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SYSTEMATIC REVIEW

Systematic Review Examining the Effectiveness of Professional, Organisational and Structural Interventions in Primary Care to Reduce Medication-Related Hospitalisations and Deaths

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Abstract

Background Medication-related adverse events in primary care are a leading cause of hospital admissions and mortality, commonly resulting from medication errors. Previous reviews have assessed interventions broadly across healthcare settings, but few have focused specifically on interventions targeting medication errors in primary care.

Objective To evaluate the effectiveness of professional, organisational, and structural interventions in primary care settings in reducing medication-related hospital admissions, emergency department (ED) visits, and mortality.

Methods We conducted a systematic review using the Cochrane methodology of systematic reviews and PRISMA guidelines for reporting. A comprehensive search of CENTRAL, MEDLINE, Embase, CINAHL, and trial registries up to October 2024 was undertaken. Randomised controlled trials conducted in primary care that assessed the impact of interventions on hospital admissions, ED visits, and mortality were included. Cochrane Risk of bias assessments and random-effects meta-analyses were performed.

Results Interventions were classified according to the Cochrane Effective Practice and Organisation of Care criteria into Professional, Organisational and Structural. Sixty-two studies met the inclusion criteria. Professional interventions, including educational training and clinical decision tools, showed little to no effect on primary outcomes (risk ratio [RR] 1.01, 95% confidence interval [CI] 0.94–7.00 for hospital admissions; RR 1.00, 95% CI 0.98–1.02 for mortality; very-low to low certainty evidence). Organisational interventions, such as pharmacist-led medication reviews and multidisciplinary care models reduced the number of hospital admissions (RR 0.81, 95% CI 0.70–0.95; low-certainty evidence), but had uncertain effects on ED visits and mortality. Structural interventions, such as system-level support and quality monitoring, showed a reduction in hospital admissions (RR 0.90, 95% CI 0.83–0.97; moderate-certainty evidence), but evidence for other outcomes showed limited or very-low certainty.

Conclusion Organisational and structural interventions in primary care may reduce medication-related hospital admissions and may help inform clinical practice through implementation of multidisciplinary care models and system-level quality monitoring approaches. However, the overall certainty of evidence is low to very low, highlighting the need for high-quality trials to better inform clinical practice and policy.

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Key Points

The evidence from this review supports the benefits of organisational and structural interventions to reduce medication errors with respect to the number of hospital admissions, but not with respect to patients admitted to hospital, number of emergency department visits and mortality. However, there was no evidence supporting the benefits of professional interventions.

For clinical practice, these findings support implementing multidisciplinary approaches to medication management, including regular medication reviews by pharmacists and collaborative care models integrated into routine primary care. Relying solely on educational strategies is unlikely to have a significant impact. For researchers, the findings point to the need for high-quality trials to better inform clinical practice and policy.

Policymakers should consider investing in system-level reforms such as incentivising structured medication reviews, improving data sharing between care settings, and embedding safety monitoring tools within electronic health systems.

1 Introduction

Medication-related adverse events (AEs) in primary care represent an important cause of hospital admissions and mortality [1]. They can be the result of people either experiencing adverse drug reactions (not usually preventable) or as a result of medication errors (usually preventable) [2, 3]. For this review, primary care refers to a patient's initial contact within the healthcare system, encompassing general practice, community pharmacies, and community-based clinics. Medication management refers to the clinical, cost-effective and safe use of medication to ensure that patients get the maximum benefit from the medication they need, while at the same time minimising potential harm. A medication error is defined by Ferner 2006 as "a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient". It arises mainly from errors in prescribing or medication management [4]. Reducing prescribing errors has been a high priority for international healthcare policy in order to improve the safety profile of the healthcare delivery system [5].

A recent scoping review found that the incidence of adverse drug reactions varied significantly in primary care ranging between 6 and 80% of all AEs reported in primary care. The nature of these AEs varied significantly from mild to severe and, in some instances, resulting in mortality [6]. Most of the AEs reported were due to drug-related medication errors (wrong dose, drug interactions, wrong route, etc.) followed by allergic drug reactions.

Prescribing medications is the most common intervention made by general practitioners in the prevention and treatment of disease, and alleviation of symptoms [7]. However, medication-related AEs arising as a result of primary care prescribing are an important source of morbidity, much of which could be prevented by higher-quality prescribing and medication management [1]. To date, there is little information about interventions aimed at reducing preventable medication-related AEs in primary care due to errors. A review undertaken by Ioannidis et al., addressed interventions to reduce all types of medical errors in both primary and secondary care [3]. It highlighted the complexity in studying those types of interventions aimed at minimising errors in healthcare delivery. Other reviews focused on interventions to improve professional practice and healthcare outcomes, including prescribing [8, 9]. A review by Royal et al. found that there was weak evidence to support pharmacist-led medication interventions being effective in reducing hospital admissions [10]. However, none of these reviews have focused on other types of interventions at the professional, organisational or structural level that could reduce medication errors in the primary care setting.

