Global burden of preventable medication-related harm in health care

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A systematic review

MEDICATION WITHOUT HARM
Global Patient Safety Challenge

Global burden of preventable medication-related harm in health care

A systematic review

Global burden of preventable medication-related harm in health care: a systematic review

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Definitions

The following definitions were used for this report; additional acceptable definitions are available for some concepts.

Adverse drug event: Any injury resulting from medical interventions related to a drug. This includes both adverse drug reactions in which no error occurred and complications resulting from medication errors. In the pharmacovigilance field referred as Adverse Events (AE) *(1,50)*

Medication error: Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use *(2)*

Medication-related harm: The harm caused by medication if taken incorrectly, monitored insufficiently or as the result of an error, accident or communication problem *(3)*

Patient harm: An incident that results in harm to a patient such as impairment of structure or function of the body and/or any deleterious effect arising there from or associated with plans or actions taken during the provision of health care, rather than an underlying disease or injury, and may be physical, social or psychological (e.g., disease, injury, suffering, disability and death) *(4)*

Preventable medication-related harm: Medication-related harm was considered preventable when (i) it occurred as a result of an identifiable, modifiable cause and (ii) future recurrence of medication-related harm could be prevented with reasonable adaptation to a process and adherence to guidelines *(5)*.

Severity of harm: The severity of harm caused to a patient, is described according to five key categories outlined in the WHO Conceptual Framework for the International Classification of Patient Safety *(4)*:

- *None:* patient outcome is not symptomatic or no symptoms detected and no treatment is required.

- *Mild:* patient outcome is symptomatic, symptoms are mild, loss of function or harm is minimal or intermediate but short term, and no or minimal intervention (e.g., extra observation, investigation, review or minor treatment) is required. Mild harm typically resolves within 1 month.

- *Moderate:* patient outcome is symptomatic, requiring intervention (e.g., additional operative procedure; additional therapeutic treatment), increased length of stay or temporary disability or loss of function. Moderate harm typically resolves within 1 year.

- *Severe:* patient outcome is symptomatic, requiring life-saving intervention or major surgical or medical intervention, shortening life expectancy or causing major permanent or long-term harm or loss of function. Severe harm results in permanent disability.

- *Death:* on the balance of probabilities, death was caused or accelerated in the short term by the incident.

Doctor prescribing medicines, photo credit: WHO/Fernando G. Revilla

Summary

A series of WHO initiatives, such as the Global Patient Safety Challenge: *Medication Without Harm* and the Global Patient Safety Action Plan 2021-2030, address patient harm associated with use of medications. Medication-related harm is considered preventable if it occurs as a result of an identifiable, modifiable cause and its recurrence can be avoided by appropriate adaptation to a process or adherence to guidelines. Understanding the prevalence, nature and severity of preventable medication-related harm is critical for setting targets for clinically relevant, implementable improvements in patient safety.

This report presents an updated systematic review and meta-analysis of studies of the prevalence, nature and severity of preventable medication-related harm in the international literature including in low- and middle-income countries (LMICs). A total of 100 studies were included in the review, involving 487 162 patients. Of these reports, 70 were from high-income countries (HICs) and 30 from LMICs. The results were as follows.

Global prevalence and severity of preventable medication-related harm: The pooled prevalence of preventable medication-related harm in all 100 studies was 5% (1 in 20 patients). One fourth of the harm was severe or potentially life-threatening.

Geographical distribution of preventable medication-related harm: The prevalence of preventable medication-related harm was 7% in 30 studies in LMICs and 4% (3–5%, one in 25 patients) in 70 studies in HICs. The highest prevalence rates of preventable medication-related harm were in the African (9%) and South-East Asian regions (9%).

Health care settings in which the most vulnerable patients are managed for preventable medication-related harm: Globally, the highest prevalence rates for preventable medication-related harm are for patients managed in geriatric care units (17%) and among patients in highly specialized or surgical care (9%).

Stages of medication at which most preventable medication-related harm occurs: Globally about half (53%) of all preventable medication-related harm occurred at the "ordering/prescribing" stage and 36% at the "monitoring/reporting" stage. In LMICs, almost 80% of preventable medication-related harm occurred during the "ordering/prescribing" stage.

Medicines that contribute most to medication-related harm: Antibacterials, antipsychotics, cardiovascular medications, drugs for functional gastrointestinal disorders, endocrine therapy, hypnotics, sedatives and non-steroidal anti-inflammatory products contributed most to medication-related harm globally.

Way forward: The analysis showed that at least one in 20 patients are affected by preventable medication-related harm globally and that more than one fourth of preventable harm is severe or life-threatening. The prevalence of preventable medication-related harm in LMICs was almost twice as high as in HICs; however, few data were available on the severity and nature of medication-related harm in LMICs. A prerequisite for the success of future strategies to mitigate preventable medication-related harm in LMICs would be to encourage reporting of any preventable medication-related harm and commission high-quality studies with standard methods for assessing and reporting such harm and also studies of the underlying causes for designing interventions that are most likely to work in LMICs. There is also an urgent need to implement improvement strategies in settings in which patients are managed, especially those who are vulnerable to preventable medication related harm, such as geriatric care and surgical care settings. Finally, most of the evidence summarized in this report was produced in hospitals and should be strengthened with more research in major specialties, including primary care, and mental health.

Objectives and target audience

This report describes an updated review of preventable medication-related harm. The objectives were to:

- provide the most up-to-date estimates of the prevalence, nature and severity of preventable medication-related harm globally;

- describe the prevalence, nature and severity of preventable medication-related harm in LMICs; and

- describe differences in the methods used to measure and report medication-related harm, and assess the impact of those differences on the prevalence of preventable medication-related harm.

The main target audience of this publication is policy makers, health care leaders, researchers and academics, practising clinicians, pharmaceutical industry and advocacy groups on medication safety.

Medicine being dispensed at a pharmacy, photo credit: WHO/Atul Loke

Background

Global prevalence, burden and cost of medication-related harm

Patient harm during health care is a leading cause of morbidity and mortality globally, and medication safety is an international priority. WHO defines patient harm as "an incident that results in harm to a patient such as impairment of structure or function of the body and/or any deleterious effect arising there from or associated with plans or actions taken during the provision of health care, rather than an underlying disease or injury, and may be physical, social or psychological (e.g., disease, injury, suffering, disability and death)" *(4)*.

Medication errors are one of the leading causes of patient harm in health care, along with errors in additional therapeutic management, surgical procedures, health care-related infections and diagnosis *(8)*. Medication errors can occur throughout the use of medicines, which usually includes the prescribing, dispensing, administration and monitoring stages *(9)*. Various health and care workers are involved in medication use process at several levels of care or locations. The severity of medication-related harm at any stage can range from minor to serious harm and death, with associated health care and other costs. For example, harm can occur even at the time a medicine is prescribed; if questions are raised about whether the prescription was appropriate, the resulting harm can be considered "preventable" and considered to be "preventable medication-related harm" *(10)*.

The report by the US Institute of Medicine "To err is human: Building a safer health system" *(11)* helped to generate a movement for patient safety after it reported that, each year in the USA, up to 98 000 deaths were due to medical errors, at least some of which could have been prevented *(12)*. In March 2017, WHO launched a global initiative, the Global Patient Safety Challenge: *Medication Without Harm* with the goal to reduce severe, avoidable medication-related harm in all countries by 50% over a period of 5 years *(3)*. The aim of the Global Patient Safety Challenge: *Medication Without Harm* is to correct the weaknesses in health systems that lead to medication errors and severe harm with focus on four domains patients and the public, health care professionals, medicines and systems and practices of medication.

Evidence from a study commissioned by the Department of Health and Social Care in England in 2021 showed that 237 million medication errors occur at some point in medication use in England annually, 66million of which are potentially clinically significant *(13)*. A systematic review and meta-analysis of 81 observational studies conducted in HICs and LMICs comprising 285 687 patient records showed that 3% of patients in various health care settings experienced preventable medication-related harm and that at least one fourth of such harm was severe or potentially life-threatening *(14)*. In another systematic review and meta-analysis of studies in HICs and LMICs, the prevalence of preventable patient harm (i.e., harm due to any type of medical error, not only medication) was 6%, one tenth of which was severe or potentially life-threatening *(8)*. Thus, medication-related harm may account for up to half of all preventable harm in medical care. Preventable medication-related harm may also be severe or life-threatening more often than other types of patient harm *(8, 14)*. Although these figures are probably underestimates as the number of medication related harm cases are likely to be much greater in LMICs due to overuse of medication *(15)*.

Medical errors are the third most common cause of death in the USA, after heart disease and cancer *(16)*. It was estimated that 7000–9000 people in the USA die due to a medication error each year, and

approximately 1.3 million experience medication-related harm *(17)*. As a consequence of medication errors and medication-related harm, patients may experience psychological and physical distress and lose trust in their health care system *(17)*.

Medication-related harm also poses a major financial burden on health care systems worldwide. Globally, the cost associated with medication errors has been estimated at US$ 42 billion annually *(19)*. Medication-related harm considered to be "definitely preventable" was estimated to cost the National Health Service in England £98 million per year, use 181 626 bed-days and cause or contribute to 1708 deaths. The medication-related harm comprised that in primary care leading to hospital admission (£83.7 million; 627 deaths) and that in secondary care leading to longer hospital stays (£14.8 million; causing or contributing to 1081 deaths) *(13)*.

Medication-related harm in low- and middle-income countries

Although most of the studies of patient safety, including studies of medication errors and medication-related harm, have been conducted in HICs, the prevalence of medication errors in LMICs is estimated to be at least as high or higher and the impact on patient harm potentially worse *(20)*.

The findings with regard to the prevalence, nature and severity of medication-related harm in LMICs are mixed. A systematic review and meta-analysis of 81 studies in 2019 *(14)* showed no difference in the prevalence of preventable medication-related harm in HICs and in LMICs; however, the quality of the methods and reporting standards (i.e., on preventability, severity and nature of medication-related harm) of studies in LMICs were lower than those of studies in HICs. Additionally, some of the studies in LMICs were excluded from the analyses because they did not provide data on the preventability of medication-related harm. Thus, the prevalence of such harm and its severity in LMICs may have been underestimated because of limited data and methodological flaws in the studies. For example, one of the few good-quality studies, conducted in 26 hospitals in eight LMICs, showed a prevalence of patient harm of about 8%. Of the types

of harm reported, 83% was preventable and about 30% caused the death of the patient *(23)*. Even these rates are likely to be underestimates, as higher rates of excess death were not accounted for, suggesting that the number of preventable deaths is likely to be a much larger problem in LMICs *(23)*. Up-to-date estimates of the prevalence, nature and severity of preventable medication-related harm in LMICs would be particularly useful to inform policy changes and to take actions.

Systematic reviews have shown that medication errors affect up to one third of patients in South Asian countries during an interaction with the health care system *(21)*. Possible reasons for the high prevalence of medication errors in LMICs include dispensing of medications a by less-qualified health professionals, hospital pharmacy services only in contemporary hospitals, little use of hospital drug information services and use of handwritten prescriptions. *(22)*. The review concludes that, in LMICs, medication errors and medication-related harm are often not reported because of a blame culture, fear of litigation, lack of support from hospital management and lack of capacity to detect medication-related harm. Although these issues are not unique to LMICs and also affect HICs, they might be more pronounced in LMICs.

Measuring and mitigating preventable medication-related harm

In the third Global Patient Safety Challenge: *Medication Without Harm*, WHO emphasizes early detection of medication errors and prevention of medication-related harm in health care as an international priority. In principle, zero medication-related harm is the goal; however, this goal is not feasible at present because some such harm cannot be avoided in clinical practice. For example, adverse drug reactions that occur with no error in medication use processes are less likely to be preventable. A better understanding of medication-related harm, which is easier to prevent than others, requires the recognition and measurement of the key types of such harm that are definitely or possibly preventable, along with their mitigation through appropriate policies or interventions.

