td>
</tr>
<tr>
<td>Are there any drug-disease interactions?</td>
<td>Was the doses, route and frequency of administration not appropriate for the patients’ age, weight and disease condition?</td>
</tr>
<tr>
<td>Is there an indication for the drug?</td>
<td>Was therapeutic drug monitoring or other laboratory tests not performed?</td>
</tr>
<tr>
<td>Is the drug effective for the indication?</td>
<td>Was there a history of allergy or previous (immunologic) reactions to the medicine?</td>
</tr>
<tr>
<td>Is there unnecessary duplication with other medicines (from the same class)?</td>
<td>Was a pharmaceutical (drug-drug) interaction involved in the reaction?</td>
</tr>
<tr>
<td>Is the duration of the therapy acceptable?</td>
<td>Was toxic serum drug levels documented?</td>
</tr>
<tr>
<td>Is the dosage correct?</td>
<td>Was non-compliance involved in the reaction?</td>
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</tbody>
</table>
| Are the directions for use correct? | Notes: Questions in the left column are part of a tool (Medicines Appropriateness Index) with scoring weights assigned to each question. Responses to these questions determine whether medicine use was appropriate or not. Questions in the right column indicate ADE preventability. If the answer to one or more of the questions in the right column is YES, then ADE may be preventable or avoidable. An ADE is an unavoidable ADR if the answer to all of the questions in the right column is NO.
failure caused by ethylene glycol) were thought to be the “outbreak of disease of unknown etiology” and detection was delayed by the fact that victims were often given several medications including chloroquine. Similar incidents have been reported in Haiti and Panama. In the US, an unusual cluster of allergic-type reactions among patients undergoing haemodialysis in a paediatric hospital was later found to be due to heparin contaminated with oversulphated chondroitin sulphate. Paradoxically, in these situations, inappropriate underuse of medicines of questionable quality will reduce safety risk or harms to consumer-patients. Appropriate use, overuse and misuse use will most likely aggravate medication-induced harm.

What will it take to reduce avoidable harm?

Theory and missing data

For health planners in low-income countries, the question of what it will take to reduce avoidable medication-related harm requires (1) determining what fraction of ADEs are avoidable or preventable, and (2) given a finite pot of societal resources available and the frequency of avoidable ADEs, determining whether it is worthwhile to invest in treatment or prevention.

With “treatment” of pADEs, we mean clinical management of morbidity associated with pADEs, with the view of avoiding loss of life. With “prevention” on we are interested in reducing to any extent possible (by modifying underuse, overuse and incorrect use in ineligible patient populations) the probability or frequency of pADEs occurrence so as to reduce morbidity and mortality attributable to pADEs. Economic theory suggests that the optimal course of action requires considering the resource costs of treatment, the resource costs of prevention and the number or frequency of pADEs. The costs of treatment rises with the number of cases of pADEs whilst the costs of a series of fixed/one-off investments in prevention can only be spread over a given number of cases. As shown in Fig. 2, optimality (i.e., the most desirable outcome) is attained at point $p^*$ whether an upward-sloping treatment-cost curve (in relation to the frequency of ADRs) intersects a downward-sloping prevention-cost curve. This is the point at which the cost savings from treatment of pADEs is maximized. As one moves to the left of that optimum, a prevention strategy does not offer a positive value (i.e., positive net benefits) whilst it does to the right of that optimum. Application of the framework in Fig. 2 crucially depends on (1) what constitutes an “ADE-preventive strategy” and the associated (fixed) costs of implementing that strategy; (2) the number of case or frequency of pADEs and the costs of treating incident or prevalent pADEs. The resource allocation problem depicted by Fig. 2 will differ from one country context to the other but the starting point is to ask the question: do health planners in each low-income country know the fraction of medication-related harm (ADEs) that can be avoided?

Evidence (we know of) indicate that although ADEs preventability assessments are not always reliable (not least because of the absence of a gold standard), 21% (11–38%) is a reasonable estimate (range) for the general patient population whilst for hospitalized patients ADE preventability ranges from 19% to 73% (median 39%) or from 15% to 90%. Kumar et al. evaluation of spontaneously reported ADEs related to antiretroviral therapy (ART) in Jharkhand, India showed that out of 1356 patients on ART, 197 experienced ADR/ADEs of which 41.12% was not preventable and 68.8% were preventable (21.82% were definitely preventable and 37.06% were probably preventable). Hakkarainen et al. analysis of self-reported ADEs by Swedish residents from the general public (not hospitalised patients) over a period of 1 month showed that, of 7099 survey respondents, 19.4% experienced at least one ADE and 2.9% experienced one or more pADEs. Most ADEs were attributable to commonly-dispensed drugs – whilst ADRs and subtherapeutic effects (treatment failure) that could be prevented constituted 19.2% of all self-reported ADEs. A similar study using a sample of 5025 Swedish adults drawn from a population register in 2008 reported that, over a 3-month period, the prevalence of ADEs was 12%, of which 5.6% were considered preventable. Of all ADEs reported, 39% were preventable. To add, a meta-analysis of original studies on outpatient and inpatients indicated that for outpatients 2% of ADEs were preventable whilst 52% of ADEs at the time of hospitalization and emergency visits were preventable which 52% of ADEs during hospitalization and emergency care were preventable. For inpatients, 1.6% of ADEs were preventable during hospital stay whilst 45% of all ADEs were preventable.

A recent retrospective analysis of confirmed medication-related harms recorded at the national level in Iran, over a two-year period 2015–2017, suggests that out of 17988 ADEs, 1231 (6.84%) were preventable – 601 and 630 pADEs reported in the first and second years respectively. This suggests the underlying causes or sources of pADEs in Iran remained uncorrected over the study period. Generally, as reported by Olsson et al., scientific evidence on the local burden of medication-related harm in resource-limited (low-income) countries....
and their preventability is missing. African countries in particular are yet to uncover the magnitude of (avoidable) medication-related harm.

**A way forward**

Putting aside issues about improving and harmonizing definitions and classifications for ADRs/pADEs, what is preventable and unavoidable, the estimates above can only be generalized to countries with similar epidemiology, mix of products and consumption patterns, and similar healthcare financing and provision structures. Assuming each low-income country is able estimate the fraction of ADEs that are avoidable (say on a yearly basis), the next question is: do health planners know what the costs of pADE-treatment or the costs of ADE-prevention are? Chan et al., using data from the period 2001–2004, estimated the mean cost of treating an adverse drug reaction (which refers to both preventable and non-preventable ADEs) in hospitalized patients in Taiwan to be $3489. The US study by Hug et al. report the mean cost of treating a preventable ADE as $3511 and the mean cost of patients in Taiwan to be $3489. The US study by Hug et al. report the mean estimated the mean cost of treating an ADE in hospitalized patients to be $3489.