Given that medication errors in primary care are associated with hospital admissions, emergency department (ED) visits, and mortality, it is important to know if any interventions have been found that are effective in reducing the occurrence of these outcomes. Building on an older review [11], this study examined interventions in primary care to reduce medication errors that resulted in hospital admissions, ED visits, and mortality compared to standard care [11]. The three main types of interventions that we examined included Professional, Organisational, and Structural interventions as described by the Cochrane Effective Practice and Organisation of Care (EPOC) [12]. Professional interventions included quality assurance tools that provided educational interventions for practitioners or participants, such as teaching the use of structured assessments with general practitioners (GPs). Organisational interventions included revision of professional roles (e.g. nurse- or pharmacist-led chronic disease clinics and nurse prescribing) and revision of clinical multidisciplinary teams (e.g., pharmacist-managed medication reviews). Structural interventions included the organisation of quality monitoring services. This updated systematic review builds upon our earlier review published in 2017, expanding the evidence base with studies published since then and providing a more comprehensive analysis of intervention effectiveness.

2 Materials and Methods

The protocol and an older version of this review have been published previously and registered in PROSPERO [11, 13]. The eligibility criteria of the participants, interventions, comparators, outcomes and study types are provided in Table 1. We used the Cochrane EPOC framework to classify the studies, the Cochrane methodology of systematic reviews of effectiveness to undertake the review and the PRISMA guidelines for reporting [12–15].

2.1 Search Strategy

A comprehensive search was conducted on 30 October 2024 across CENTRAL, MEDLINE (Ovid), Embase (Ovid), and CINAHL (EBSCO), from January 2000 onwards [11]. No language limits were applied. The strategy included both natural language and controlled vocabulary terms. The search timeframe from January 2000 was chosen because systematic electronic databases became more comprehensive from this period, and medication safety initiatives gained prominence in healthcare policy from 2000 onwards. Grey literature searches were conducted across multiple platforms

Table 1 Eligibility criteria

Participants	We included studies directed at healthcare professionals and organisations involved in the provision of primary care in the community setting who were authorised to prescribe, sell or administer medications, including primary care physicians (GPs, family doctors, family physicians, family practitioners), dental practitioners, community nurses, nurse practitioners, community pharmacists, dispensers in community pharmacies and any other relevant healthcare providers We included all adult participants who were receiving a medication through the intervention of the previously mentioned primary healthcare professionals Examples of community settings included general practice, community pharmacies, and nursing and residential homes We excluded studies of interventions for outpatients in a clinic attached to a hospital or a day hospital unless these were specifically described as primary care clinics
Interventions	Using the taxonomy of interventions developed by EPOC, we categorised interventions that improved patient safety by reducing hospital admissions, ED visits, and mortality (Appendix 1). We compared the interventions with inactive control interventions such as no treatment, or standard or conventional care. We divided interventions into the following three categories Professional interventions Professional interventions included the use of health information technology to identify people at risk of medication problems, computer-generated care suggested and actioned by a physician, electronic notification systems about dose changes, drug interventions and follow-up, and educational interventions on drug use aimed at physicians to improve drug prescriptions Organisational interventions Examples of organisational interventions included medication reviews by pharmacists, nurses or physicians, clinician-led clinics, and home visits by clinicians Structural interventions Structural interventions included the organisation of quality monitoring services. Structural approaches included social, economic, and political interventions that could improve public health outcomes by increasing the willingness and ability of individuals to practice prevention. An example of the latter would be the introduction of financial incentives to healthcare workers to reduce medication errors
Comparators	Standard/usual care
Outcomes	Primary outcomes 1. Number of hospital admissions (this outcome allows that one patient can have multiple admissions) 2. Number of people admitted to hospital (this outcome reports on the no. of people admitted to hospital irrespective of the no. of times they were admitted during the study period) Secondary outcomes 1. Number of ED visits (measured as no. of visits to EDs, this outcome allows that one patient can have multiple visits). We reported all-cause visits to EDs. 2. Mortality (measured as the no. of patients reported to have died). We reported all-cause mortality included in the primary studies All-cause mortality measures were reported as this was the most common outcome reported in all the included studies. It was difficult to differentiate between all-cause outcomes and intervention-specific outcomes
Studies	We included randomised trials in this review. We excluded controlled before-after studies and other non-randomised designs as they provided much weaker evidence due to the potential for bias. We did not impose any restriction on the language or country or status of publication. We searched for study reports and any ongoing studies. We included cluster randomised trials where the unit of analysis was the site rather than the individuals and that they had to have at least two intervention and two control sites as described in Higgins 2017

ED emergency department, *EPOC* Cochrane Effective Practice and Organisation of Care, *GP* general practitioner

and databases. Trial registries including ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) were searched using terms such as "pharmaceutical care," "medication review," "medication error," and "inappropriate prescribing". Additional grey literature sources included OpenGrey (opengrey.eu), Grey Literature Report (New York Academy of Medicine), Agency for Healthcare Research and Quality (AHRQ), Joanna Briggs Institute, and National Institute for Health and Care Excellence (NICE). Search strategies were adapted for each platform using relevant combinations of terms including "pharmaceutical care", medication review", "medication error", and "medication reconciliation", with appropriate filters applied where available (e.g., interventional studies, systematic reviews, primary research). Reference lists of included studies were screened. The search strategy is detailed in Supplementary file 1.