Several definitions of "preventable medication-related harm" can be found in the literature, and consensus has not yet been reached on the precise criteria for preventability *(24)*. In most studies, patient harm is classified as preventable if it is the result of an identifiable, modifiable cause and its recurrence can be avoided by appropriate adaptation of a process or adherence to guidelines *(5)* (for example, when a medicine is prescribed for a patient who has a known allergy to that medicine) *(25)*. Medication-related harm can be prevented by improving the practices of health and care workers (errors of omission or commission), health care system failures or, usually, a combination of mistakes made by individuals, system failures and patient characteristics.

A focus on preventable medication-related harm has advantages with respect to improving quality, as it can result in greater tangible clinical benefits and better translation of research on medication safety into clinical practice. Strategies to improve medication safety, with better understanding of the nature of preventable medication-related harm, increase efficiency because they are more specific and are more readily implemented, because clinicians readily recognize their value *(26)*. Better understanding of the nature of preventable medication-related harm could also improve communication among practising clinicians on reducing or eliminating the risk of harm in specific populations or settings.

Moreover, a focus on preventable medication-related harm is patient-centred, targeting the system rather than the individual to improve clinical outcomes; reduces concern about punishment for errors if they are reported; reveals unintended results; and encourages learning from events to improve the process continually *(27)*. Measurement of preventable medication-related harm should be include measurement of its dimensions, such as severity, stages of the medication use process (prescribing, ordering, storage, dispensing, administering and monitoring) and classification of harm according to the five rights for medication safety (patient, drug, dose, route and time) and medication type, as these factors are useful in improving quality *(28)*.

A judgement on the preventability of medication-related harm should not, however, be rigid but dynamic and context-specific and be subjected to review every few years. Types of medication-related harm that are considered possibly or definitely non-preventable currently might be considered possibly or definitely preventable in the future if more advanced health and care technology and systems become available. Hence, a focus on preventability is a pragmatic approach that allows prioritization of funding and other resources to ensure tangible benefits in medication safety. Rigid judgements might result in missed opportunities for innovation and mitigation of medication-related harm in the long term.

Medicine being dispensed at a pharmacy, photo credit: WHO/Atul Loke

Methods

Overview

This report presents the findings of all eligible studies including those presented in previous systematic review of preventable medication-related harm (14) and the studies found in the search updates. This report also focuses on further analyses of studies conducted in LMICs. The methods used were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement for conducting and reporting systematic reviews (29) and the reporting checklist for Meta-analyses of Observational Studies (MOOSE) (30) and followed the standards outlined in the Cochrane handbook (31). The protocol of the original systematic review was registered in PROSPERO: CRD42020164156. Studies were coded as LMIC or HIC according to the World Bank classification (32).

Eligibility criteria

Studies included in the review met the following criteria:

- empirical quantitative observational (retrospective and prospective) or cross-sectional study design;

- reported data on the prevalence of preventable medication-related harm in medical-care settings (primary, secondary and tertiary care);

- published from January 2000 onwards, because the volume of published research on patient safety began to increase significantly from that date (33, 34), after publication of the reports "To err is human" in 1999 in the USA (11), "An organisation with a memory" in 2000 in the United Kingdom (35) and a number of reports on preventable iatrogenic harm (36);

- studies on any general population group in any country; and

- studies written in English.

Harms due to adverse drug events were included. In some studies, such events were referred to as "adverse drug reactions", even though reviewers agreed to use adverse drug event as overarching term. No specific criterion was established for preventability. It was anticipated that the method for assessing preventability would differ by study, and that the differences would probably affect the results. Medication-related harm was classified as preventable if it was possibly or definitely preventable according to standard scales including WHO scales (P method), Schumock and Thornton, Hallas, Bates or equivalent (51, 37, 38). Similarly, no formal assessment of causality between a drug and an event was necessary for eligibility. Although the prevalence of preventable medication-related harm was the primary outcome of interest, all measures of such harm were eligible, with secondary outcomes, including the distribution of causes of preventable medication-related harm (i.e., stage of the medication use process at which harm occurred, drug class) and evaluations of the severity of harm.

Following were excluded:

- case series, case reports, randomized controlled trials and qualitative studies with no reporting of prevalence;

- studies of incidents of patient harm not linked to the prevalence of medication-related harm;

- studies that provided data on total medication-related harm but not preventable medication-related harm;

- studies on any type of harm and not specifically medication-related harm;

- studies of harm in a specific population (e.g., patients with a specific condition); and

- studies conducted in community settings and care homes.

Searches

Five electronic bibliographic databases were searched: Medline/Pubmed, Cochrane library, CINAHL, Embase and PsycINFO. Several search terms were combined in two blocks representing "patient harm" and "observational study designs and systematic reviews". Searches were limited to papers published between 28 January 2020 (when the original searches were conducted) and 24 April 2022. The list of studies excluded from the original review was searched, and eligible studies were identified by screening relevant systematic reviews and checking the reference lists of eligible studies identified in the searches.

The original searches (conducted in 2019) were supplemented by screening conference abstracts and grey literature sources, including databases (WHOLIS, Google Scholar, SIGLE) and reports such as "The grey literature report" (http://www.greylit.org/) and the Agency for Healthcare Research and Quality Patient Safety Network (http://www.psnet.arhq.gov). Time constraints for the updated systematic review did not allow replication of the search in these complementary grey literature sources.

Study selection and data extraction

The search results from each database were combined in EndNote, and duplicate records were identified and removed. Screening was conducted according to the process outlined in the original review *(14)* in two stages.

Stage 1: Title and abstract screening

Titles and abstracts were independently screened by pairs of authors according to the eligibility criteria described above. The titles and abstracts of studies in LMICs that were excluded from the original review because the data were not available were also screened. The titles and abstracts of citations in the bibliographical lists from both searches were then obtained for full text screening.

Stage 2: Full text screening

Full texts were independently screened by pairs of authors. Any disagreements were discussed within the pairs and, when necessary, with the whole team.

A patient at a pharmacy, photo credit: WHO/Colin Cosier

For eligible studies, an MS Excel® template was used to record descriptive data on study characteristics (e.g., number and age of participants, research design, method of data collection, assessment of preventability) and quantitative outcomes (prevalence, stage of medication use, severity of preventable patient harm, drug class). Descriptive data were extracted and checked . Two independent researchers extracted data on prevalence and severity. Any disagreements were resolved by discussion. During the updating of the review, 10 of the authors of the original study were contacted, and missing data and/or confirmation of data were received from three.

Critical appraisal

The quality of the studies that were included was assessed on the Newcastle-Ottawa scale adapted for cross-sectional and cohort studies *(39)*. The studies in the original review were appraised independently by two researchers. Those identified in the new searches were also assessed independently. The Newcastle-Ottawa scale is used to assess the representativeness of the sample, its size, response rate, ascertainment of the exposure, control of confounding variables, assessment of preventability and the appropriateness of the statistical analysis, scored from 0 (lowest grade) to 10 (highest grade). A higher grade indicates a lower risk of bias. For our analyses, studies that scored 7 or higher were considered to have a low risk

of bias, whereas those that scored less than 7 were considered to have a high risk of bias.

Statistical methods and data analysis

To address the three aims of this review, the original meta-analyses – the main analyses, several sub-group analysis, meta-regressions and sensitivity analyses – had to be updated, adding more rigour to the original systematic review *(14)*.

The primary outcome was the pooled prevalence of preventable medication-related harm expressed as the percentage of patients with at least one such harm. The prevalence estimates were recalculated with the crude numerators and the denominators provided in the individual studies. Authors were contacted when data were not reported or unclear.

In the secondary analysis, different health care settings (i.e., general hospital/internal medicine, emergency department or intensive care unit (ICU), highly specialized or surgical unit, paediatric health, community health care and geriatric centres); severity (i.e., mild, moderate, severe/life-threatening), including death; stage of medication use process (i.e., prescribing, ordering, transcribing, dispensing, administering); drug classification (any system) and other factors, such as WHO region, patient age (≤18 years, 19–50 years, 51–80 years, > 80 years), gender (≥ 60% male, ≥ 60% female, mixed), health care system funding (private, social, mixed) and prevalence over time were included. The severity of preventable medication-related harm was classified into three categories as "mild", "moderate" and "severe" and analysed as a proportion of the identified harm. Deaths were included in the severe preventable harm category but were also analysed separately. Similarly, the stages of the medication use process and drug classes were also analysed as proportions of the identified harm.

Meta-regression and subgroup analyses were performed to investigate possible sources of heterogeneity in the aforementioned variables (preventable data available by drug class, sample size split using the median value study sample, age group (adults, children/adolescents), health care setting (as above), assessment method (medical record review, chart review or observation; survey, telephone, spontaneous report), standard method for assessing preventability (yes/no), length of study (less or more than 6 months) and design (prospective cohort, cross-sectional)) and sensitivity analysis for studies with a lower risk of bias (total score ≥ 7).

Heterogeneity, which refers to variation in prevalence rates among studies in each meta-analysis, was assessed and quantified with I^2 *(40)*. As is recommended in the Cochrane handbook, values of 25%, 50% and 75% for I^2 represent low, medium and high heterogeneity, respectively *(41)*. The presence of publication bias was assessed by inspection of funnel plots and Egger's test. All analyses were conducted with the statistical software R (v.3.2.2).

A doctor prescribing medicines, photo credit: WHO/Fernando G. Revilla

Results

Search results

The updated search of bibliographic databases identified 2321 records. After removal of 334 duplicates, the titles and abstracts of 1987 records were screened. A total of 1934 did not meet the eligibility criteria and were excluded. After a review of the full texts of the remaining 53 records, an additional 38 were excluded. The studies were excluded because: they focused on a specific population *(13)*, did not have useable data on preventable harm *(13)*, reported on adverse events *(7)* and for other reasons *(5)*.

By re-examining the studies excluded from the previous review, 325 studies were identified, and 317 were screened after removal of duplicates. After exclusion of 292 citations, 25 full-text records were reviewed; of these, 11 were excluded because they focused on adverse events, 5 because they provided no useable data on preventable harm, 2 that focused on a disease-specific population and 3 for other reasons. Thus, 4 studies met the eligibility criteria for inclusion, with additional data obtained from the authors.

Studies included

In total, 100 studies were included in the updated review. They included 81 studies from the original review and 19 from the updated searches (15 from bibliographic databases and 4 from the list of studies excluded from the previous review).

Characteristics of the studies

In total, 30 studies were carried out in LMICs and 70 in HICs. The numbers of studies conducted in the WHO regions were: Europe *(33)*, Americas *(23)*, South-East Asia *(15)*, Western Pacific *(14)*, Eastern Mediterranean

(8) and Africa *(7)*. The breakdown by country is shown in Fig. 1. The median number of patient incidents (sample size) in all the studies was 1147 (spread of the middle half of the distribution, inter-quartile range [IQR]: 516–3473 patients).

Most studies were conducted in a general hospital or internal medicine setting *(34)*, followed by paediatrics *(15)*, highly specialized or surgery *(15)*; emergency medicine *(14)*; elderly care *(9)*; ICU *(7)*; primary care *(5)* and psychiatric care *(1)* (Fig. 1). A total of 45 studies were set in public health care systems, 28 were in private health care systems, and 9 in a mixture of public and private health care systems; the type of funding of the health care system was not reported in 18 studies. Most studies *(59)* were less than 6 months in duration, while 41 had a duration of > 6 months.