Without the requisite data and evidence to solve the resource allocation problem (i.e., whether ADE-prevention saves costs or is cost-effective relative to ADE-treatment), this paper proceeds to describe the composition of a package of preventive strategies that we believe will help reduce avoidable medication-related harm in low-income countries and thereby contribute to the goal of reducing avoidable medication harm by 50% globally. In doing so, we hope health planners in low-income countries will, at least, gain an appreciation of the extent of the problem and range of preventive interventions needed even if they do not agree with our suggestions.

**Prevention**

**Safety evaluations as a global public good**

Much of the evidence supporting the safe use of medicines in humans comes from RCTs or non-RCTs that have been conducted over a definite period of time with a finite number of subjects. It is therefore not possible to ascertain all possible health benefits and safety risks associated with a given medicine at the time of market launch. According to Ajayi et al., most clinically-relevant ADRs occur at a rate of 1 in 10000 or less and yet to observe and rule out ADRs that occur at a rate of 1 in 3000 or 1 in 6000, one needs RCT sizes in the proximity of 10000 and 20000 respectively. Obviously, RCTs could be larger and conducted over longer time periods but the question is whether the additional information collected (and possible additional gains in health benefits) is worth the additional R&D costs, foregone revenues from delayed access and shorter effective patent lives. As noted by Pedroni, the additional information collected from longer and larger RCTs (designed to detect rare, previously unknown ADRs that might arise from appropriate use of medicines) will still not be comprehensive or exhaustive. The pragmatic compromise to longer and larger RCTs is to integrate pre-launch RCTs with pharmacovigilance and other forms of post-marketing surveillance over products’ lifecycles. Pharmacovigilance refers to the science and activities of detecting (via data collection), assessing, understanding, and preventing ADEs associated with medicine use. And the accumulation and consolidation of post-market drug information from such activities is what allows re-evaluations of the efficacy and safety of medicines on an ongoing basis – for as long as it is in use., The main obstacle here is not a reliance on lower-grade non-RCT evidence. Golder et al. have shown that there are no systematic or consistent differences in ADR risk estimated using RCT or observation data; the pooled ratio of odds ratios obtained from RCTs versus observational studies was 1.03 (95%CI: 0.93–1.15). The real difficulty is: whether, at any point in time, the cumulative wealth of pre- and post-market information DRAs have keeps drug withdrawals at the lowest possible levels, and at these (near-zero) levels, drug withdrawals are not preceded by frequent reports of significant ADR morbidity or mortality?

The outcome of safety (re)evaluations over a product’s lifecycle is often the development of a risk evaluation and mitigation strategy (REMS) or drug withdrawal, if an REMS is not feasible. For example, the US FDA REMS (formerly called Risk Management Action Plans (RiskMaps)) and the Risk Management Plans (RMP) crafted by the EMA provide medication guides (specifying patient monitoring and treatment-stopping criteria), “elements to assure safe use” and safety risk communication plans. Issuance of REMS or RMP effectively transform unavoidable ADRs into pADEs: usage restrictions embedded in REMS or RMP are by definition ADE-preventive strategies. Evidence available indicate that the US FDA over the period 2008–2012 issued REMS for 1 out of 3 large-molecule biologics and 1 out of 13 small-molecule chemically-synthesized medicines with, on average, a time lag of fourteen and a half years between regulatory approval and evaluation of safety risks that warrant issuance of REMS, Drug withdrawals, on the other hand, indicate unavoidable ADRs that outweigh any health benefits from restricted or unrestricted use. A recent study has shown that of the 492 medicines that were withdrawn from a number of countries examined over the period 1953 and 2013, the time interval between market launch and the first report of ADR associated with drug withdrawal as well as the time interval between market launch and drug withdrawal has shortened but there was no change in time interval between first report of ADR associated with drug withdrawal and drug withdrawal. This suggests stricter regulation to guarantee efficacy and safety: significant improvements in ADR reporting and in establishing causality, and immediate actions being taken to protect patient safety (once causality has been ascertained). As argued by Rawson, looking at the number of previously approved medicinal products withdrawn only provides an incomplete picture of the problem of medication safety. Compared to the number of medicines approved, withdrawal rates has remained at 2% since the 1960s with some steady decline over the years.

Granted, there is a less highlighted safety risk that has to do with the design and conduct of RCTs: should new medicines be compared with placebo alone (i.e., placebo-controlled RCTs) or should they be compared with existing medicines that are proven to be efficacious? Consider the case of Vioxx® (rofecoxib versus Naprosyn® (naproxen). Rofecoxib was withdrawn following post-market findings of clinically 1 Data from the study also showed there are inconsistencies in the pattern of pharmaceutical drug withdrawals: 43 (9.34%) were withdrawn from all countries, 179 (39%) were withdrawn from one country only and pharmaceutical drugs launched in African countries were less likely to be withdrawn compared to countries in other continents (Europe, Americas, Asia, Australasia and Oceania). If referencing of safety decisions and regulations of foreign DRAs by African countries is common practice, we will expect similar patterns of drug withdrawals. Thus the differences reported are most likely due to differences in mix of products launched, which in turn depends on country’s epidemiological profiles, country income levels, medicine prices charged in the presence (or absence) of comprehensive universal health insurance coverage as well as variations in clinical practice styles (in particular differences in country’s EMLs, formularies and STGs).
important adverse cardiovascular events associated with rofecoxib, a Cox-II inhibitor. It appears the risk of adverse cardiovascular events was masked during the pre-market RCTs by comparison of rofecoxib to an active drug naproxen known to reduce the incidence of such events. Differences in cardiovascular ADEs between the two drugs were erroneously attributed to the expected health effects of the comparator drug naproxen. Had rofecoxib been compared with placebo, incidence of cardiovascular ADRs attributable to the drug alone would have been identified. A solution suggested by Scherer et al. to conduct a pivotal RCT comparing a new drug with the best proven alternative at the time plus another (pivotal) RCT comparing the same drug with placebo. An alternative is to conduct three-arm RCTs designed to test non-inferiority between active medicines and which includes a placebo arm. Evidence available, however, suggests that the design and conduct RCTs for regulatory purposes do not follow this recommendation. Goldberg et al. report that over 197 new molecules approved by the US FDA between 2000 and 2010, 100 (51%) has comparative efficacy (and safety) data available, that is having a minimum of one pivotal RCT comparing the new medicine with existing ones. This varied from 33% for hormones and contraceptives to 89% for diabetic medications. Van Luijn et al. likewise report that between 1999 and 2005, only 48% of new molecules approved by the EMA were evaluated against existing molecules. Downing et al. report that 188 new molecules approved by the US FDA between 2005 and 2012 for 206 indications, although the median number of pivotal RCTs was two for per indication, comparative information was available for less than half of the indications. Of course, conducting two pivotal RCTs or three-arm RCTs (requiring larger patient populations) will increase R&D costs compared to just placebo-controlled trials. But then the greater amount of information collected, if acted on, should reduce the frequency of ADR-related drug withdrawals and provide a safeguard of against post-launch demand shocks.