2.2 Study Selection

Two reviewers from this list of authors (HK, BB, MF, PL, AT, RNK, BI) independently screened each title, abstract, and full text for inclusion, extracted study data independently and resolving any disagreements by consensus with a third reviewer, as detailed in Table 1. Cochrane Review Manager 5 was used to document included studies. A PRISMA flowchart outlines the selection process, as shown in Fig. 1.

2.3 Data Extraction

Two review authors (HK and BB) extracted data using a customised EPOC checklist and grouped studies by similar interventions and outcomes. Any discrepancies were checked by the primary author (HK). Review Manager 5 was used to manage data. We have provided an overview of the selection process in a PRISMA flow diagram in Fig. 1, including the studies included in our original review [15].

2.4 Risk of Bias Assessment

For parallel group randomised controlled trials (RCTs), risk of bias was assessed across standard domains using Higgins 2011 criteria [16]. Cluster-RCTs were also assessed for recruitment bias, baseline imbalances, and analytical appropriateness. Studies with any high-risk domain were considered high risk overall.

2.5 Measures of Treatment Effect

Outcomes were reported in natural units (e.g., number of events per total participants). Dichotomous outcomes were analysed using risk ratios (RRs) with 95% confidence intervals (CIs). Funnel plots were used to assess publication bias [11].

2.6 Data Analysis

Random-effects meta-analyses were used due to expected heterogeneity. Studies were grouped by intervention type (professional, organisational, structural). Cluster RCTs were adjusted using design effect calculations as per the Cochrane handbook [14].

2.7 Assessment of Heterogeneity

Heterogeneity was evaluated using the I^2 statistic and visually via forest plots. Thresholds followed Higgins 2003 guidelines [17, 18].

2.8 Reporting Bias

Funnel plots and Egger's test were planned if ≥ 10 studies were available. Due to insufficient trials, this was not performed for professional and structural interventions [14].

2.9 Summary of Findings and Certainty of Evidence

The GRADE handbook was used to assess evidence certainty. Three 'Summary of findings' tables were developed for comparisons between each intervention type and usual care, including justifications for any downgrading/upgrading of evidence, as per the GRADE handbook [12, 19] (summary of findings Tables 2, 3, 4).

3 Results

3.1 Study Selection

We identified a total of 6328 records through all searches undertaken in this review update. After removing duplicates, 4148 titles and abstracts were screened, and 4028 were excluded. We then reviewed the full text of 120 records for a more detailed evaluation. Of these, a total of 58 studies were excluded and 62 studies were included in the current review, as shown in Fig. 1. Studies were excluded due to unsuitable design (i.e., not RCTs), settings not in primary care, interventions not relevant to reducing medication errors, population not specific to adults, or withdrawal after publication [20, 21].