Fig. 1. *Health care settings of the studies in this systematic review*

- Psychiatric
- Elderly
- Emergency departmen
- General hospital or internal medicine
- Highly specialised care or surgical
- ICU
- Paediatric
- Primary care
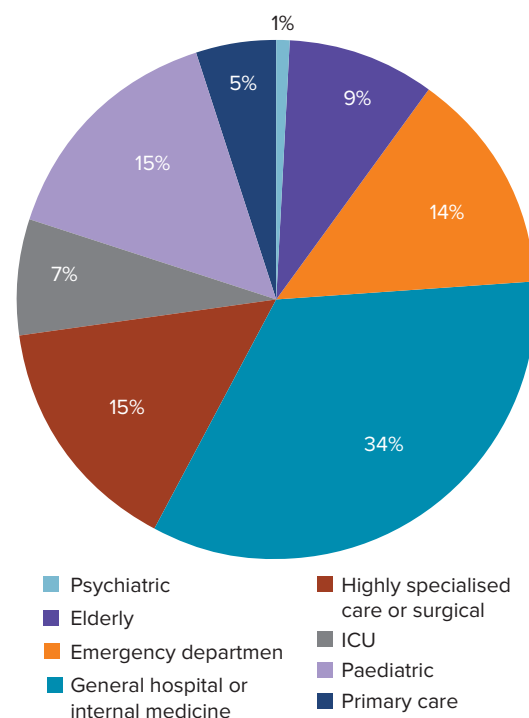
Of the 100 studies included, 69 had a cross-sectional design and 31 a prospective cohort design. Most assessed medication-related harm from medical record reviews or observations (70), while the remainder used survey, telephone or spontaneous reporting surveillance systems (30). Most of the studies assessed preventability on a standard scale (60), including the Schumock and Thornton, Hallas, Bates and WHO scales. Other authors used a non-standard scale, and the remainder did not report the scale used. Sixty-nine studies reported the system used to classify severity, the most common being those of Hartwig and Siegal (22), Bates (12) and WHO (8); 15 used other systems, while 12 considered classification of severity unnecessary, and the remaining 31 studies did not include information on the classification system used. Only 39 of the studies reported medication-related harm by drug classification, which were grouped according to the international Anatomical Therapeutic Chemical (ATC) system.

Characteristics of studies in LMICs

Half of the 30 studies conducted in LMICs were conducted in the South-East Asian Region (15), followed by the African Region (7), the Eastern Mediterranean Region (7) and the Region of the Americas (1). The median sample size in these studies was 949 patients (IQR: 430–1239), whereas that in studies in HICs was 1105 patients (IQR: 509–3487).

In total, 19 studies lasted 6 months or less, and 11 studies were longer than 6 months. A prospective cohort design was used in 21 studies and a cross-sectional design in 9; 14 were conducted in a general hospital or internal medicine setting, 4 in a highly specialised or surgery ward and 3 each in paediatrics, emergency medicine, elderly care settings and ICUs. No studies were conducted in primary or psychiatric care in LMICs. Most of the studies assessed medication-related harm from medical record reviews or observations (18) and the remainder by survey, telephone or spontaneous reporting surveillance systems (12).

Preventability was assessed on a standard scale in most studies (25) and on a non-standard scale in 5; 24 studies reported harm by drug classification, whereas 6 did not.

Characteristics of the populations

Age: The median age of patients in all the studies was 60 years (IQR: 45–67 years; range: 1–87 years). Most studies (14) included patients aged 51–80 years, and fewer studies included patients aged < 18 (9) and > 80 years (7); 23 studies did not report data on age.

Of the studies in LMICs, 2 involved patients aged < 19 years, 11 studies involved patients aged 19–50 years, and 9 involved patients aged 51–80 years; data on age was not reported in 8 studies. In the studies in HICs, 7 involved patients aged < 19 years, 6 involved patients aged 19–50 years, 35 involved patients aged 51–80 years, 7 involved patients aged > 80 years, and 15 did not report ages.

Gender: Most of the studies involved both genders (62). Sixteen studies involved ≥ 60% females, and 11 studies involved ≥ 60% males. Eleven studies did not report data on gender. In studies in LMICs, 19 involved both genders, 7 involved ≥ 60% males, and only 1 involved more females than females; 3 studies did not report data on gender. In the studies in HIC, 43 involved both genders, 15 involved mostly females, 4 involved mostly males and 8 did not report the gender of the participants.

Quality of the methods used

The methodological appraisal showed that most of the studies (33; 33%) had a high risk of bias; 62 studies (62%) had a low risk. The median Newcastle-Ottawa score for all the studies was 7 (range, 2–10). Sensitivity analyses showed no significant differences between all studies at low and high risk of bias (P = 0.222) and between all studies in LMICs at low and high risk of bias (P = 0.445).

Meta-analysis

A total of 41 040 patients with medication-related harm were reported (median, 109; IQR, 56–256), one fourth of whom experienced preventable medication-related harm (n=10 237 patients; median, 42; IQR, 20–92).

Prevalence of preventable and all medication-related harm by income level, WHO region and medical setting

Preventable medication-related harm

The meta-analysis of the 100 studies showed that the overall prevalence of preventable medication-related harm was 5% (1 in 20 patients receiving health care; 95% confidence interval [CI]: 4–6%); 10 237 patients with preventable medication-rlated harm/487 162 total patients).

The prevalence of preventable medication-related harm in the 30 studies in LMICs was 7% (7 in 100 patients) (95% CI 3–12%, I^2 =99%; 1767 patients with harm/43 967 total patients) (Fig. 2). The prevalence in the 70 studies in HIC was 4% (1 in 25 patients) (95% CI 3–5%, I^2 = 100%; 8470 patients with harm/443 195 total patients) (Fig. 3). The test for differences between LMICs and HICs was statistically significant (P = 0.046). The high level of hetergenity was assessed in several subgroup analysis and formal meta-regressions.

Fig. 2. *Results of the meta-analysis of the prevalence of preventable medication-related harm in LMICs*

Study	Events	Total	Events per 100 observations	Prevalence, %	95% CI	Weight
Adedapo 2021	42	1280		3.28	[2.37; 4.41]	3.4%
Alam 2014	40	1105		3.62	[2.60; 4.90]	3.4%
Alam 2020	21	316		6.65	[4.16; 9.98]	3.3%
Aljadhey 2013	20	977		2.05	[1.25; 3.14]	3.4%
Alsbou 2010	8	200		4.00	[1.74; 7.73]	3.3%
Alsbou 2015	16	2000		0.80	[0.46; 1.30]	3.4%
Baniasadi 2008	22	6840		0.32	[0.20; 0.49]	3.4%
Benkirane 2009a	8	1390		0.58	[0.25; 1.13]	3.4%
Benkirane 2009b	24	696		3.45	[2.22; 5.09]	3.3%
Calderon–Ospina 2010	13	104		12.50	[6.83; 20.43]	3.2%
Chanie Eshetie 2015	15	634		2.37	[1.33; 3.87]	3.3%
Dedefo 2016	8	233		3.43	[1.49; 6.65]	3.3%
Devi 2012	68	595		11.43	[8.98; 14.26]	3.3%
Geer 2016	279	5482		5.09	[4.52; 5.70]	3.4%
Haile 2013	60	1033		5.81	[4.46; 7.41]	3.4%
Harugeri 2011	143	920		15.54	[13.26; 18.05]	3.3%
Kemal 2022	109	423		25.77	[21.66; 30.21]	3.3%
Kurian 2016	2	1082		0.18	[0.02; 0.67]	3.4%
Mandavi 2012	114	4005		2.85	[2.35; 3.41]	3.4%
May L 2020	25	160		15.62	[10.37; 22.20]	3.3%
Mouton 2021	24	998		2.40	[1.55; 3.56]	3.4%
Patel 2007	158	6899		2.29	[1.95; 2.67]	3.4%
Pourseyed 2009	24	400		6.00	[3.88; 8.80]	3.3%
Reeja 2021	28	450		6.22	[4.17; 8.87]	3.3%
Remesh 2014	50	550		9.09	[6.82; 11.81]	3.3%
Sahilu 2020	53	319		16.61	[12.70; 21.16]	3.3%
Sahoo 2022	212	236		89.83	[85.25; 93.37]	3.3%
Sharma 2020	32	1000		3.20	[2.20; 4.49]	3.4%
Sriram 2011	20	3117		0.64	[0.39; 0.99]	3.4%
Yadesa 2021	129	523		24.67	[21.03; 28.59]	3.3%
Random effects model		**43967**		**6.93**	**[3.41; 11.55]**	**100.0%**

Heterogeneity: I^2 = 99% [99%; 99%], τ^2 = 0.05, p = 0

20 40 60 80

Fig. 3. *Results of the meta-analysis of the prevalence of preventable medication-related harms in HIC*

Study	Events	Total	Events per 100 observations	Prevalence, %	95% CI	Weight
Ahern 2014	43	1258		3.42	[2.48; 4.58]	1.4%
Alghamdi 2022	27	302		8.94	[5.97; 12.74]	1.4%
Al–Tajir 2005	92	5235		1.76	[1.42; 2.15]	1.4%
Ayani 2016	50	1234		4.05	[3.02; 5.31]	1.4%
Bernad–Laribiere 2015	47	2692		1.75	[1.29; 2.31]	1.4%
Brown 2022	68	936		7.26	[5.69; 9.12]	1.4%
Buckley 2007	7	357		1.96	[0.79; 4.00]	1.4%
Carayon 2014	38	1805		2.11	[1.49; 2.88]	1.4%
Castro 2013	157	588		26.70	[23.16; 30.47]	1.4%
Chan 2001	56	240		23.33	[18.13; 29.20]	1.4%
Chen 2012	332	58569		0.57	[0.51; 0.63]	1.5%
Damen 2017	53	8071		0.66	[0.49; 0.86]	1.5%
Davies 2009	291	3695		7.88	[7.03; 8.79]	1.4%
Davies 2010	34	290		11.72	[8.26; 16.00]	1.4%
de Boer 2013	20	567		3.53	[2.17; 5.40]	1.4%
Dequito 2011	42	609		6.90	[5.02; 9.21]	1.4%
Easton 2003	4	16187		0.02	[0.01; 0.06]	1.5%
Farcas 2010	9	1854		0.49	[0.22; 0.92]	1.4%
Farcas 2014	90	6605		1.36	[1.10; 1.67]	1.5%
Forster 2004	14	543		2.58	[1.42; 4.29]	1.4%
Forster 2005	12	400		3.00	[1.56; 5.18]	1.4%
Franceschi 2008	78	1756		4.44	[3.53; 5.51]	1.4%
Gallagher 2012	41	6821		0.60	[0.43; 0.81]	1.5%
Gandhi 2003	18	661		2.72	[1.62; 4.27]	1.4%
Garrido–Corro 2021	74	99797		0.07	[0.06; 0.09]	1.5%
Grenouillet–Delacre 2007	53	405		13.09	[9.96; 16.77]	1.4%
Gurwitz 2000	421	27617		1.52	[1.38; 1.68]	1.5%
Gurwitz 2003	276	2916		9.47	[8.43; 10.59]	1.4%
Gurwitz 2005	338	1247		27.11	[24.65; 29.66]	1.4%
Hamilton 2011	73	600		12.17	[9.66; 15.05]	1.4%
Hardmeier 2004	28	6383		0.44	[0.29; 0.63]	1.5%
Harkanen 2015	51	463		11.02	[8.31; 14.23]	1.4%
Honhout 2010	45	7926		0.57	[0.41; 0.76]	1.5%
Howard 2003	178	4093		4.35	[3.74; 5.02]	1.4%
Hug 2010	106	1200		8.83	[7.29; 10.58]	1.4%
Iwasaki 2021	31	907		3.42	[2.33; 4.82]	1.4%
Jha 2001	21	3238		0.65	[0.40; 0.99]	1.4%
Jonsson 2010	15	1574		0.95	[0.53; 1.57]	1.4%
Kaushal 2001	5	10778		0.05	[0.02; 0.11]	1.5%
Kaushal 2007	56	1788		3.13	[2.37; 4.05]	1.4%
Khan 2021	7	8912		0.08	[0.03; 0.16]	1.5%
Klopotowska 2013	37	250		14.80	[10.64; 19.82]	1.4%
Kopp 2006	22	185		11.89	[7.60; 17.45]	1.3%
Kunac 2009	6	495		1.21	[0.45; 2.62]	1.4%
Lagnaoui 2000	93	444		20.95	[17.25; 25.03]	1.4%
Laroche 2013	32	1332		2.40	[1.65; 3.37]	1.4%
Leitch 2021	229	9076		2.52	[2.21; 2.87]	1.5%
Li 2021	439	5521		7.95	[7.25; 8.70]	1.4%
Ligi 2008	4	388		1.03	[0.28; 2.62]	1.4%
Lombardi 2020	1436	61855		2.32	[2.20; 2.44]	1.5%
López 2009	190	2582		7.36	[6.38; 8.43]	1.4%
Lovborg 2012	96	7322		1.31	[1.06; 1.60]	1.5%
Meier 2015	227	2262		10.04	[8.83; 11.35]	1.4%
Miller 2006	75	8215		0.91	[0.72; 1.14]	1.5%
Morimoto 2011	101	3459		2.92	[2.38; 3.54]	1.4%
Olivier 2002	14	671		2.09	[1.15; 3.48]	1.4%
Park 2013	10	346		2.89	[1.39; 5.25]	1.4%
Peyriere 2003	19	156		12.18	[7.49; 18.36]	1.3%
Phillips 2014	25	370		6.76	[4.42; 9.81]	1.4%
Pirmohamed 2004	882	18820		4.69	[4.39; 5.00]	1.5%
Rothschild 2007	25	1871		1.34	[0.87; 1.97]	1.4%
Sakuma 2014	18	1189		1.51	[0.90; 2.38]	1.4%
Schade 2006	29	1011		2.87	[1.93; 4.09]	1.4%
Senst 2001	11	3187		0.35	[0.17; 0.62]	1.4%
Takata 2008	16	960		1.67	[0.96; 2.69]	1.4%
Tangiisuran 2012	51	560		9.11	[6.86; 11.80]	1.4%
Van der Hooft 2008	35	3515		1.00	[0.69; 1.38]	1.4%
Woo 2020	809	3328		24.31	[22.86; 25.80]	1.4%
Zandieh 2008	55	1689		3.26	[2.46; 4.22]	1.4%
Zed 2008	83	1017		8.16	[6.55; 10.02]	1.4%
Random effects model		**443195**		**4.14**	**[3.01; 5.44]**	**100.0%**