Clearly, more should be done beyond the current state of affairs although we don’t know whether new requirements in terms of RCT design and conduct would alter the number and disease-focus of future R&D investments. This is important since in the case of withdrawing Vioxx®, the lost health benefits of the drug was, in the US, compensated by positive and negative demand shifts to and from other Cox-II inhibitors in its therapeutic class (aggregated demand for Cox II inhibitors declined however) as well as an aggregate increase in use of substitutes belonging to the class of non-steroidal anti-inflammatory drugs (NSAIDs) including older analgesics. That is to say, the so-called wasteful R&D competition hypothesis (i.e., the duplication of R&D effort in the production of me-too products) offers a way out in the event of post-market technology shocks. A related issue is the potential use of REMS by innovators to delay post-patent generic entry by (1) using restricted voluntary or mandated distribution systems (intended to ensure safe medicine use) to block access to product samples for bioequivalence testing, and (2) delaying negotiations on details of shared REMS between innovators and generic manufacturers. (REMS will have to be shared because both innovator and generic products contain the same therapeutic molecule.) These entry-detering strategies can be thought of as a risk-averse response of innovators to declining R&D profitability, especially post-patent erosion of demand volumes that have already been reduced by the usage restrictions in REMS or RMP. But since supplying innovator-product samples for bioequivalence testing can in no way constitute a significant safety risk, the best solution seems to be setting a time limit as to when negotiations between innovators and generic entrants should be completed. This should ensure consumer welfare gains from instituting REMS or RMP doesn’t come at the cost of consumer welfare loss from delayed generic competition.

In all, we can say safety evaluations over products’ lifecycles does or can do an excellent job in assuring that only medicines offering positive health benefits (after taking into account safety risks) get onto the market and remain on the market – without incurring welfare losses in other segments of society. This approach of assessing the efficacy and safety of medicinal products over their lifecycle (i.e., from the controlled settings of RCTs to the uncontrolled settings of routine practice) can be adopted by DRAs in low-income countries, safeguarding the health of patients via similar REMS or RMP for medicines in use. In practice, and beyond pre-market product registration, DRAs in low-income countries are more likely to reference post-market regulatory decisions of foreign DRAs, i.e., a form of informational arbitrage where REMS or RMP instituted for products on low-income country markets are directly based on that instituted by the US FDA and EMA. Obviously, this is not applicable to (post-conflict) countries without a DRA; and most importantly, it means DRAs in countries that are the loci of ethical pharmaceutical R&D (the US FDA and EMA in particular) will have to take on the responsibility of providing a global public good in ensuring that, over products’ lifecycles, the mix of evidence on efficacy/ effectiveness and safety keeps morbidity and mortality associated with (appropriate) medicine use low.

Pharmacovigilance for quantifying avoidable harm

From the above, we know national-level pharmacovigilance systems and other forms of post-marketing data collection are needed to solve the inadequacies of pre-market RCTs in providing less than perfect information on the health effects of medicines over their lifecycles. Setting aside regulation referencing, development of REMS or RMP (and its addition to treatment protocols of existing medicines) require infrastructure for pharmacovigilance to be in place in each low-income country. There is however another reason for instituting pharmacovigilance systems and this has to do with quantifying the local burden of (avoidable) medication-related harm. Pharmacovigilance systems and other forms of post-market data collection are needed even if DRAs in low-income countries prefer to reference regulations and safety decisions made by foreign DRAs (in high-income countries). Arbitrage of foreign post-market regulatory decisions is simply not enough.

In line with the arguments above, WHO has recommended the following minimum requirements for post-marketing data collection. One is a national pharmacovigilance (PV) systems with designated staff, stable source of funding and clear mandates including collaboration with the WHO Programme for International Drug Monitoring (PIDM). The last, in particular, involves the submission of ADR/ADE reports to the global database, Vigibase™ that is managed by the Uppsala Monitoring Centre (UMC) in Sweden. Two, a national spontaneous reporting system that makes use of ADR/ADE reporting forms available to healthcare practitioners and the general public. Three, a national database for collecting and managing ADR reports. Four, a national PV advisory Committee to provide technical expertise and experience in causality assessments, benefit-risks assessments, safety risk and crisis management. And finally, a clear communication strategy for routine information provision and in times of crises. Country membership or collaboration with WHO PIDM in the first requirement is key. As Amadu et al. the number of African countries in the WHO PIDM has increased from 2 in 1992 to 35 at the end of September 2015 although cumulatively the reports submitted by African member countries make up less than 1% of the total case reports in the global database. However, evidence from India, Uganda and South Africa suggests that low- and middle-income countries lack “adequate capacity” to monitor the safety risks of medicines according to the WHO minimum standards. (Inadequate capacity here refers to lacking of funding, limited number of trained staff, unclear roles and poor coordination of pharmacovigilance activities and absence of legal mandates on manufacturers and healthcare practitioners to report ADRs/ADEs.)

For the rest of this subsection, we will proceed by assuming existence of the minimum recommended PV infrastructure in each low-income country. Given that assumption, we can say WHO-UMC provides a public good in the form of (1) conducting signal analyses [signal here refers to statistical associations between ADRs/ADEs and a drug];
and (2) distributing the results of such analyses to all (associate) members of the PIDM.\textsuperscript{3,5} As far as we know, these activities are geared towards investigating the incidence of unknown or unexpected safety risks associated with appropriate use of medicines. It is true that integrating prelaunch RCTs with post-marketing data collection is the closest we can come to what will be a fully and perfectly informed demand curve for medicines. But the welfare improving effects of pharmacovigilance systems need not be restricted to tracking ADRs that are not observed within the finite period RCTs are conducted with a finite number of patients. Credible assessments of the safety of medicines as it evolves over products’ lifecycles requires, at least, some differentiation as to (1) ADRs that arise from optimal or appropriate use of quality-assured medicines, (2) pADEs that originate from inappropriate use of quality-assured medicines, and (3) pADEs that originate from appropriate or inappropriate use of medicines of questionable quality. Pharmacovigilance systems in low-income countries can or should be designed for this purpose.