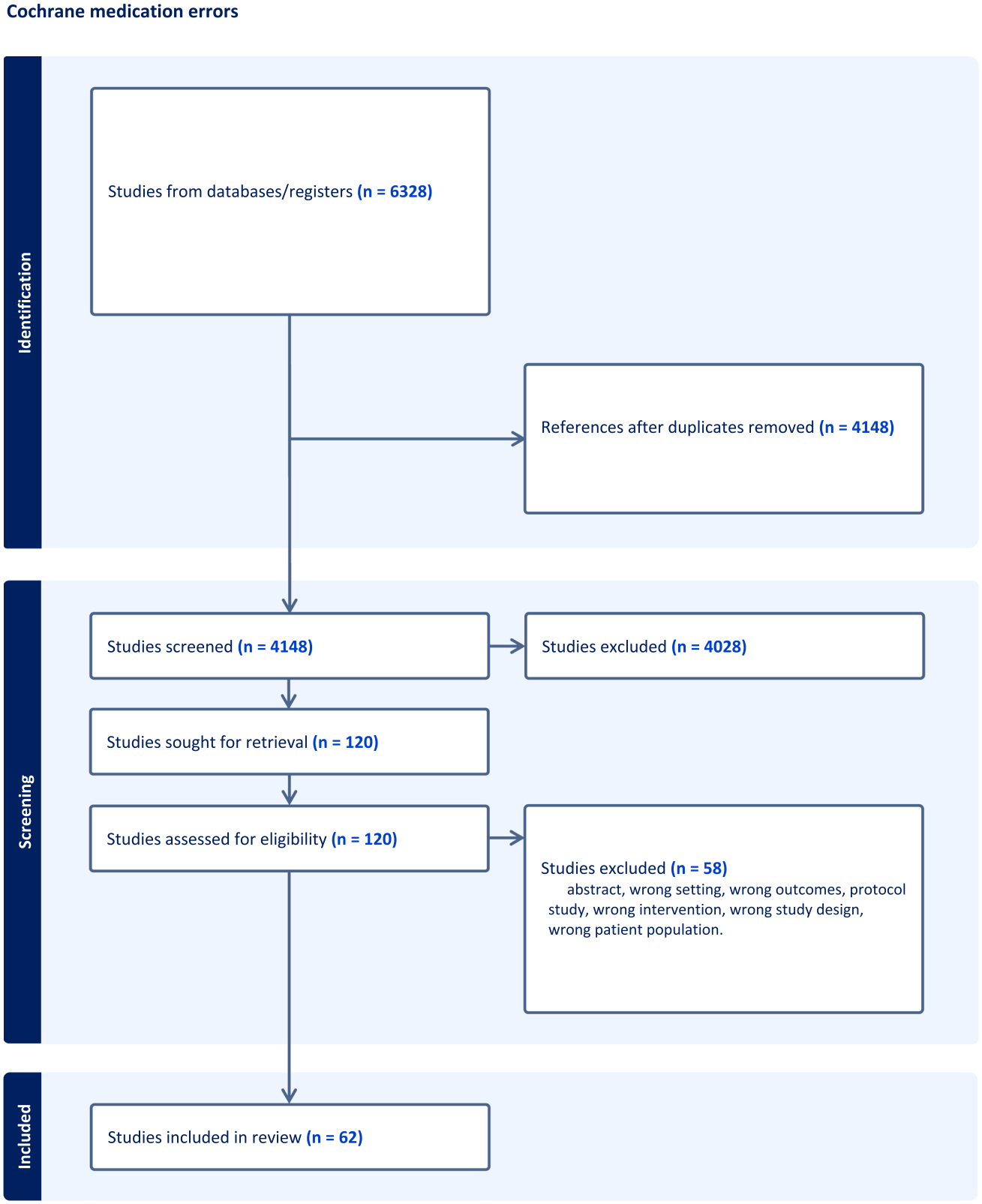

Figure 1 PRISMA chart

Table 2 Summary of finding—professional interventions

Professional interventions compared to standard/usual care for patients with preventable medications errors that lead to hospital admissions, emergency visits and mortality

Patient or population: patients with preventable medications errors that lead to hospital admissions, emergency visits and mortality

Setting: Primary care

Intervention: Professional interventions

Comparison: standard/usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard/usual care	Risk with Professional interventions				
Number of hospital admissions	42 per 1,000	**39 per 1,000** (25 to 58)	**RR 0.91** (0.60 to 1.36)	3672 (2 RCTs)	⨁⨁◯◯ Low[a,b,c]	Two studies had unclear risk of bias (selection and other bias), one study had performance and assessment bias, the studies had wide confidence intervals
Number of patients admitted to hospital	183 per 1,000	**185 per 1,000** (172 to 1,000)	**RR 1.01** (0.94 to 7.00)	23299 (7 RCTs)	⨁⨁◯◯ Low[a,b,c]	Four studies had unclear selection bias, six studies had high risk of bias (performance and detection) and three studies had unclear risk of protection against contamination.
Number of emergency departments visits	259 per 1,000	**230 per 1,000** (196 to 269)	**RR 0.89** (0.76 to 1.04)	17387 (5 RCTs)	⨁◯◯◯ Very low[a,b,c]	Three studies had unclear risk of bias of selection,, three studies had high risk of performance bias), high heterogeneity and wide confidence intervals
Mortality	354 per 1,000	**354 per 1,000** (347 to 361)	**RR 1.00** (0.98 to 1.02)	39604 (8 RCTs)	⨁◯◯◯ Very low[a,b,c,d]	Five studies had unclear risk of selection bias, Four studies had high risk of performance bias and wide confidence intervals

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

3.2 Characteristics of Included Studies

3.2.1 Study Design

Of the 62 randomised trials included in this review, 21 (33.9%) were cluster-randomised trials [22–37] and 41 (66.1%) were randomised trials [38–64]. Follow-up ranged from 21 days to 4.7 years.

3.2.2 Participants

A total of 431,526 patients were included across all studies. In 42 studies (42/62, 67.7%), the number of healthcare professionals delivering the intervention was not reported. Most interventions were delivered by pharmacists, physicians, or a combination of both. Fourteen studies (14/62, 22.6%) were pharmacist-led, ten (10/62, 16.1%) were delivered by

Table 3 Summary of finding—organisational interventions

Organisational interventions compared to standard/usual care for patients with preventable medications errors that lead to hospital admissions, emergency visits and mortality

Patient or population: patients with preventable medications errors that lead to hospital admissions, emergency visits and mortality