Heterogeneity: I^2 = 100% [99%; 100%], τ^2 = 0.02, p = 0

5   10   15   20   25   30

The WHO regions with the highest prevalence of preventable medication-related harms were the African Region (9%, 95% CI 3–18%; 380 patients with preventable medication-related harm/4410 total patients; 7 studies) and the South-East Asian Region (9%, 95% CI 2–18%; 1252 patients with preventable medication-related harm/26 950 total patients; 15 studies) (Fig. 4). The prevalence of preventable medication-related harm was low in the Eastern Mediterranean Region, but this is probably an underestimate, as the methods used in these studies were potentially less sensitive in capturing this harm (e.g., case note reviews were not used in 7 of the 8 studies, although this is considered the most robust method for assessing medication-related harm).
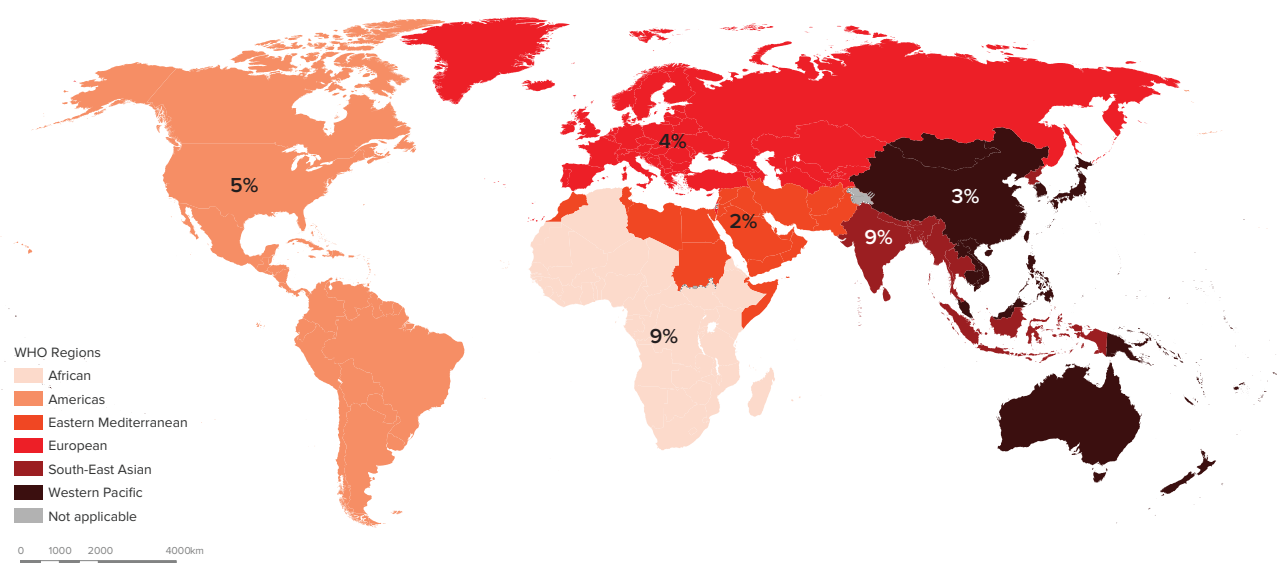
Overall, the highest estimated prevalence of preventable medication-related harm was observed in geriatric care units (17%, 95% CI 4–35%, 9 studies, 1009 patients with preventable medication-related harm/11 492 total patients), highly specialized or surgical care (9%, 95% CI 5–14%, 15 studies, 1200/16 259), ICUs (7%, 95% CI 4–11%, 7 studies, 172 patients with preventable medication-related harm/2438 total patients) and emergency departments (6%, 3 in 50 patients, 95% CI 3–10%, 14 studies, 3693 patients with preventable medication-related harm/145 440 total patients).

The prevalence of preventable medication-related harm in LMICs was highest in highly specialized or surgical care (13%, 95% CI 4–26%, 4 studies, 3605 patients with preventable medication-related harm/16 259 total patients) and geriatric care units (11%, 95% CI 2–25%, 3 studies, 2144 patients with preventable medication-related harm/11 492 total patients).

All medication-related harm (preventable and non-preventable)

The overall prevalence of all medication-related harm was 12% (3 in 25 patients, 95% CI 10–15%, 41 040 patients with medication-related harm/487 162 total patients]. The prevalence of medication-related harm in the 30 studies in LMICs was 14% (7 in 50 patients, 95% CI 8–21%, 3375 patients with medication-related harm/43 967 total patients), and the prevalence in the 70 studies in HICs was 12% (3 in 25 patients, 95% CI 9–15%, 37 665 patients with medication-related harm/443 195 total patients). The highest prevalence of medication-related harms was found in the African Region (17%, 95% CI 7–30%, 684 patients with medication-related harm/4410 total patients, 7 studies) and the South-East Asian Region (16%, 4 in 25 patients, 95% CI 6–31%, 2284 patients with medication-related harm/26 950 total patients, 15 studies).

Fig. 4. *Prevalence of preventable medication-related harm by WHO region*

A patient taking medicines, photo credit: WHO/Eduardo Martino

The estimated prevalence of medication-related harm was highest in geriatric care units (33%, 95% CI 12–58%, 9 studies, 2144 patients with medication-related harm/11 492 total patients) and highly specialized or surgical care (24%, 6 in 25 patients, 95% CI 16–32%, 15 studies, 3605 patients with medication-related harm/16 259 total patients).

Severity of preventable medication-related harm, including harm resulting in death

Preventable medication-related harm

Of all preventable medication-related harm, 38% was mild (95% CI 26–50%, median 38% (IQR 18–52%), 23 studies, 934 mild preventable medication-related harm/3220 total preventable medication-related harm), 44% was moderate (95% CI 34–53%, median 41% (IQR 28–58%), 26 studies, 1601 moderate preventable medication-related harms/3320 total preventable medication-related harm), and 23% was severe or potentially life-threatening (95% CI 17–30%, median 20% (IQR 9–33%), 28 studies, 911 severe preventable medication-related harm/3618 total preventable medication-related harm).

In the six studies in LMICs that reported clinical severity, 24% of preventable harm was mild (95% CI 2–46%, 3 studies, I² = 99%, 58 mild preventable medication-related harm/996 total preventable medication-related harm), 60% was moderate (95% CI 43–77%, 4 studies, I² = 93%, 661 moderate preventable medication-related harm/1027 total preventable harm), and 14% was severe or potentially life-threatening (95% CI 1–27%, 6 studies, I² = 96%, 308 severe preventable medication-related harm/1094 total preventable medication-related harm). Due to few studies reporting severity of preventable medication relate harm in LMICs it was not possible to perform subgroup analysis or meta-regressions to assess for the large amount of hetergenity present.

All medication-related harm (preventable and non-preventable)

Of all harm, 47% was mild (95% CI 40–54%, median 47% (IQR 28–64%), 62 studies, 7948 mild medication-related harm/14 941 total medication-related harm), 42% was moderate (95% CI 36–47%, median 37% (IQR 24–54%), 69 studies, 6586 moderate medication-related harm/17 041 total medication-related harm), and 15% was severe or potentially life-threatening (95% CI 7–33%, median 10% (IQR 6–20%), 70 studies,

2862 severe medication-related harm/19 529 total medication-related harm).

In the studies in LMICs, 40% of all harm was mild (95% CI 23–57%, 14 studies, 1091 mild medication-related harm/2587 total medication-related harm), 42% was moderate (95% CI 30–55%, 14 studies, 1712 moderate medication-related harm/3456 total medication-related harm), and 17% was severe or potentially life-threatening (95% CI 11–24%, 13 studies, 651 severe medication-related harm/3438 total medication-related harm).

Deaths

The proportion of deaths due to all medication-related harm was not statistically significantly different in LMICs (0%, 95% CI 0–1%, 16 studies, 88 deaths/20 464 total medication-related harm) and HIC (0%, 95% CI 0–1%, 29 studies, 67 deaths/564 401 total medication-related harm). The mortality rates calculated from

the exact total number of patients and deaths due to medication-related harm were 4.3 per 1000 patients in LMICs and 0.12 per 1000 patients in HICs but these rates do not account for the effect of specific country/region, age, sex and timeframe.