To explain further, suppose there is a new medicine that is used appropriately and sometimes inappropriately. New novel drugs (offering significant health benefits above existing medicines) in particular are known to have a higher risk of serious ADRs requiring hospitalization or leading to deaths.\textsuperscript{50} It is then possible that pADEs associated with that medicine might erroneously be classified as an ADR. Depending on the frequency of ADR reports, a given low-income country’s DRA or pharmacovigilance centre may communicate warnings and cautions to healthcare practitioners and the general public; in which case previously positive demands for medicine may fall to zero. Submission of country-specific case reports is likely to show that the strength of association is not strong enough to confirm causality, unless we have the unusual case where patterns of (in)appropriate medicine use is the same across all countries that submit reports to the WHO-UMC database. Communication of updated information that a suspected pADE is not an ADR may or may not bring demand for the medicinal product back to original levels. Thus a useful medicine offering positive health benefits would have been abandoned or under-utilized simply because regulatory authorities failed to manage the risky business of differentiating ADRs from pADEs. As argued by Visconti\textsuperscript{51} there is inconsistency in societal response to health risks: depending on differences in safety risk perception and biases in perception, we have on some occasions overreaction to exaggerate safety risks whilst on other occasions we have little or no concern for safety risks that have grave implications. Such inconsistencies rest unsurprisingly on the imperfect information currently available and it strengthens the theoretical models that suggest ineffective medicines or medicine quality issues. It is worth noting this approach produced a number of false positives. Focusing on reports that were not dismissed by national reporting centres, these false-positives were attributed to (1) increase in reporting due to bad publicity (notoriety effect), (2) data clusters due to medication errors or switching of branded products or treatment regimens, and (3) time delays in transferring country-specific reports to the global database. Will this clustering approach help in differentiating ADRs from pADEs? Possibly but only if the nature and format of reporting forms contain the requisite, more detailed information needed to ascertain the preventability of ADEs. Certainly, ADR/ADE reporting forms should be re-structured to make it possible to systematically detect and assess the preventability of ADEs in case reports – whether these are associated with quality-assured medicines or medicines of questionable quality. ADE preventability can then be assessed using the Preventability-method (also P-method) with its twenty criteria or “risk factors” for inappropriate medicine use; plus tertiary sources of information such as summary of product characteristics and reference documents, example, EMLs, formularies and STGs,\textsuperscript{5} Indeed, the study by Karimiani et al.\textsuperscript{50} to estimate the fraction of pADEs in Iran utilized the original and a modified version of the P-method after confirming ADEs using the WHO-UMC causality assessment system.

There are two alternative solutions for quantifying the local burden of avoidable medication-related harm. First is to conduct prospective nationwide studies where patients in different healthcare settings are observed over defined period of times to assess the prevalence and incidence of ADRs and pADEs associated with the consumption of quality-assured medicines and medicines of questionable quality. Second is to combine information gained from spontaneous reporting pharmacovigilance systems with that obtained from (electronic) medical records including prescription reviews, reviews of hospital discharge and mortality reports, and elicited reports of medication errors.\textsuperscript{5} One can even extend the argument to include primary and meta-analytic studies reported in medical literature, simulated data, and consumer reports about ADR/pADEs on health forums. Apparently the 880000 episodes of cardiotoxicity associated with Vioxx® would have been detected prior to withdrawal of the drug using this mixed-sources approach.\textsuperscript{53,54} In fact some studies\textsuperscript{55} suggest that it is possible to identify ADEs using just electronic health records after controlling for confounders. Problems of the second approach include: (1) the administrative burden of storing, accessing and sharing data across healthcare providers, i.e., the need for records linkage, and (2) differences in data structure and content given differences in documentation procedures and data coding. But it is feasible. Bencheikh and Benabadallah,\textsuperscript{56} for instance, discuss how the pharmacovigilance and poison control centres in Morocco collaborated in undertaking “root-cause analysis” to detect pADEs and to identify proximate contributing factors, for example, deviations from recommended treatment protocols.

In summary, ADR/ADE reporting systems (supplemented by other sources of information) should be structured in a way that, at least, supports analyses of morbidity, mortality and recovery rates from ADEs as well as differentiation of pADEs from unavoidable ADRs. The wealth of information that this could generate should help efficient selection and targeting of preventive interventions as well as measurement of the effectiveness of these interventions in reducing avoidable medication-related harm.

Quality assurance along the supply chain

Because medicinal demands by a given patient population persists year after year and medicines procurement or sales involve large sums of money, perfect or imperfect mimicry of quality-assured medicines makes the business of counterfeiting and falsification profitable. Theoretical models suggests that strategies to address the issue of medicines with questionable quality should aim to lower the expected algorithm that matches pADE terminology with terminology that suggests ineffective medicines or medicine quality issues. It is worth noting this approach produced a number of false positives. Focusing on reports that were not dismissed by national reporting centres, these false-positives were attributed to (1) increase in reporting due to bad publicity (notoriety effect), (2) data clusters due to medication errors or switching of branded products or treatment regimens, and (3) time delays in transferring country-specific reports to the global database.
net gains from quality-distorting activities by increasing the costs of such activities.57 This appears to be more effective than simply educating consumer-patients and healthcare practitioners acting on their behalf. Lowering the expected net gains from quality distortions will require increasing the probability of detection (by reducing the scope for transactional monopoly, i.e., no clear performance standards, unmanaged decision space, lack of accountability etc.) and the size of punishment contingent on detection. Besides cooperation with law enforcement agencies, this means conducting, along the whole of the supply chain (from domestic manufacturing plants, wholesaling and retailing units to healthcare facilities etc.), random sampling of medicinal products on a country’s market and unpredictable inspections of manufacturing facilities, wholesaling and dispensing pharmacy units in the public and private sectors. Randomness and unpredictability has to do with time, date and place, irrespective of whether medicinal products are branded or unbranded, originator or generic. And it should reduce or eliminate any safe harbour wrongdoers have to run profitable and growing quality-distorting ventures.