Setting: Primary care

Intervention: organisational interventions

Comparison: standard/usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard/usual care	Risk with organisational interventions				
Number of hospital admissions	309 per 1,000	**250 per 1,000** (216 to 293)	**RR 0.81** (0.70 to 0.95)	15893 (20 RCTs)	⨁⨁◯◯ Low[a,b,c]	Eleven studies had unclear risk of selection bias, six studies had high risk of performance bias, and high heterogeneity.
Number of patients admitted to hospital	272 per 1,000	**270 per 1,000** (248 to 294)	**RR 0.99** (0.91 to 1.08)	10358 (22 RCTs)	⨁◯◯◯ Very low[a,b,c]	Some studies had unclear risk of bias (selection, attrition and performance bias) and wide confidence intervals
Number of emergency departments visits	229 per 1,000	**181 per 1,000** (147 to 222)	**RR 0.79** (0.64 to 0.97)	10507 (13 RCTs)	⨁◯◯◯ Very low[a,b,c]	Twelve studies had unclear risk of selection bias, eight studies had high risk of performance bias, nine studies had high risk of attrition bias, high heterogeneity and wide confidence intervals
Mortality	172 per 1,000	**161 per 1,000** (148 to 175)	**RR 0.94** (0.86 to 1.02)	15169 (27 RCTs)	⨁◯◯◯ Very low[a,b,c,d]	Thirteen studies had high risk of selection, ten studies had high risk of performance bias and wide confidence intervals

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

both pharmacists and physicians, eight (8/62, 12.9%) were physician-led and six studies (6/62, 9.7%) were nurse-led interventions. The age of participants ranged from 60 to 90 years in most studies. However, in four studies (4/62, 6.5%) the participants were aged between 40 and 60 years, and in two studies (2/62, 3.2%), participant age was not specified.

3.2.3 Description of the Interventions

All 62 included studies are described in detail in Supplementary file 3. Ten studies (10/62, 16.1%) were categorised as professional interventions, two (3.2%) as structural interventions, and the remaining 50 (50/62, 80.6%) as organisational interventions. Studies were classified into single intervention categories based on their primary intervention focus, with no overlap between categories within individual studies. Professional interventions included activities such as the distribution of educational materials, educational meetings, local consensus processes, educational outreach visits, audit and feedback, reminders (including computer-aided decision support and drug dosage), marketing, and mass mailings. Organisational interventions included revision of professional roles (e.g., nurse- or pharmacist-led clinics, nurse prescribing), use of clinical multidisciplinary teams (e.g., pharmacist-managed medication reviews), and the involvement of quality monitoring services. Structural

Table 4 Summary of finding table—structural interventions

Structural interventions compared to Standard care for [patients with preventable medication errors that lead to hospital admissions, emergency department visits and mortality

Patient or population: patients with preventable medication errors that lead to hospital admissions, emergency department visits and mortality

Setting: Primary care

Intervention: Structural interventions

Comparison: Standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with [Standard care]	Risk with [Structural interventions]				
Number of hospital admissions	62 per 1,000	**56 per 1,000** (52 to 61)	**RR 0.90** (0.83 to 0.97)	23321 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	one study had high risk of bias, two studies had high of performance bias and one study had high risk of attrition bias
Number of people admitted to hospital	82 per 1,000	**85 per 1,000** (60 to 122)	**RR 1.04** (0.73 to 1.49)	1521 (2 RCTs)	⨁◯◯◯ Very low[b,c]	this study had unclear selection and performance bias, the other study had high risk of performance bias
Number of emergency visits	31 per 1,000	**59 per 1,000** (5 to 680)	**RR 1.88** (0.16 to 21.77)	67 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	This study had unclear risk of selection and performance bias
Mortality	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

interventions included the presence and organisation of quality monitoring services and broader social, economic, or political actions aimed at improving public health through preventive behaviours, as per the EPOC categorisation [12]. The effects of these interventions are reported in Summary of Findings Tables 2 (Professional), 3 (Organisational), and 4 (Structural).

3.2.4 Setting

Most studies were conducted in the USA (20 studies [32.3%]) [24, 25, 28, 31, 44–46, 52, 54–56, 58, 60–62, 65–69] or the UK (10 studies, 61.1%) [29, 42, 47, 50, 51, 63, 64, 70–72]. Other countries represented were Spain (5, 8.1%), Australia (4, 6.5%), Denmark (2, 3.2%), the Netherlands (3, 4.8%), Norway (2, 3.2%), Austria (1, 1.6%), Canada (2, 3.2%), Israel (1, 1.6%), Sweden (1, 1.6%), Switzerland (1, 1.6%), Singapore (1, 1.6%), Italy (1, 1.6%), Ireland (1, 1.6%), Germany (1, 1.6%), Brazil (1, 1.6%), New Zealand (1, 1.6%), and the United Arab Emirates (1, 1.6%). Two studies (2/62, 3.2%) were conducted across multiple countries: Bernsten [40] included sites in Denmark, Germany, the Netherlands, Northern Ireland, Portugal, Republic of Ireland, and Sweden; and Rieckert [34] in Austria, Germany, Italy, and the UK. All the details of these studies are included in Supplementary file 3.

Settings varied and included general practices (n = 15 studies), community pharmacies (n = 8 studies), patient homes or community settings (n = 12 studies), outpatient clinics (n=18 studies), and aged care facilities (n = 9 studies). Professional interventions were predominantly delivered in general practice settings, organisational interventions

were most implemented in outpatient clinics and community pharmacies, while structural interventions were typically system-wide implementations.