Stages of medication use process at which medication-related harm occurs

The highest proportions of medication-related harm occurred at the stages of "ordering/prescribing" (53%, 95% CI 42–65%, median 49% (IQR 32-74%), 19 studies, 982 medication-related harm/2098 total medication-related harm) and "monitoring/reporting" (36%, 95% CI 19–59%, median 36% (IQR 20-69%), 11 studies, 676 medication-related harm/1912 total medication-related harm). The box plot displaying the distributions of medication-related harm at each stage is present in

Fig. 5. *Boxplot of the distribution of stages of reporting medication-related harms with medians*
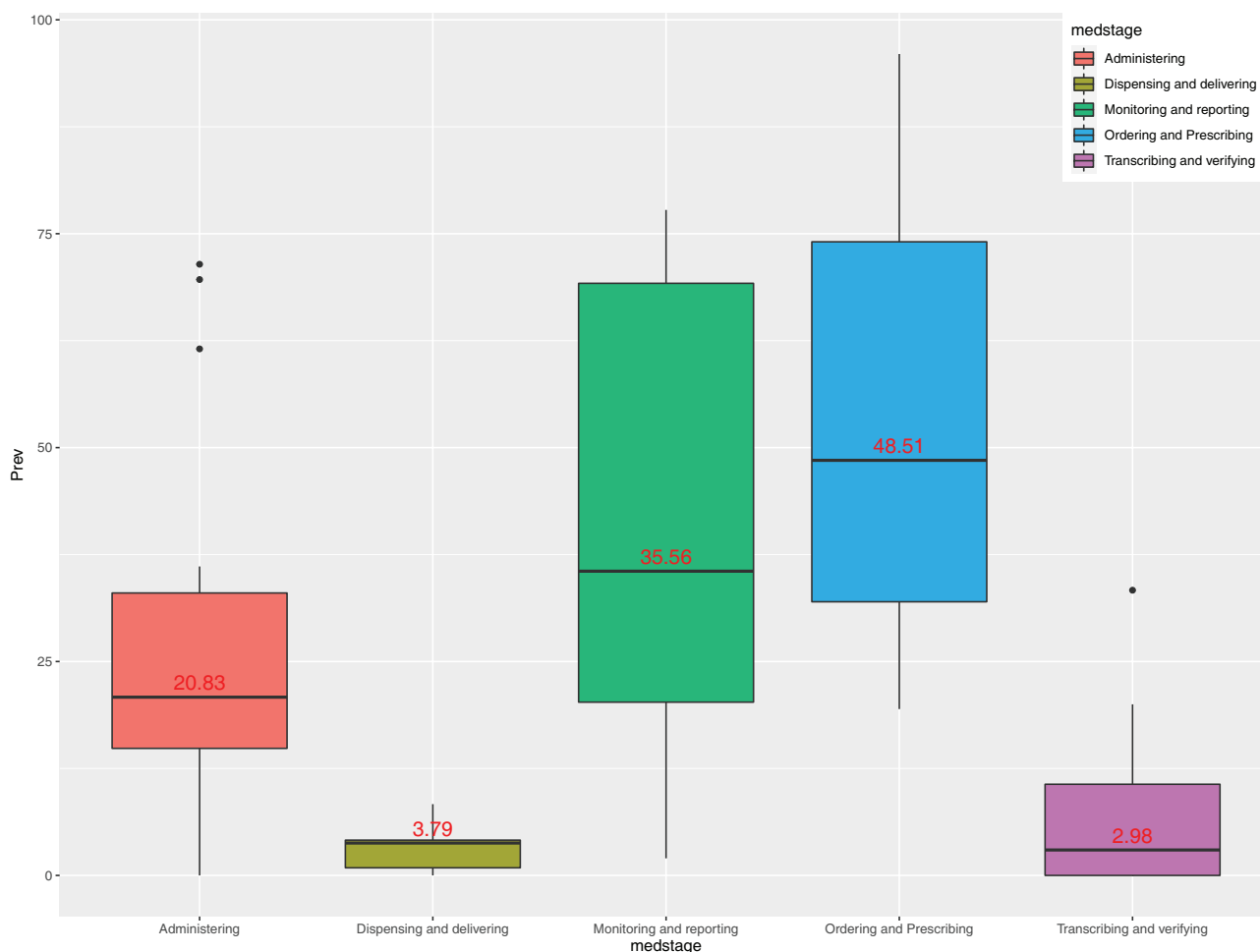
Table 1. *Stages of medication use at which most medication-related harm occurs*

Stage of medication	No. of studies	Prevalence (%)	95% confidence interval	
			Lower bound	Upper bound
All studies				
Ordering/prescribing	19	53.24	41.52	64.62
Transcribing and verifying	10	6.81	2.87	15.33
Administering	17	22.15	13.38	34.40
Monitoring and reporting	11	36.43	18.51	59.11
Dispensing and delivering	6	4.24	2.03	8.65
LMICs				
Ordering/prescribing	4	78.36	48.90	93.20
Transcribing and verifying	4	8.31	1.91	29.61
Administering	4	21.43	6.16	53.14
Monitoring and reporting	1	11.90	5.04	25.59
Dispensing and delivering	2	4.08	1.02	14.91
HICs				
Ordering/prescribing	15	47.00	36.04	58.26
Transcribing and verifying	6	5.63	1.76	16.53
Administering	13	22.14	12.24	36.71
Monitoring and reporting	10	39.66	19.89	63.50
Dispensing and delivering	4	4.30	1.79	9.97

Fig. 5. In LMICs, the highest proportion of medication-related harm occurred at the stages of "ordering/ prescribing" (78%, 95% CI 49–93%). Similarly in HICs, the highest proportion of medication-related harm occurred at the stages of "ordering/prescribing" (47%, 95% CI 36–58%) (Table 1).

A health worker giving medicines, photo credit: WHO/Eduardo Martino

Main drug classes associated with medication-related harm

Antibacterial medicines accounted for the largest proportion of medication-related harm (ATC code J01) (20%, 95% CI 12–30%) (Table 2), and the proportions were above 10% in a meta-analysis of more than two studies in the ATC medication groups "antipsychotics" (N05A; 19%, 95% CI 4–41%), "central nervous system" (code N; 16%, 95% CI 10–24%), "cardiovascular" (code C; 15%, 95% CI 10–20%), drugs for "functional gastrointestinal disorders" (code A03; 14%, 95% CI 6–26%), "endocrine therapy" (code L02; 14%, 95% CI 4–29%), "hypnotics and sedatives" (code N05C; 13%, 95% CI 8–18%) and "non-steroidal anti-inflammatory products" (code M01A; 11%, 95% CI 6–18%). The proportions were below 5% for "antiviral drugs" (code J05; 5%, 95% CI 2–8%), "antiepileptics" (code N03A; 3%, 95% CI 1–7%), "immunosuppressant" (code L04; 3%, 95% CI 0–8%), "musculoskeletal" (code M09A; 5%, 95% CI 3–7%) and "respiratory therapeutics" (code R07; 3%, 95% CI 1–5%).

Table 2. *Proportions of medication-related harm by ATC drug classification in all studies*

Drug class	ATC code	No. of studies	Prevalence (%)	95% CI		I²
				Lower bound	Upper bound	
Gastrointestinal disorder	A03	9	14.30	5.84	25.51	97.40
Insulins and analogues	A10	9	8.77	3.38	16.03	92.10
Vitamins	A11	2	5.20	3.86	6.73	0
Blood disorders	B	5	7.62	3.98	12.24	70
Anticoagulants	B01	13	8.96	5.19	13.53	80.90
Cardiovascular	C	25	14.53	9.99	19.71	93.80
Diuretics	C03	7	5.93	1.61	12.32	93.80
Beta-blocking agent	C07	2	4.33	2.52	6.53	0
Herbal remedies	DDD	1	5.80	1.27	12.79	NA
Corticosteroids	H02A	7	7.97	1.54	17.98	91.80
Antibacterials[a]	J01	24	20.23	11.89	30.02	96.40
Antiviral drugs	J05	7	4.63	2.14	7.83	27.80
Vaccines	J07	2	0.44	0.00	2.28	41.20
Antineoplastic agents	L01	2	2.38	0.28	5.95	32.30
Endocrine therapy	L02	2	14.10	3.84	29.17	92
Immunosuppressants	L04	4	3.34	0.46	8.01	59.20
Non-steroidal anti-inflammatory	M01A	11	11.16	5.70	18.01	89.50
Musculoskeletal	M09A	10	4.99	2.96	7.46	67.90
Nervous system[b]	N	14	16.35	10.03	23.78	94
Anaesthetics	N01	1	5.56	0.10	16.02	NA
Analgesics	N02	8	6.57	2.40	12.27	76.90
Opioids	N02A	8	6.68	3.62	10.48	74.50
Anticonvulsants	N03	1	18.75	10.01	29.34	NA
Antiepileptics	N03A	5	3.40	1.12	6.52	0
Antipsychotics	N05A	6	19.17	4.30	40.72	96.40
Anxiolytics	N05B	1	10.64	3.14	21.33	NA
Hypnotics and sedatives	N05C	8	12.54	8.15	17.62	75.40
Antidepressants	N06A	6	6.61	1.97	13.38	92.50
Respiratory therapeutics	R07	10	2.76	0.91	5.39	88.50

NA, not available

[a] In antibacterial medication-related harm, the most harm was associated with amoxicillin, with 137 cases in four studies. Four cases were associated with penicillin in two studies.

[b] This category is not the sum of the N01 to N06A. As the lower drug classification for nervous system drugs (N01-N06A) was not reported within the individual studies, wepooled them at the highest ATC level which was reported (N) across 16 studies.

Table 3. Proportions of medication-related harm by ATC drug classification in studies in LMICs

Drug class [a]	No. of studies	Prevalence (%)	95% CI	
			Lower bound	Upper bound
Insulins and analogues	6	8.77	3.55	20.05
Vitamins	2	5.52	4.25	7.14
Anticoagulants	4	7.89	2.38	23.18
Cardiovascular	9	13.16	6.01	26.42
Herbal remedies	1	5.80	2.19	14.45
Antibacterial	11	24.22	12.42	41.87
Antiviral drugs	5	5.81	2.96	11.12
Antineoplastic agents	2	2.73	0.95	7.60
Non-steroidal anti-inflammatory	7	8.77	4.26	17.20
Analgesics	5	6.12	3.04	11.92
Antiepileptics	2	2.67	0.77	8.79
Nervous system	4	9.48	4.17	20.12
Hypnotics and sedatives	2	7.18	5.12	9.98
Gastrointestinal disorder	4	14.76	7.41	27.26
Vaccines	2	0.66	0.19	2.26
Antipsychotics	3	17.33	2.04	67.80
Diuretics	2	8.75	6.46	11.76
Corticosteroids	3	19.51	8.81	37.81
Musculoskeletal	5	3.29	2.25	4.79
Anxiolytics	1	10.64	4.50	23.13
Antidepressants	2	7.63	2.00	25.03
Opioids	3	8.00	3.90	15.71
Immunosuppressants	3	4.12	1.04	14.89
Anticonvulsants	1	18.75	10.97	30.18
Blood disorders	5	7.86	4.59	13.13
Beta blocking agent	1	4.74	3.08	7.23
Respiratory therapeutics	4	2.31	0.87	5.96
Endocrine therapy	1	21.55	15.00	29.96

[a] The ATC codes for each drug class are listed in Table 2.

LMICs

In the studies in LMICs, antibacterial medicines also accounted for the largest proportion of medication-related harm (24%, 95% CI 12–42%) (Table 3). Corticosteroids (20%, 95% CI 9–38%), antipsychotics (17%, 95% CI 2–68%), drugs for "functional gastrointestinal disorders" (15%, 95% CI 7–27%) and cardiovascular drugs (13%, 95% CI 6–26%) were associated with 10% or more of preventable medication-related harm.

The studies in HICs showed a larger proportion of medication-related harm associated with non-steroidal anti-inflammatory drugs (20%, 95% CI 13–29%, 4 studies), nervous system drugs (18%, 95% CI 10–30%, 10 studies), analgesics (17%, 95% CI 13–22%, 3 studies), hypnotics and sedatives (17%, 95% CI

*A health worker at a hospital, photo credit: WHO/Colin Cosier*

14–20%, 6 studies), antipsychotics (14%, 95% CI 2-51%, 3 studies) and antibacterials (13%, 95% CI 6-24%, 13 studies).

Prevalence by study period

The highest prevalence of preventable medication-related harm was observed between 2020 and 2022 (5.9%, 95% CI 2.4–13.8%, 19 studies) and the lowest between 2000 and 2004 (1.8%, 95% CI 0.7–5.0%, 15

studies). Fig. 6 shows the prevalence of preventable medication-related harm at various times, which indicates an increase in the prevalence of medication-related harm after 2017. The reasons for this increase is hard to ascertain but the launching ofthe third WHO Global Patient Safety Challenge: *Medication Without Harm* might have led to better reporting of medication-related harm with increased interest and prominence.