How often such random sampling and unpredictable inspections are carried out depends on how pervasive the problem is and the (financial) capabilities and capacity of DRAs in low-income countries to deal with the issue. There are various technologies that can be used including devices for visual inspection; devices for detecting the presence of the correct active ingredient; portal devices for detecting the correct active ingredient with and without sample preparation, and devices intended for confirmatory and forensic testing. The cost of these testing technologies range from low (< US$10000) to modest (US$10000–100000) to high (> US$1000000). Given significant constraints on healthcare resources available, it has been suggested that random sampling and unpredictable testing could be made more effective nationwide by using a hierarchical approach where low-cost technologies are used for rapid assessments of the quality of medicines consumed in rural areas, modest-cost technologies are used for medicines consumed in urban areas whereas high-cost technologies for full pharmacopeial test are used in dedicated laboratories run by DRAs.58 This, however, is not the only way of dealing with resource constraints. One useful approach is for DRAs in each country to estimate what it will cost for nationwide quality assurance of medicines including the costs of setting up and running pharmacovigilance and other post-marketing data collection systems and the costs of frequent random sampling and unpredictable testing. From these estimates, DRAs will subtract public financing received and attempt to recover the shortfall via charging annual registration fees for the mix of medicinal and perhaps food products available on a country’s market. Holders of marketing authorization for these products may react to this increase in country-specific fixed costs of supplying medicines by (1) keeping short-run prices the same with the aim of recovering these costs in the long-run via increased revenues from zero demands for medicines of questionable quality, or (2) they could increase product prices in the short-run. This, however, is not the only way of dealing with resource constraints. One useful approach is for DRAs in each country to estimate what it will cost for nationwide quality assurance of medicines including the costs of setting up and running pharmacovigilance and other post-marketing data collection systems and the costs of frequent random sampling and unpredictable testing. From these estimates, DRAs will subtract public financing received and attempt to recover the shortfall via charging annual registration fees for the mix of medicinal and perhaps food products available on a country’s market. Holders of marketing authorization for these products may react to this increase in country-specific fixed costs of supplying medicines by (1) keeping short-run prices the same with the aim of recovering these costs in the long-run via increased revenues from zero demands for medicines of questionable quality, or (2) they could increase product prices in the short-run, with the increments in mark-ups limited by demand elasticities suppliers face. In our view, this approach is better than increasing and keeping authentic product prices high (even in off-patent periods) to imperfectly signal quality. Consumer-patients generally find it difficult ex ante to differentiate quality-assured medicines from those of questionable quality.52

Let’s now look at the results of the study by Bate et al.60 that tested 1437 samples of ciprofloxacin (a fluoroquinolone antibiotic) using the Minilab®-tuple in 18 low- and middle-income countries. This showed that 9.88% of the medicines sampled contained less than 80% of the active ingredient, and out of that subclass 41.5% of these failures are falsified. Based on the study’s sample, there are price and non-price signals that help identify counterfeits, falsified and substandard medicines – namely innovator brand status, distribution channel (i.e., whether the product is sold by a chain retail pharmacy as opposed to an independent, standalone pharmacy), price levels and place of product manufacture. Falsified and counterfeit medicines were more likely to mimic and have prices close to that of quality-assured product approved by local DRAs. (This is because inspectors often do not examine registered products assuming that pre-market regulation was more than enough for quality assurance). Prices of substandard medicines, on other hand, were 10% lower than that of quality-assured generic equivalents; and these medicines were also more easy to identify as prices that are too-good-to-be-true are often as signal of quality-distortion. An earlier study for a wider range of products (antimalarials, antibiotics and antymycobacterials) in 17 low- and middle-income countries indicated that prices of drugs that failed quality tests were 13.6–18.7% lower than prices of those that passed quality tests.61 Setting aside price signals, the Bate et al.60 study reported the proportion of falsified medicines was lower in chained retail pharmacies (31.25%) compared to standalone, independent pharmacies (42.86%). Chained pharmacies are created as part of attempts to exploit short-run spreading of fixed costs and long-run economies-of-scale related to the business of acquiring medicines, stocking and inventory control; investments in information and communication technologies etc. Thus the competitive advantage of chained retail pharmacies stems from being able to offer lower product prices and patient-centred services via lower retail mark-ups and not by selling quality-distorted products. Indeed, by virtue of serving a larger, geographically-diffuse patient base, chained pharmacies have greater incentives to protect their brand or reputation for selling lower-priced quality-assured medicines. Another reason is: if chained pharmacies are contracted by third-party healthcare payers to supply medicines listed on restrictive medicine lists or formularies, then compared to independent, standalone pharmacies who sell a wide range of products, chained pharmacies will stock and sell a more streamlined mix of medicinal products. This in turn reduces the points of entry for medicines of questionable quality but doesn’t make chained pharmacies completely immune.

Certainly, one cannot rely on price and non-price signals to consistently identify medicines of questionable quality. Although ethical pharmaceutical manufacturers have adopted a number of deterrent security and tracking devices (for example, holograms, bar codes, scratch pads etc.) to protect the quality of their brands, it is still possible that a substandard product that is priced closer to quality-assured originator and generic equivalents, sold in chained retail pharmacies and manufactured in an European country will fail standard quality tests. Perfect or imperfect mimicry is and will always remain a threat; and this means an unwavering dedication to the principle of random sampling and unpredictable testing for all products in each low-income country. Beyond that, drug distribution and supply systems must be structured in way that makes entry by or supply of counterfeits, falsified and substandard products difficult and unprofitable. As argued elsewhere,62 a medicine supply chain comprising of: (1) consolidated private drug wholesaling; (2) multiplicity of chained or standalone retail pharmacies to reduce differences in medicine access across geographical regions; (3) one-stop delivery arrangements in public supply chains; and (4) where feasible, public-sector contracting with private wholesalers and pharmacies, should help reduce the number of channels via which counterfeits, falsified, substandard and other defective medicines can be sourced.