3.2.5 Outcomes

Primary outcomes were hospital admissions and number of people admitted to hospital. Eighteen studies (18/62, 29.0%) reported on the number of hospital admissions, while 20 (20/62, 32.3%) reported on the number of people admitted. Secondary outcomes included ED visits and mortality. Eleven studies (11/62, 17.7%) reported on ED visits and 38 studies (38/62, 61.3%) reported mortality data.

3.2.6 Risk of Bias in Included Studies

Twelve studies (12/62, 19.4%) had an unclear risk of selection bias, and the remainder (50/62, 80.6%) had a low risk of selection bias as some details were provided about the randomisation process, as shown in Fig. 1 in Supplementary file 2. Thirty-two studies (32/62, 51.6%) reported adequate concealment of allocation, two studies (2/62 3.2%) had a high risk of bias, and the remainder (28/62, 45.2%) had an unclear risk of bias. Sixteen studies (16/62, 25.8%) adequately blinded measurements of participants and personnel delivering the intervention. Twenty-five studies (25/62, 40.3%) had high risk of bias and the remainder (21/62, 33.9%) had unclear risk of bias. Adequate blinding of outcome assessment was undertaken in 60 studies (60/62, 96.8%). Only two studies (2/62, 3.2%) reported unclear blinding [67, 68]. Forty studies (40/62, 64.6%) reported adequate data reporting (attrition bias), 15 studies (15/62, 24.2%) had high risk of attrition bias and the remainder (7/62, 11.3%) of the studies had an unclear risk. That is, these studies reported complete outcome data or they replaced any missing outcome data using a recognised statistical method, such as last observation carried forward with participants remaining in the group to which they had been allocated. Four studies (4/62, 6.5%) had unclear reporting bias (selective reporting). Gulla, Harnisch and Yang failed to report on all of the AEs that they initially planned to collect and Volpp reported on mortality but did not include the data [26, 62, 68, 73].

3.2.7 Protection Against Contamination Bias

Twenty-four studies (24/62, 38.7%) adequately protected against contamination bias, while 29 studies (29/62, 46.8%) had unclear risk. Contamination bias may occur when participants in the control group are inadvertently exposed to the intervention. Several studies had a high risk due to inappropriate intervention administration, insufficient training, or variation in professional knowledge and delivery, as shown in supplementary file 3, Fig. 1.

3.2.8 Cluster-Randomised Trials

Twenty-seven (27/62, 43.5%) of the included trials used cluster randomisation. Risk of bias was assessed in three additional domains: recruitment bias, baseline imbalances, and analytical methods. Twenty-one studies (21/27, 77.8%) had low recruitment bias, three (3/27, 11.1%) had high risk, and three (3/27, 11.1%) were unclear. All studies used correct statistical approaches for cluster analysis. Generalized Estimating Equations (GEE) were used for binary outcomes, while mixed-effects models were used where individual variation or nested data structures were present. Most studies adjusted appropriately for clustering using intraclass correlation coefficients (ICCs) ranging from 0.01 to 0.1 and adjustments were made for stratification, time effects, or repeated measures. Overall, the statistical approaches were well aligned with study designs and outcomes [14].

3.2.9 Publication Bias

Funnel plots were generated for outcomes from organisational interventions with more than 10 studies. These included number of hospital admissions (Supplementary file 2, Fig. 13), number of people admitted to hospital (Fig. 14), ED visits (Fig. 15), and mortality (Fig. 16). There was no evidence of publication bias.

3.2.10 Synthesis of Results

An overall summary of all the results across the three interventions is presented in Table 5.

3.2.10.1 Professional interventions The evidence for professional interventions in primary care to reduce medication-related hospital admissions, ED visits and mortality was limited and of low to very-low certainty. Across eight studies, professional interventions showed no meaningful impact on mortality (RR 1.00, 95% CI 0.98–1.02) and little to no effect on hospital admissions (RR 0.91, 95% CI 0.60–1.36; 2 studies) or the number of patients admitted (RR 1.01, 95% CI 0.94–7.00; 7 studies). There was no significant reduction in ED visits (RR 0.89, 95% CI 0.76–1.04; 5 studies). The wide CIs, small number of studies, and frequent risks of bias—particularly performance, detection, and selection biases—lowered confidence in these findings. Overall, the results suggest that professional interventions may have minimal or uncertain effects on reducing medication-related adverse outcomes in primary care (Supplementary file 2, Figs 2–5).