Fig. 6. Prevalence of medication-related harm, 2020–2022

Prevalence over time (year-by-year)
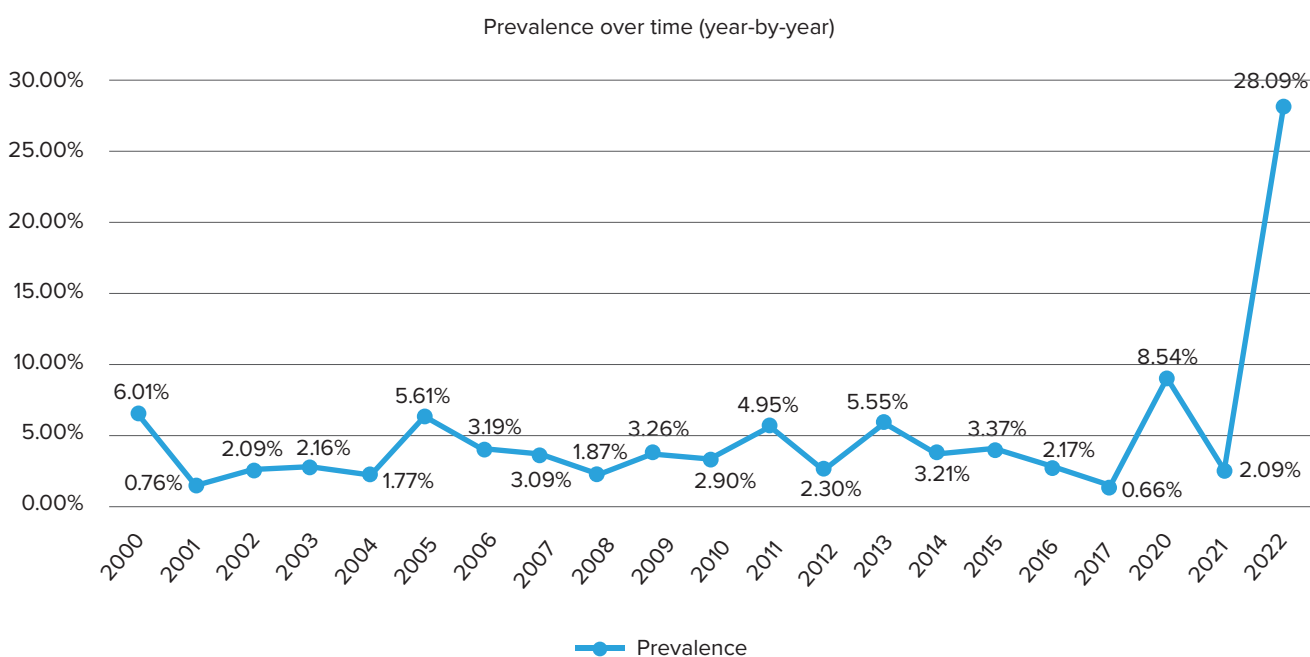
Populations, locations and medical settings most vulnerable to preventable medication-related harm

The prevalence of preventable medication-related harm was highest in patients aged > 80 years (9%, 95% CI 3–17%, 7 studies) and lowest in patients aged < 19 (0.9%, 95% CI 0.9–4%, 9 studies). No significant difference in preventable medication-related harm was observed by gender (female: 4.7%, 95% CI 2.3–7.8%, 16 studies; male: 5.1%, 95% CI 0.1–17.6%, 11 studies). While in LMICs the rate was 2% (95% CI 1–3%) in females in one study and 9% (95% CI 0–34%) in males in seven studies, the evidence for females is based on only one study. In HICs, the rate of preventable medication-related harm was higher in females than males (females: 5%, 95% CI 2–8%, 15 studies; males: 1%, 95% CI 0–2%, 4 studies).

Univariable meta-regression analyses of all 100 studies showed that the prevalence of preventable medication-related harm was lower in studies with smaller samples (≤1147 patients; b=–0.61, 95% CI, –0.08; –0.04), studies of children and adolescents (b = –0.03, 95% CI –0.05; –0.01) and studies conducted by survey, telephone or spontaneous reporting (surveillance) systems (b=–0.03; 95% CI –0.05; –0.01). Geriatric care (b=0.03, 95% CI 0.00; 0.06), emergency medicine (b = 0.05, 95% CI –0.01; 0.10, P = 0.078), highly specialized or surgical care (b=0.07, 95% CI 0.04; 0.10) and ICUs (b = 0.07, 95% CI 0.04; 0.11) were associated with significantly higher levels of preventable medication-related harm than general hospitals or internal medicine. The four variables sample size, age group, health care setting and assessment method were therefore considered eligible for inclusion in the multivariable regression analysis.

In the multivariable meta-regression model, all three variables remained statistically significant. A lower prevalence of preventable medication-related harm was seen in studies with small samples (b=–0.04, 95% CI –0.07; –0.02) and those in which medication-related harm was assessed by survey, telephone or spontaneous reporting (b=–0.02, 95% CI –0.04; –0.00), while a higher prevalence was seen in highly specialized or surgical care (b = 0.05, 95% CI 0.01; 0.08) and ICU (b = 0.05, 95% CI 0.01; 0.08).

A pharmacist at an outpatient clinic, photo credit: WHO/ David Orr

LMICs

Univariable analyses of studies in LMICs showed that the prevalence of preventable medication-related harm was lower in studies with smaller samples (b=–0.20, 95% CI –0.27; –0.12) and in studies in which harm was assessed by survey, telephone or spontaneous reporting (b=–0.11, 95% CI –0.21; –0.01). Geriatric care (b=0.13, 95% CI –0.01; 0.28, P = 0.076) and highly specialized or surgical care (b=0.19, 95% CI 0.06; 0.32) were associated with significantly higher levels of preventable harm than care in general hospitals and internal medicine.

In the multivariable model, all three variables were statistically significantly associated with a lower prevalence of preventable medication-related harm in studies with small samples (b=–0.17, 95% CI –0.24; –0.11), in paediatric care (b=–0.17, 95% CI –0.26; –0.08) and in studies in which medication-related harm was assessed by survey, telephone or spontaneous reporting (b=–0.10, 95% CI –0.16; –0.04).

Publication bias

Publication bias was indicated by visual inspection of the funnel plots (see annex 1) and the Egger regression test for the effects of small study bias on all of the studies and only LMIC studies reporting preventable medication-related harms data. The funnel plot for all studies displayed no symmetry which was supported in eggers regression test (bias coefficient, 8.87, 95% CI 8.48; 9.27, P<0.0001). Evidence of publication bias was also found in the meta-analysis involving only studies from LMICs (Egger regression test, 7.60, 95% CI 6.74; 8.46, P<0.0001).

Discussion

Summary of main findings

This large systematic review and meta-analysis of 100 studies answers a number of questions.

How common is preventable medication-related harm in health care? 5% of patients (1 in 20) experience preventable medication-related harm in health care services.

How common is preventable medication-related harm in low- and middle-income countries? Preventable medication-related harm occurs in 7% of patients living in LMICs and in 4% of those living in HICs. Thus, patients in LMICs may be almost twice as likely to experience such harm as patients in HICs. The prevalence of all medication-related harm (preventable and non-preventable) was similar in LMICs and HICs (14% and 12%, respectively). High-quality research should be conducted, therefore, to define the causes of preventable medication-related harm and to specify targets as a basis for policies and interventions to reduce such harm globally and especially in LMICs.

Which regions experience the highest rates of preventable medication-related harm? Of the six WHO regions, the African and South-East Asia regions had the highest prevalence of preventable medication-related harm.

How severe is preventable medication-related harm, and does the severity differ between LMICs and HICs? Almost one fourth of the preventable medication-related harm reported was severe or life-threatening. Although harm was more common in LMICs than in HICs, maybe tended to be less severe (14% was severe in LMICs); however, this finding was based on only 6 studies based in LMICs.

In which medical settings or specialties are patients at high risk for preventable medication-related harm

managed? The risk for preventable medication-related harm is worryingly high among patients managed in geriatric care, highly specialized care (including surgical care), ICU and emergency medicine.

Which drugs and classes of drug are most likely to be associated with medication-related harm? In LMICs, antibacterials, corticosteroids, antipsychotics and gastrointestinal and cardiovascular drugs accounted for the most medication-related harm, whereas in HICs, non-steroidal anti-inflammatory drugs, analgesics, hypnotics and sedatives, cardiovascular drugs, antipsychotics and antibacterials were associated with most medication-related harm.

Which stages of medication use are most strongly associated with medication-related harm? Approximately half of medication-related harm occurs at the prescribing/ordering stage and approximately one-third occurs at the monitoring and reporting stage of medication-related.

How common has preventable medication-related harm been during the COVID-19 pandemic? There was an increase in the prevalence of preventable medication-related harm after 2017, perhaps due to better reporting of medication-related harm following the launch of the third WHO Global Patient Safety Challenge: *Medication Without Harm* or due to the increasing complexity of management of patients. During the pandemic, a sharp fall was observed in 2020, followed by a sharp increase in 2021–2022. These fluctuations may have been due to fewer patient referrals and presentations to hospitals in 2020; however, the consumption of medications may have increased in 2021–2022.

What is the impact of low-quality research methods and assessment and reporting standards on the

results of the meta-analysis of the prevalence of preventable medication-related harm? Studies with low-quality methods and non-standard assessments, such as small samples and use of surveys (telephone or spontaneous reporting), found lower prevalence rates of preventable medication-related harm than studies with large samples and assessment of case records. High-quality methods, including triangulation of methods, are essential for obtaining reliable estimates of the frequency of common preventable medication-related harm and its severity in both HICs and LMICs. Selection or system bias were common problems in the studies found.

Strengths and limitations

The major strengths of this review are its focus on preventable medication-related harm and consideration of all health care settings, including in LMICs. A previous meta-analysis of evidence on preventable medication-related harm covered all health care settings but with less attention to LMICs settings *(14)*. This updated systematic review included examination in detail (where possible) of the prevalence, severity, stage, medical setting and drug class of preventable medication-related harm in LMICs. This report therefore adds to the evidence on such harm and particularly how it is manifested in patients living in LMICs. Rigorous search methods were used to identify relevant studies, and the review was prepared and reported in accordance with review guidelines. International guidelines on medication-related harm were used to ensure use of global classifications. Two independent researchers assessed the risk of bias and extracted data to ensure the accuracy of the systematic review.

Although this is the first large meta-analysis of the prevalence of preventable medication-related harm in health care settings, it has several limitations. A considerable proportion of the heterogeneity could not be explained in meta-regression analyses. The effects of several factors, such as differences in health care settings and procedures and differences in the timeframe for evaluating medication-related harm, are unknown and may be responsible for the unexplained heterogeneity. The impact of differences in timeframe should be examined in particular, as the estimated prevalence in cross-sectional studies may be lower than that in prospective studies.

Secondly, while an exhaustive search for unpublished studies was made for the original review *(14)*, we were unable to update the search for unpublished studies due to time constraints. Furthermore, only studies written in English were included, which is likely to have introduced a small study bias, selection bias or system bias *(42)*. This was accounted for in the analysis by adjustment for sample size, but some of the causal factors remain unexplained.

Thirdly, studies that did not report preventable medication-related harm were excluded from the analyses. Only 28% of the studies included provided data on the severity of such harm, and the system used to classify severity was sometimes unclear; therefore, some severity categories were grouped. Furthermore, causality was assessed in only a few studies that reported the assessment tool used, and only 21% of studies provided the stage of medication use in which harm occurred. While harm was reported by medication group in 39% of the studies, only one fifth provided the drug classes involved. Use of different scales of preventability might also constitute "hindsight bias", in which health care professionals may overestimate their ability to predict preventable harm *(5, 43)*. Adjustment for this bias in observational research in synthesizing evidence is, however, difficult.