**Promoting appropriate use of medicines**

**Restricting drug promotion, advertising and detailing**

To ensure appropriate use, one needs to manage one of the key modifiers of medicinal demands: promotion and advertising. Promotion and advertising of medicines however has multidimensional effects: (1) serving as a source of information on the health benefits and safety risks of specific pre-packaged products, the available therapeutic substitutes and generic equivalent whilst (2) simultaneously exerting persuasion effects, i.e., creating deeply rooted habits that negate the expression of price-sensitive demands.63 Advertising and promotion by (ethical) pharmaceutical manufacturers represents a competing source of information to EMLs, formularies and STGs. And, as far as medication-
related harm is concerned, we are not sure drug suppliers will consistently offer unbiased information on the health benefits and safety risks of medicines given their objectives to maximize net revenues and profit. Brody and Light, for instance, have argued that profit-driven, market expansion effects expose a lot more patients to medicines that have lower benefits-harm ratios compared to existing alternatives (so-called inverse benefit law) – due mainly to extending treatment-eligibility criteria, exaggerated efficacy and safety claims, creation of “new diseases” and unapproved, off-label usage. What is more, even if the information channelled through promotion and advertising are unbiased and not misleading, it is not guaranteed we will not have inappropriate overuse in a community of apparently informed healthcare practitioners and consumer-patients. For these reasons, it will be better to regulate the content of industry-sponsored drug promotion and advertising, and use the alternative measures described below.

Professionally-determined clinical choices

For the sake of clarity, the argument in this subsection for ensuring professionally-determined clinical choices are appropriate, apply to every healthcare facility or institution where healthcare practitioners make some recommendations on medicines and medicine use to consumer-patients. But consider first what happens in a single healthcare facility or institution. Healthcare practitioners can only prescribe medicines they consider as efficacious and safe based on what they know at the time. For this reason, one has to ensure prescribing healthcare practitioners have access to unbiased and up-to-date information with which they make their decisions. This means that EMLs, formularies and STGs as tools for standardizing drug choices are revised as often as possible in tandem with accumulation of relevant clinical evidence and the assessment of this ‘new’ evidence base by drug information centres. This process will have to be supported by face-to-face academic detailing of healthcare practitioners as to the contents of the revised versions of EMLs, formularies and STGs. A simple way of doing this is to have a “What’s New” section in each of these manuals of recommended treatment protocols that highlights the revisions made (what has been added or deleted). Another way is organizing conferences, seminars and workshop or generally speaking drug education and information programs for healthcare practitioners to inform them about the revised manuals and the advances made in pharmaceutical medical knowledge.

Making sure these manuals or guidelines are up-to-date and contain unbiased information is just as important as ensuring drug prescribing, transcribing of drug information, drug dispensing and administration by health practitioners complies with the recommended treatment protocols. In particular transcribing errors (which are more likely with medicines that are used frequently) could be dealt with by developing, for all medicinal products available on a country’s market or those in EMLs and formularies, a list of pairs of products that look-alike in terms of both name and non-name attributes (orthographic similarity) and have names that sound-alike (phonological similarity). It might be best if these lists are incorporated into the training and education curricula such that healthcare practitioners are aware of these potential sources of medication errors and pADEs prior to entry into the clinical practice. They could be also be included in post-entry continuous professional development programs for healthcare practitioners. In addition, some simple practical measures such as (1) careful prescription writing; (2) using in routine clinical practice (and not just policy documents) only one convention for generic names, i.e., avoid mixing US, British and international recommended generic names; (3) avoiding excessively rapid speech and issuing clinical orders in quiet places without a lot of background noise; and (4) physical separation of medicines that look-alike and sound-alike. Automated alerts in electronic administrative systems, special packaging and shelf-placement markers for manual systems, font variations including the use of tall-man lettering have also been proposed as countermeasures, however have argued that the presence of multiple similar medicines in close proximity to a target medication may impair visual search for the target medication and tall-man lettering has no impact on this impairment.

Irrespective of the origin of pADEs, some form clinical audit and feedback (what is generally described as clinical governance) is necessary within any healthcare facility. Altruistic motivations, an oath to care for the sick, competition for professional status and peer recognition may encourage appropriate medicine use to the extent that final clinical outcomes are affected. Yet, we cannot rely solely on intrinsic motivations. Evidence suggests that clinic audit and feedback does indeed have a positive effect on moderate preference on professionally-de termined clinical choices and clinical outcomes. A study by Dreischulte et al. of physician-owned primary care practices in Scotland showed that an intervention comprising of (1) financial incentives to review patients’ charts and medicine use profiles, (2) healthcare practitioner education and (3) information systems to extract medicine-use data from compatible electronic medical records, reduced (1) the rate of “high-risk” prescribing of NSAIDs and antiplatelet drugs without gastroprotection and in patients with chronic kidney disease and (2) the rate of hospital admissions due to gastrointestinal bleeding and ulcer. (In that study, financial incentives were designed as lump-sum payments to physicians and variable payments linked to the number of medicine-use reviews conducted.) This paper believes that financial incentives plus clinical governance should serve as the platform for promoting appropriate medicine use. That is, correcting deviations from recommended treatment protocols and judging the appropriateness of non-standard individualized treatment protocols for atypical patients who failed to respond to any of the standard treatment protocols. As long as clinical governance initiatives ensure practitioner compliance with recommended treatment protocols, the only safety risk that can be attributed to healthcare practitioners is unavoidable ADRs. Clinical governance is often the responsibility of a Drugs and Therapeutics Committee (DnTC) in each healthcare facility or institution. And we can say that the involvement of such DnTCs in pharmacovigilance activities is a natural extension of their functions to ensure appropriate use of medicines. Depending on how DnTCs execute clinical governance, we might observe some variation across different settings with regards to healthcare quality measured in terms in the frequency of preventable ADEs. A way of dealing with such institutional-level variations in quantity and quality of healthcare is having (1) registries of consumer complaints about service delivery and experiences (2) agreed service and performance indicators, and (3) financial incentives to pharmaceutical companies, (2) healthcare practitioners and consumer-patients, (3) agreed service and performance indicators, and (3) financial incentives to pharmaceutical companies, (4) agreed service and performance indicators, and (3) financial incentives to pharmaceutical companies, (4) agreed service and performance indicators, and (3) financial incentives to pharmaceutical companies, (5) agreed service and performance indicators, and (3) financial incentives to pharmaceutical companies, (6) agreed service and performance indicators, and (3) financial incentives to pharmaceutical companies, (7) agreed service and performance indicators, and (3) financial incentives to pharmaceutical companies, (8) agreed service and performance indicators, and (3) financial incentives to pharmaceutical companies, (9) agreed service and performance indicators, and (3) financial incentives to pharmaceutical companies, (10) agreed service and performance indicators, and (3) financial incentives to }
prescription-only medicines without prescriptions. Part of the problem has to do with the fact that clinical governance in healthcare facilities do not extend to standalone independent or chained pharmacies. So the risk of pADEs that exists where and when healthcare practitioners have to work with incomplete medical histories is elevated by variations in drug choices and treatment protocols.