3.2.10.2 Organisational interventions Organisational interventions in primary care, such as pharmacist-led reviews and multidisciplinary care models, appeared to have a mod-

Table 5 Summary of intervention effects by type and outcome with evidence certainty

Intervention Type	Hospital Admissions (Number)	Patients Admitted (Number)	Emergency Department Visits	Mortality
Professional Interventions	**RR 0.91** (0.60-1.36)	**RR 1.01** (0.94-7.00)	**RR 0.89** (0.76-1.04)	**RR 1.00** (0.98-1.02)
	n=2 studies	n=7 studies	n=5 studies	n=8 studies
	⬤ **VERY LOW certainty**	⬤ **VERY LOW certainty**	◍ **LOW certainty**	◍ **LOW certainty**
	No effect	*No effect*	*No effect*	*No effect*
Organisational Interventions	**RR 0.81** (0.70-0.95)	**RR 0.99** (0.91-1.08)	**RR 0.79** (0.64-0.97)	**RR 0.94** (0.86-1.02)
	n=20 studies	n=22 studies	n=13 studies	n=27 studies
	◍ **LOW certainty**	⬤ **VERY LOW certainty**	⬤ **VERY LOW certainty**	⬤ **VERY LOW certainty**
	Beneficial effect	*No effect*	*Uncertain effect*	*No effect*
Structural Interventions	**RR 0.90** (0.83-0.97)	**RR 1.04** (0.73-1.49)	**RR 1.88** (0.16-21.77)	**No data available**
	n=2 studies	n=2 studies	n=1 study	
	◍ **MODERATE certainty**	⬤ **VERY LOW certainty**	⬤ **VERY LOW certainty**	
	Beneficial effect	*Uncertain effect*	*Inconclusive*	

ED emergency department, *RR* risk ratio

est beneficial effect on reducing hospital admissions due to preventable medication errors (RR 0.81, 95% CI 0.70–0.95), supported by low-certainty evidence from 20 RCTs. However, they showed no clear effect on the number of patients admitted to hospital (RR 0.99, 95% CI 0.91–1.08; very-low certainty evidence, 22 studies) and uncertain impact on ED visits (RR 0.79, 95% CI 0.64–0.97; $n = 13$ studies, very-low certainty). Similarly, mortality outcomes did not differ significantly between groups (RR 0.94, 95% CI 0.86–1.02; $n = 27$ studies, very-low certainty). A subgroup analysis by professional groups was considered but not conducted due to the limited number of studies within each subgroup and high heterogeneity, which would limit the interpretability of results. Future research should explore intervention effectiveness by different professional groups. The overall certainty of evidence was downgraded due to high or unclear risk of bias across several domains, wide CIs, and significant heterogeneity. While these interventions may reduce hospital admissions, the overall quality of evidence limits confidence in their effectiveness across all outcomes.

3.2.10.3 Structural interventions Structural interventions in primary care—such as quality monitoring systems and policy-level changes that use social, economic, and political interventions to improve public health outcomes—showed a moderate-certainty reduction in hospital admissions (RR 0.90, 95% CI 0.83–0.97) across two large trials, suggesting they may help reduce admissions related to preventable medication errors. However, their effect on the number of people admitted to hospital was uncertain (RR 1.04, 95% CI 0.73–1.49; very-low certainty evidence), and one small trial showed inconclusive and highly imprecise results for ED visits (RR 1.88, 95% CI 0.16–21.77; very-low certainty). No data were available on mortality outcomes. The limited number of studies, small sample sizes for some outcomes, and concerns about risk of bias and wide CIs contributed to very-low certainty in most outcomes. While structural interventions may modestly reduce hospital admissions, their overall impact on broader patient outcomes remains uncertain. (supplementary file 2, Figs 10–12).

4 Discussion

Our review evaluated the effectiveness of professional, organisational, and structural interventions in reducing preventable medication-related hospital admissions, ED visits, and mortality in primary care. Compared to our earlier 2017

review, which included 39 studies, this update incorporates 62 studies and provides stronger evidence for organisational and structural interventions, particularly regarding hospital admission reductions. Overall, the evidence suggests modest and variable effects across intervention types, with limitations in certainty due to methodological concerns.

Professional interventions, such as educational programmes or decision-support tools for prescribers, demonstrated little to no impact on hospital admissions, ED visits, or mortality. While some studies showed a trend toward benefit, the evidence was of low to very-low certainty, largely due to risks of bias, high heterogeneity, and imprecise estimates.

Organisational interventions, including pharmacist-led medication reviews and multidisciplinary care models, were associated with a probable reduction in the number of hospital admissions. However, they showed no significant effect on the number of people admitted to hospital, ED visits, or mortality, with very-low certainty of evidence. These findings suggest potential value in modifying care delivery structures but highlight inconsistency in results and study quality.

Structural interventions, such as system-level quality monitoring or policy-based changes, showed a moderate certainty reduction in hospital admissions, although no effect was observed on the number of patients admitted or ED visits, and mortality data were not available. While promising, the small number of studies and wide confidence intervals for most outcomes limit confidence in these results.

The limited benefits observed in the review may be attributed to substantial heterogeneity among studies. Variations existed in the types of interventions, the health professionals delivering them, and patient characteristics, including comorbidities and age. The outcome measures used may have lacked sensitivity to detect direct intervention effects on medication errors, as they represent downstream consequences rather than direct measures of medication safety improvements. Additionally, the interventions were complex and multifaceted, further contributing to heterogeneity across studies. While this complexity creates challenges for research synthesis and comparison between studies, it reflects the reality that medication management interventions necessarily need to be multifaceted to address the various factors contributing to medication errors. This presents a fundamental challenge for evidence synthesis while being essential for effective practice implementation. This variability—along with differences in settings, healthcare systems, and delivery—suggests the pooled results should be interpreted with caution. Study quality was another concern, with evidence of bias: only 32 studies reported adequate allocation concealment, 16 had low performance bias, and 24 adequately addressed contamination risk, all of which may have impacted the overall findings.