Fourthly, the impact of patient factors such as age, gender and comorbidity on the prevalence of preventable medication-related harm were not examined in detail. The main reasons were that all the analyses were based on aggregated data and many studies did not report the characteristics of their sample. Data on individual patients are required to examine the role of patient factors.

Fifthly, some of the prevalence estimates for preventable medication-related harm in this report might be biased. For example, although it has been reported that medication errors and the associated harm are major problems in countries in the Eastern Mediterranean Region *(44)*, a surprisingly low prevalence of preventable medication-related harm (2%) was identified in studies in that Region. This inconsistency probably reflects the methodological caveat of pooled studies and perhaps also limited training in capturing and reporting preventable medication-related harm in those countries. In

addition, publication bias was detected in the prevalence meta-analysis of preventable medication-harms suggesting that there was a greater number of studies showing higher prevalence estimates. Hence the results should be considered with some caution with publication bias being present.

Sixthly, more than two thirds of the cases of preventable medication-related harm were studied retrospectively from medical case notes and chart reviews. Although case note reviews are the most common method for assessing medication-related harm, patients and health care providers have suggested that they are inadequate for detecting diagnostic errors and are susceptible to time-delay in the absence of regular patient consultation *(45)*. Better, more promising approaches for the detection of preventable medication-related harm include combining methods for prospective detection of preventable harm by use of "failure mode and effect analysis", the "structured what-if technique" *(28)*, pharmacist screening or patient surveys with retrospective error detection methods, including trigger tools, voluntary reporting systems, root-cause analysis or mortality reviews *(42, 46)*.

Lessons learnt and implications for research, policy and practice

This review shows that more than one in 20 patients in a health care system are exposed to preventable medication-related harm, and patients in LMICs are almost twice as likely to experience such harm as patients in HICs. This prevalence estimate presented in this report is higher that the prevalence estimate reported in the previous systematic review published in the topic (1 in 30 patients). This difference mainly reflects a comprehensive effort to acquire supplementary data which enabled the inclusion of studies conducted in LMIC settings in this report which were excluded from the previous systematic review due to insufficient data availability. It also reflects the fast growing evidence in the field, this report is based on 100 studies whereas the previous systematic review was based on 81 studies. Medication safety is a major concern in the health policies of LMICs *(3)*. The rates of preventable harm and death due to medication-related harm are higher than those reported in other studies, raising concern for policy-makers and practitioners *(23)*. High-quality

studies are required, with renewed effort to identify underlying causes and solutions that would be feasible for implementation in resource-constrained health systems. The problem will not be solved by providing more staff and equipment, even if that were immediately possible. Effective clinical diagnosis and treatment demand a person-centered approach, guided by standardized clinical policies and protocols rooted in best practices and implemented under careful supervision.

Improved reporting standards for future studies on preventable medication-related harm would make a major contribution to ensuring safe care for patients. Although a large number of studies was included in this review, the depth of the data on preventable medication-related harm were very low. Specifically, preventability was reported as a secondary outcome in the majority of the studies and limited information was provided about the stages of medication use as well as the types of medicines which led to preventable medication related harm (the studies tended to provide this information for the overall medication related harm but not for preventable medication-related harm). Hence, the reporting of the nature of preventable medication-related harm must be improved in order to understand how to mitigate it with existing practices and tangibly improve patient safety. Research on patient safety should reflect and meet the needs of clinical practice. Increasing emphasis on the types of medication-related harm that clinicians consider to be preventable is a critical step in this direction. Research should be conducted on the major sources of severe medication-related harm, on the stages of the medication use system at which they occur and on the health care settings and practitioners involved. Such detailed analysis is fundamental for designing more efficient strategies to prevent medication-related harm in health care.

The highest prevalence rates of preventable medication-related harm were seen in studies in geriatric care units, in which patients often have high rates of comorbidity, frailty and polypharmacy – a priority in the WHO Global Patient Safety Challenge: *Medication Without Harm*. ICUs and specialized care units for surgery are also associated with higher rates of preventable medication-related harm and should therefore be considered settings in which high-risk patients are commonly managed. It is not, however,

the settings or specialties in which harm is detected that are necessarily problematic; rather, the high estimates of harm detected in these settings may represent the greater clinical complexity managed, less integration of care and inadequate staff training and awareness of preventable medication-related harm. Little information was found on the prevalence and severity of preventable medication-related harm in primary care and psychiatry, with only five studies in primary care, where over 80% of health care is delivered internationally, and only one study in psychiatry in an HIC. Much preventable harm in psychiatric care is undetected, as it may be subsumed by multiple interacting errors in violation-provoking conditions and latent system failures *(47)*. More research is therefore required in both these care settings.

The prescribing/ordering and monitoring/reporting stages of medication use are frequent sources of preventable medication-related harm. Widespread use of electronic health records has helped to avert preventable harm at the ordering and transcribing stages, but it persists at all stages of medication use. This is probably due to underlying system flaws that lead to transfer of individual prescribing or administration errors to patients. Human factors play an important role in system flaws. For instance, there are often no standard procedures for storing medications that look alike, poor communication among providers, no verification before administration of medications and lack of involvement of patients in their own care. The effects of system flaws and human factors on the occurrence of preventable medication-related harm may be even more pronounced in LMICs. Better safety processes are necessary at all stages of medication use to ensure that correct measures contribute to improving health care.

The review shows that the medication groups associated with most cases of preventable medication-related harm are antibacterial agents, antipsychotics, central nervous system stimulants, cardiovascular medicines, hypnotics and sedatives and non-steroidal anti-inflammatory drugs, many of which are currently on the WHO Model List of Essential Medicines. Some of these groups have been assessed for measures to reduce the risks of hazardous prescribing; however, the studies have not included preventable medication-related harm, and it is important to include this in assessing medication errors.

A doctor at a hospital, photo credit: WHO/Blink Media - Tali Kimelman

Way forward

This is the largest review of the prevalence, severity and types of preventable medication-related harm in health care systems globally and specifically in LMICs. The findings affirm that preventable medication-related harm is a common problem in all health care systems and especially in LMICs. Although patients in LMICs are almost twice as likely to experience preventable medication-related harm as patients in HICs, only one third of the studies in this review were conducted in LMICs, and the quality and reporting standards of those studies were lower than in the studies in HICs. For example, there was found less consistent evidence from LMICs about the severity of preventable medication-related harm, the stage of medication use at which harm occurs and the drug classes associated with harm. Thus, the quality of the methods used to collect and report data on preventable medication-related harm in LMICs is a concern.

Future action should include commissioning of high-quality studies for in-depth analysis of the severity, nature and causes of preventable medication-related harm (medication use stage, drug classes, human factors and unique contextual factors in LMICs and in HICs). This should result in important information and suitable targets and strategies for improvement and mitigation of preventable medication-related harm. The medication safety programmes should include improved methods and systems for assessing and detecting preventable medication-related harm in LMICs as well as devising strategies to prevent harm to patients in health care delivery.

The report identifies a number of targets for future research, policy and practice to reduce preventable medication-related harm. It is also urgent to continue to identify the causes of preventable medication-related harm, to support specialties in which such harm is prevalent (e.g., geriatric care, surgical care, ICU and emergency medicine) and to raise awareness in settings in which inappropriate prescription is frequent. Finally, more evidence is required in settings such as primary care, and mental health and psychiatry, where relatively little research has been conducted.

Doctor performing tests on a patient, photo credit: WHO/Julio Takayama

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Annexes

Annex 1

Table A1.1. MEDLINE Search Strategy

Ovid MEDLINE(R) <1946 to April Week 3 2022>		
1	((preventable or avoidable or unnecessary or untoward or ameliorable) adj2 (harm or complication* or omission)).mp.	2468
2	exp Medical Errors/cl, mt, pc, st, sn [Classification, Methods, Prevention & Control, Standards, Statistics & Numerical Data]	29176
3	exp medical error/pc or medical error.mp.	23293
4	Drug-Related Side Effects and Adverse Reactions/	37914
5	((Adverse drug or adverse medication) adj1 (event* or incident or reaction* or effect* or outcome*)).mp.	27388
6	Human error*.mp.	2537
7	((service* or system* or communication* or organization* or organisation* or treatment or therap* or diagnos*) adj1 (weak* or fail* or error* or mistake* or delay*)).mp.	158842
8	(adverse* adj1 (event* or outcome* or complication* or effect* or reaction*)).mp.	2255369
9	((psychological or emotional or physical) adj1 (harm or complication*)).mp.	1786
10	patient safety.mp. or Patient Safety/	49349
11	(death* or accident or serious incident* or injur* or adverse event*).mp.	2365381
12	10 and 11	8745
13	(never event* or near miss*).mp.	2829
14	(iatrogenic adj (harm or injur* or complication*)).mp.	4068
15	Patient Harm/ or patient harm.mp.	1951
16	Diagnostic Errors/	39728
17	(preventable or avoidable or unnecessary or untoward or ameliorable).mp.	105646
18	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 12 or 13 or 14 or 15 or 16	2421801
19	17 and 18	21900
20	1 or 19	23215
21	Prevalence/ or prevalence.mp.	769630
22	incidence.mp. or Incidence/	904306
23	Epidemiologic Studies/	9349
24	exp Case-Control Studies/	1427090
25	(epidemiologic* adj (study or studies)).mp.	92205
26	case control.mp.	363235
27	exp Cohort Studies/	2496881
28	Cross-Sectional Studies/	470651

Ovid MEDLINE(R) <1946 to April Week 3 2022>		
29	(cohort adj (study or studies)).mp.	486166
30	Cohort analy*.mp.	10992
31	(follow up adj (study or studies)).mp.	712019
32	longitudinal.mp.	337903
33	Retrospective.mp.	1218107
34	Prospective.mp.	875560
35	(observ* adj1 (study or studies)).mp.	226881
36	(analytical adj (study or studies)).mp.	5440
37	(comparative adj (study or studies)).mp.	1961970
38	(evaluation adj (study or studies)).mp.	388986
39	Meta-analysis/	183300
40	((Systematic or narrative) adj review).mp.	266361
41	Clinical Trial/ or Randomized Controlled Trial/	917554
42	or/23-41	6138749
43	20 and 42	9702
44	21 or 22	1581393
45	20 and 44	4603
46	43 or 45	11570
47	limit 46 to (yr="2000 -Current")	9329
48	limit 47 to yr="Jan 2020 - Current"	1621

Global burden of preventable medication-related harm in health care — A systematic review