Promoting continuity in care via (1) the adoption of a common set of EMLs, formularies and STGs across all healthcare providers patients transition to and from; and (2) electronic linkage of medical records and medicine-use profiles arguably should help reduce the risk of avoidable ADEs. This is workable in the case of in-house pharmacies of healthcare facilities and community pharmacies that form part of a provider network contracted to a healthcare insurer or payer. Clinical governance of what happens in community pharmacies will then be executed by a body (DnTCs, for instance) internal to the provider network. In the case of unmanaged standalone (independent or chained) pharmacies the only option is the self-regulatory version of clinical governance, which some are not convinced is the best way to optimize self-prescribed medicine use. Drug education and information programs targeting community pharmacies have been suggested and they might help but equally important is developing the habit and culture of consumer-patients keeping medication diaries, patient-information booklets or patient-held records. The latter seems to be a fairly simple way of dealing with incomplete medical histories – even though there are issues of patients not complying with (paper-based) medical diaries,57,73

**Consumer-driven consumption**

There is no guarantee that appropriate professionally-determined clinical choices will translate into improvements in consumer-patient welfare without concordance between professionally-determined clinical choices and consumer-driven consumption. Behavioural deviations on the part of consumer-patients from this ideal can be categorized into: (1) intentional or rational non-compliance where patients’ valuations of the health benefits (the “necessity” for medicines) and safety risks (“concerns” about medicines) differs from that of healthcare practitioners; and (2) cases of unintentional non-compliance (for example, the stress and anxiety of illness makes consumer-patients forgetful). Horne et al.74 for example have shown the higher concern and lower necessity scores are associated with lower compliance rates, whilst a larger difference between necessity and concern scores is associated with higher compliance rates. That said, biopsychosocial models of health, in contrast to biomedicine, suggests that for any primary disease condition there might exist behavioural comorbidities or behavioural hazards that encourage (in)appropriate use of medicines. Consumer-patients may present with non-medical needs that may or may not encourage inappropriate medicines use; and healthcare practitioners should be aware of this. Beyond diagnosis, prescribing, dispensing and attempts to ensure concordance between healthcare practitioner and patient beliefs about the health benefits and safety risks of medicine, there is a need for every healthcare practitioner (doctors, nurses, pharmacists, laboratory personnel, physical therapists, dentists, dieticians, healthcare educators, mental health staff etc.) to recognize and respond to any unmet non-medical needs patients might have. This the basis of the concept of effective therapeutic relationships (sometimes referred to as therapeutic alliances, working alliances or helpful relationships). The emphasis of therapeutic relationships however are not the pharmacologic effects of medicine but rather effective communication, shared decision-making and shared responsibility for clinical outcomes, warmth, friendliness, genuine or unconditional interest, empathy and unwavering desire to support patients,5,76 The evidence available suggests that a “moderate but reliable association” between good therapeutic alliances/relationships and positive clinical outcomes,77,78

How can one develop such effective therapeutic relationships taking into account the informational and non-medical needs of patients? This paper suggest healthcare practitioners (the pharmacist in particular) should have in mind a minimum information exchange set (see Fig. 3)13 that will guide and determine what they communicate to consumer-patients on each and every encounter with them. Time constraints and excess demands (with possible income losses) may not make it feasible to provide all that information on each encounter. Although some might argue the minimum amount of information is actually the “standard”, what is commonly observed is the window-system of dispensing with little or no time set aside for patient counselling due to heavy workloads. A possible solution is for healthcare practitioners to take the pragmatic approach of identifying in their interactions with consumer-patients, the following broad groups of patients: (1) those informed enough to use their medicines appropriately, (2) those who are uninformed, especially patients on new medications, and (3) those who are inadequately informed and are likely to use their medicines inappropriately. Healthcare practitioners could then skew their information provision efforts towards patients in groups (2) and (3). They may, given time constraints and excess demand, provide only a subset of the minimum information to patients, especially information that is rarely provided (special storage requirements, importance of treatment adherence, lifestyle modifications and psychosocial support). This may be supplemented by (1) use of product package inserts and patient information leaflets and (2) putting up “public-health” adverts on alcohol addiction, smoking cessation, sexual health, preventing heart disease and dietary disorders etc. But note that some medicinal products are supplied without package inserts and the absence of technical information on the drug or even directions for medicine use is likely to increase pADE risk,9 DRA’s ensuring all products available on a country’s market have, at least, a patient information leaflet will help a lot. The pragmatic solution suggested above requires that (1) patients have question-asking behaviours and (2) pharmacists and other healthcare practitioners have a commitment to information provision, patient counselling, disease prevention and prolonging the life of the members of the community they serve. So it should not surprise researchers if they find patient counselling rates and the content of such counselling;

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**Fig. 3. Minimum information exchange set.**

- Name of medicine(s)
- What the medicine(s) prescribed are supposed to do
- How efficacious the medicine(s) are thought to be
- How medicines should be taken, for how long and how often
- Common side effect(s)
- Interactions with concomitant medicine(s)
- How to fit medicine(s) into daily routine of patients
- Special storage requirements
- Relationship between patients’ adherence to health advice and treatment resistance or failure
- Lifestyle modifications and preventive health measures

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sessions differ across therapeutic classes. (In fact it is recommended that the effects of therapeutic class should be controlled for in studies that investigate such variations.\textsuperscript{75})

Putting patients' passivity aside, what's the incentive for healthcare practitioners to follow the tact suggested here? It has been shown that patients show loyalty to a pharmacy not because of the pharmacists' technical competencies but because of lifestyle and psychosocial exchanges, patients' age and the unconditional interest pharmacist show technical competencies but because of lifestyle and psychosocial exchanges, patients' age and the unconditional interest pharmacist show.\textsuperscript{59} This means time costs, costs of infrastructural changes to pharmacies or place of practice; and possible income losses from their information provision and relationship-building efforts (when there is excess demand), can be compensated by such pharmacy loyalty, putting aside the flexibility to adjust retail mark-ups, margins or dispensing fees. Given pharmacy loyalty, competition for professional status and peer-recognition plus any other incentives that can fashioned, this paper will argue that repeated interactions characterised by continuous medicine information exchanges should in the long-run create communities of informed consumer-patients capable of using the medicines appropriately (whether these medicines are self-prescribed or professionally-determined). This process can be further accelerated by drug education and information programs for patients that aim to provide general information on how to use any medicine, focusing on elements that are not product-specific, for instance, how to fit medicine use into the daily routines; why adherence to recommended protocols is necessary for treatment success; why lifestyle modifications and preventive health measures are important and why the future, long-term benefits of these measures should not be over-discounted.\textsuperscript{13}

Concluding comments

The Challenge to reduce medication-related harm by 50% over a period five years, or as some texts put in, within the next five years, does not clearly specify what the reference or starting point is or will be. Perhaps, the reference point will be specified after health ministers and health-system leaders in low- and high-income countries have expressed their commitment to the challenge. Irrespective of the reference or starting point, it is clear that each low-income country will need to make significant investments in ADE prevention in order achieve the global target. Ideally, one will need prior knowledge of what fraction of ADEs is avoidable or preventable, and the composition of the package of prevention strategies that is cost saving or cost-effective relative to treating cases of pADEs as they build up. Future research may consider the empirical task of determining the point at which ADE prevention ceases to be optimal (i.e., no longer cost saving or cost-effective) in different low-income country contexts; but here in this paper, we make no claim as to which interventions are the “best-buys”, i.e., offer the highest value-for-money for low-income countries, preferring to defer those decision choices to health planners in each low-income country. However, we believe that given the supply of a global public good by high-income countries in terms of updated safety data and usage restrictions over products' lifecycles, low-income countries can make significant strides in achieving the global target by (1) designing pharmacovigilance to quantify avoidable medication harm, (2) ensuring quality assurance along supply chains, and (3) encouraging appropriate use of medicine. Priority areas identified under the Challenge (the high-risk situations of medicine use in young children, elderly and hospital inpatients, polypharmacy and transitions of care) suggests that preventive strategy is one centred on appropriate, rational or responsible use of medicines. Prioritizing appropriate medicine use (in “high-risk situations”) is the right tact since beyond reducing or eliminating avoidable medication harm, there are other reasons why interventions to support appropriate medicine use benefits societies. Such interventions (together with those that help lower medicine acquisition costs) help reduce wasteful expenditures, slow down the development of antimicrobial resistance and encourage positive healthcare seeking behaviours as consumer-patients are confident of receiving affordable, effective and safe medicines (good quality care).\textsuperscript{13}

This should not, however, mask the need for interventions aimed at ensuring demands for, or consumption of, medicines of questionable quality falls to zero. One cannot assume that when medicines do not work, they do not inflict any injury or harm to the patient. Arguably, the more difficult problem is pADEs associated with substandard or counterfeit medicines as in the absence of effective and functional regulatory structures, these medicines often go undetected. That said, our arguments from the onset have been based on the notion that medicines prescribed and consumed (whether they are of good or questionable quality) are affordable to all consumer-patients. It is obvious that exposure to the financial risks of medical care (using medicines when appropriate), especially care costs exceeding what consumer-patients can afford, may encourage deviations from recommended treatment protocols, either by consuming an incomplete course of treatment or abandoning treatment completely. The problem exists even if there is concordance between patients and healthcare practitioners’ beliefs about the health benefits and safety risks of medicines. A better arrangement is some form of health insurance that guarantees consumer-patients financial access to (basic) healthcare by reducing or eliminating the financial risks (and uncertainty) associated with illness. Paying premiums whether well or sick is a better coping measure compared to a reliance on savings, selling assets (livestock, dowry, jewellery etc.), borrowing, transactional sex or extended family support.\textsuperscript{81,82} In layman's language, consumer-patients, by paying insurance premiums whether sick or not, buy a “peace of mind” as far as their medical bills are concerned – which in turn leaves little room for healthcare affordability constraints to induce or encourage inappropriate use of medicines and its attendant pADEs. So to the package of preventive measures described in the preceding section, one will want to add universal health insurance coverage. Adopting this package of prevention measures (plus universal insurance coverage) will surely require major, significant investments in health-system strengthening in low-income countries.

It is true that some of the interventions suggested have been implemented in high-income countries and yet this has not reduced or eliminated morbidity and mortality associated with avoidable medication-related harm. The issue in our opinion has to do with differences in how these preventive interventions are implemented and executed. The selective evidence presented here in this paper show that these interventions are or can be effective. If efforts to strengthen health systems in low-income countries are continuous and successful, i.e., functional healthcare systems providing good quality healthcare become a reality and no longer a mirage, the number of cases or the fraction of preventable ADEs theory suggest should be at very low” to “low” levels. Frequency of avoidable medication-related harm in low-income countries should lie somewhere to the left of P* in Fig. 2; prevention will no longer be worthwhile and treatment of pADEs will be either cost saving or cost effective. The suggestions put forward in this paper are relevant even if, in a given low-income country, existing healthcare infrastructure is limited in terms of geography; health insurance coverage is not universal; and there is a high proportion of people who are poor, who have high medical needs and yet lack access to medicines. The only time one doesn't have to worry about medication-related harm is when there are no medicines available. Incidence of medication-related harm, however, cannot be used to justify lack of or limited access to medicines. Losing positive health benefits (net of any safety risks) is clearly undesired, and for that reason, health systems in low-income countries should consider simultaneously improving medicines access and reducing (avoidable) medication-related harm.

Can avoidable medication-related harm be reduced globally by 50% over the next five years? Our response is: yes, it can be achieved. But from the discussions above, reducing medication-related harm will require a series of multifaceted interventions targeting all possible
sources of avoidable ADEs. This will include country-specific implementation of functional health-insurance arrangements and the supply of updated safety data over products' lifecycle as a global public good. The package of interventions needed therefore to reduce avoidable medication-related harm is broad, the associated costs of implementing them will be high – and these interventions will have to be coordinated and executed in tandem. The reality is healthcare systems in resource-poor settings are plagued with so many constraints and competing claims on societal resources that we doubt if the stipulated objective can be achieved over the stipulated timeframe. Since the fraction of avoidable ADEs, resources available, existing structures in place, political support and interventions needed will vary from one low-income country context to another, it might be possible to achieve something close to the global target over a five-year period but even that will hide differences across and within countries. Progress have been made in some countries, for other countries we cannot say the same thing and more needs to be done on an ongoing basis. But if health-systems development and strengthening in low-income countries continues at the current pace, reducing severe avoidable medication-related harm over a period of five years, irrespective of the reference point chosen, will be a herculean task. The period over which avoidable medication-related harm can be reduced by 50% will depend, at least, on whether significant continuous investments in health-system strengthening and reforms are made prior to and within that period.

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