Annex 2

Fig. A2.1. Funnel plot of preventable medication-related harms for all studies
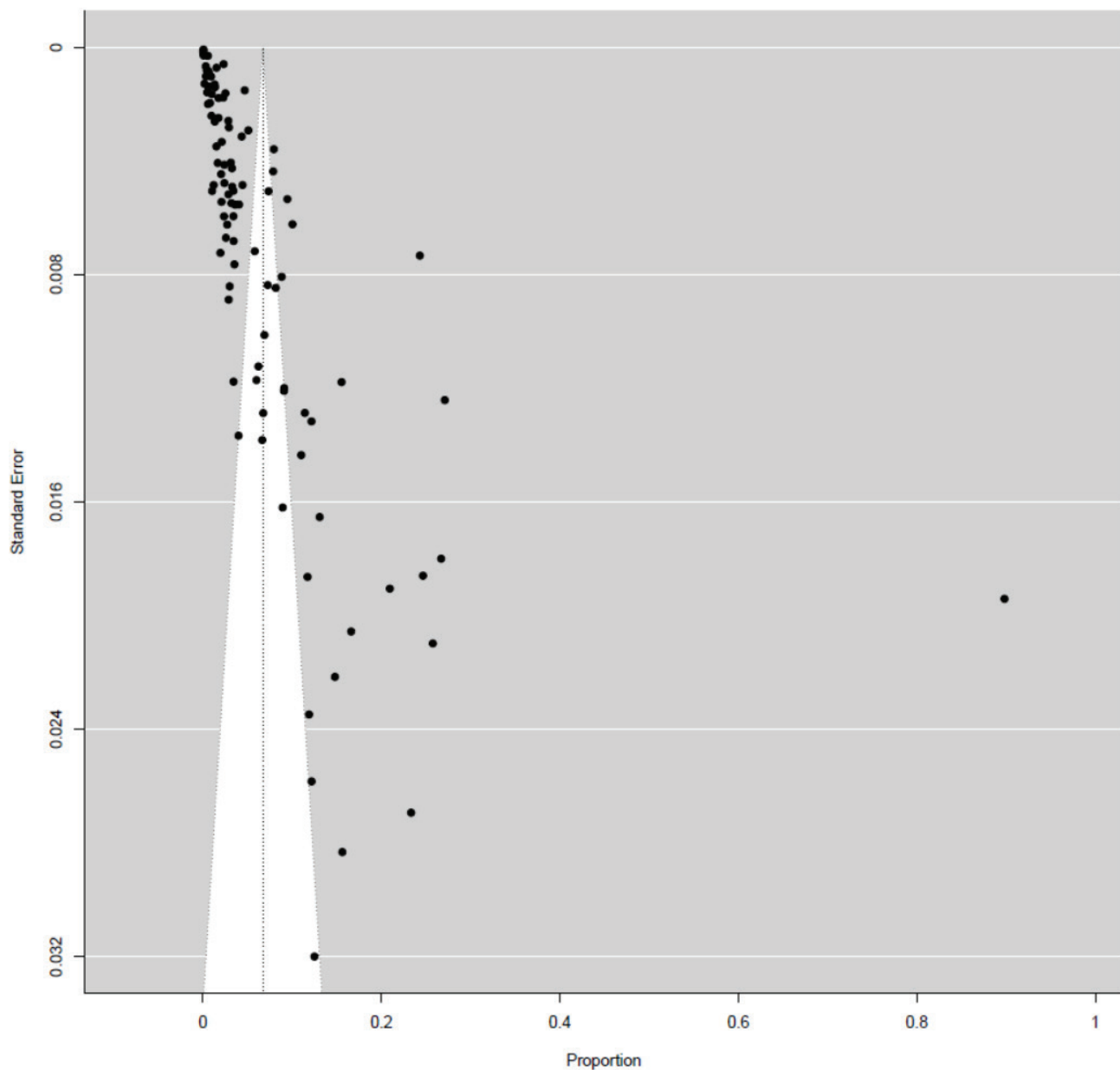
Egger's regression test Results:

Mixed-Effects Model (k = 100; tau^2 estimator: DL)

tau^2 (estimated amount of residual heterogeneity): 0.0000 (SE = 0.0000)

tau (square root of estimated tau^2 value): 0.0055

I^2 (residual heterogeneity / unaccounted variability): 98.19%

H^2 (unaccounted variability / sampling variability): 55.33

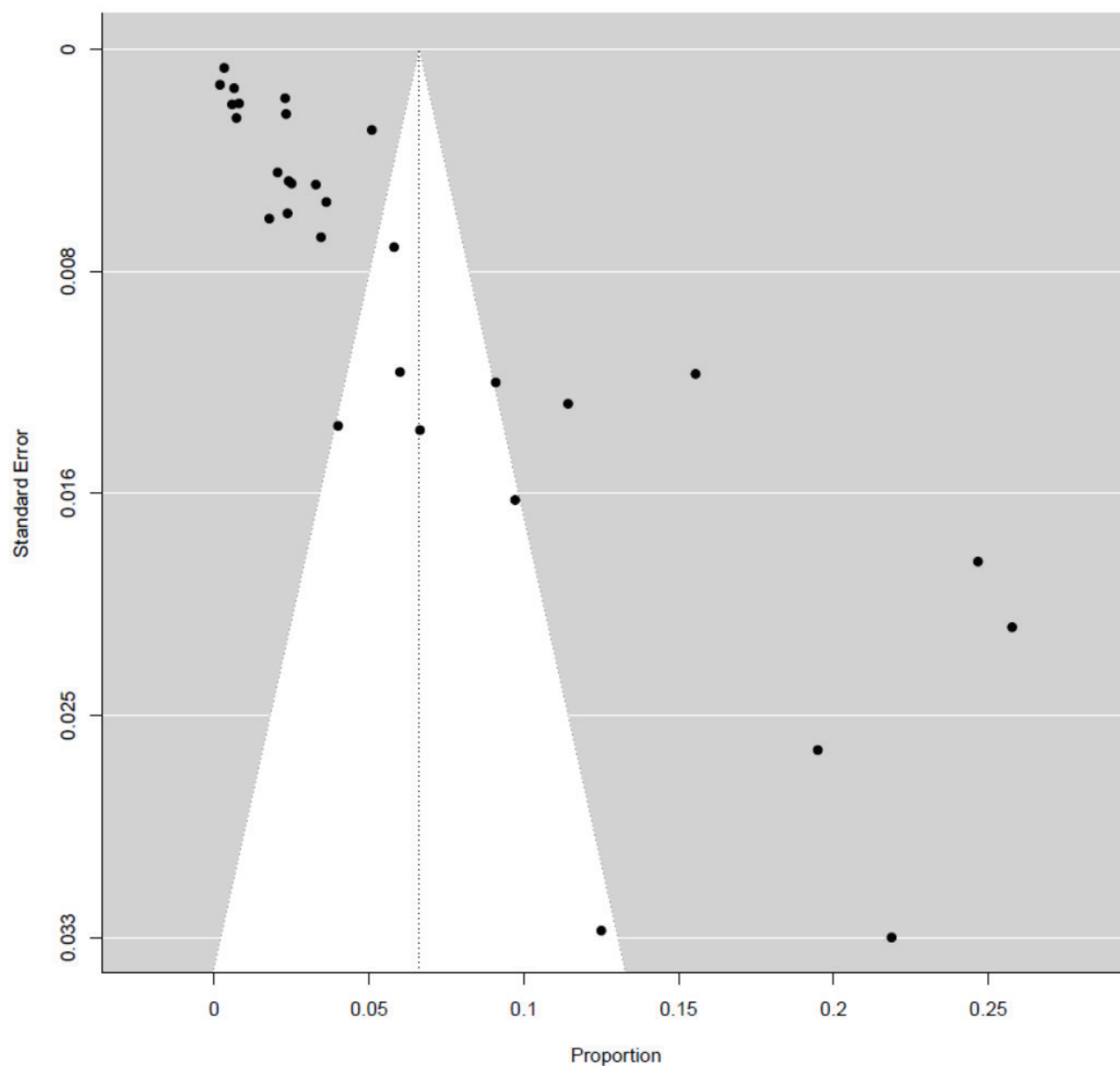R^2 (amount of heterogeneity accounted for): 54.58%

Test for Residual Heterogeneity:
QE(df = 98) = 5422.8048, p-val < .0001

Test of Moderators (coefficient 2):
QM(df = 1) = 1941.2649, p-val < .0001

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-0.0012	0.0011	-1.1720	0.2412	-0.0033	0.0008
mods	**8.8746**	0.2014	44.0598	**<.0001**	**8.4798**	**9.2694*****

Fig. A2.2. Funnel plot of preventable medication-related harms for LMICs studies

Egger's regression test Results:

Mixed-Effects Model (k = 30; tau^2 estimator: DL)

tau^2 (estimated amount of residual heterogeneity):   0.0001 (SE = 0.0001)

tau (square root of estimated tau^2 value):   0.0104

I^2 (residual heterogeneity / unaccounted variability): 92.95%

H^2 (unaccounted variability / sampling variability):   14.19

R^2 (amount of heterogeneity accounted for):   67.83%

Test for Residual Heterogeneity:
QE(df = 28) = 397.2528, p-val < .0001

Test of Moderators (coefficient 2):
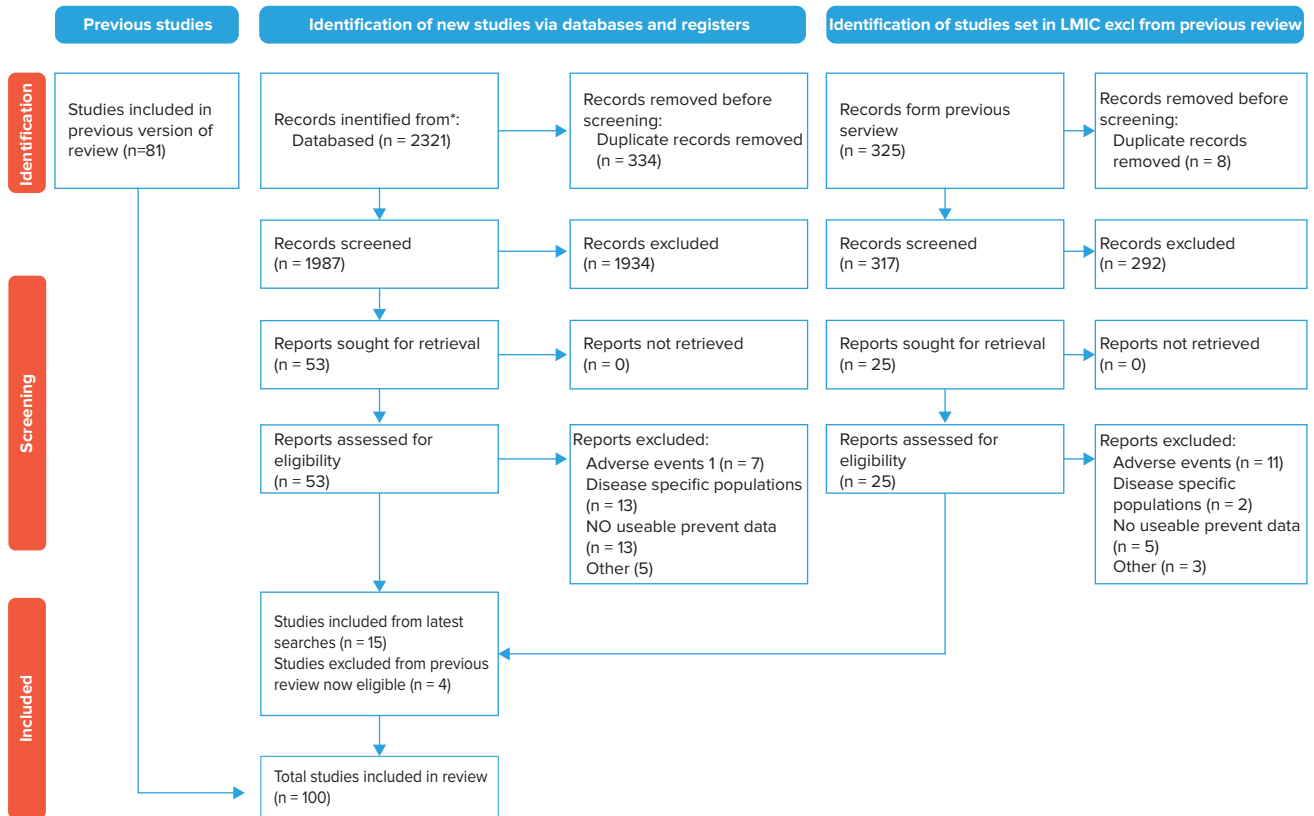QM(df = 1) = 302.2385, p-val < .0001

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-0.0048	0.0035	-1.3732	0.1697	-0.0115	0.0020
mods	**7.6012**	0.4372	17.3850	**<.0001**	**6.7442**	**8.4581*****

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Annex 3

Box A3.1. PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases, registers and other sources