Moreover, The included studies predominantly represented well-resourced healthcare systems, with limited representation from diverse socioeconomic populations or resource-constrained settings. This might affect the generalisability of the results to populations and settings. A retrospective cohort study by Sluggett et al., found that Residential Medication Management Reviews (RMMRs) were associated with a modest 4.4% reduction in 12-month all-cause mortality among 57,719 older Australians in residential aged care, but showed no effect on ED visits, unplanned hospitalisations, or fall-related admissions. In contrast, for organisational interventions in primary care, our systematic review found no significant mortality reduction but did observe a probable reduction in hospital admissions. These differences likely reflect variations in populations, settings, and intervention types—RMMRs targeted frail aged-care residents, while the review addressed broader primary care interventions—highlighting how context influences outcomes. The inclusion of the Sluggett et al. retrospective cohort study provides important contextual comparison to our RCT findings, demonstrating how similar medication review interventions may have different outcomes depending on population characteristics and care settings. While their study found mortality benefits in residential aged care, our primary care-focused RCTs showed hospital admission reductions, highlighting the importance of context in intervention effectiveness [74].

For clinical practice, these findings highlight the importance of implementing multidisciplinary approaches to medication management. Interventions such as regular medication reviews by pharmacists or collaborative care models may help reduce hospitalisations when integrated into routine primary care. A recent review [75] found that integrating pharmacists into general practice has beneficial effects, especially on medication use. However, one recent study [76] concluded that pharmacists may experience ambiguity in their role and have concerns with inappropriate utilisation when given incentives to participate more fully in general practice. Clinicians should be cautious about relying solely on educational strategies, as these alone may be insufficient to prevent adverse outcomes.

From a policy perspective, the evidence supports investment in system-level reforms, such as incentivising structured medication reviews, improving data sharing between care settings, and embedding safety monitoring tools within electronic health systems [77, 78]. Given the modest effect sizes and variability in outcomes, future policies should focus on targeting interventions to high-risk populations, ensuring implementation fidelity, and evaluating cost effectiveness to guide sustainable adoption. Furthermore, improved standardisation of outcome measures and study designs across future trials would strengthen the evidence base and ultimately support better policy decisions to reduce preventable harm.

In summary, while organisational and structural interventions show potential to reduce medication-related hospital

admissions, the current evidence base highlights a pressing need for higher-quality research and coordinated policy responses to optimise medication safety in primary care.

This review is strengthened by its inclusion of 62 randomised controlled trials focused on medication-related errors and their impact on hospitalisations, ED visits, and mortality. First, the end points chosen are not necessarily a direct consequence of medication errors. To measure the effect of these interventions on reducing medication errors, a more direct outcome would be the number of preventable medication-related AEs reduced. Also, we did not consider studies where participants were treated in the ED of hospitals, although we are aware that at times people could receive treatment in the ED without being admitted to hospital. We did not consider the effect of data collection at various time points on the outcomes of interest. A further limitation of this review was the inconsistent reporting of hospital admission outcomes across studies, where it was often difficult to distinguish between medication-related hospital admissions and all-cause hospital admissions from the available data, highlighting the need for improved standardised outcome reporting in future studies to enable more precise synthesis of medication safety interventions.

5 Conclusion

The evidence from this review supports the benefits of organisational and structural interventions to reduce medication errors with respect to the number of hospital admissions, but not with respect to patients admitted to hospital, number of ED visits and mortality. However, there was no evidence supporting the benefits of professional interventions on any of the outcome measures.

Further large well-designed studies exploring the interventions that involve healthcare professionals (nurse, physician or pharmacist) are required with longer time frames (more than 12 months). Further, a focus on high-risk participants/therapies would also help, in addition to including patient-specific outcomes and outcomes related to error rates and AEs.

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Declarations

Conflict of interest Hanan Khalil, Brian G Bell, Richard N Keers, Penny Lewis, Megan Foreman, Amelia Taylor, Barbara Iyen and Darren Ashcroft have no conflicts of interest to declare. Aziz Sheikh received a WHO grant addressing patient safety in primary care. Anthony Avery received BUPA Foundation funding in 2001 to 2002 on a much earlier version of this review (Smeaton 2002). Anthony Avery is National Clinical Director for Prescribing for NHS England.

Ethics approval Ethics approval was not required for this systematic review as it involved analysis of previously published studies and did not involve primary data collection from human participants.

Consent to participate Not applicable—this systematic review did not involve direct participation of human subjects.

Consent for publication Not applicable—this systematic review did not involve individual patient data requiring consent for publication.

Availability of data and material The datasets supporting the conclusions of this article are included within the article and its supplementary information files. The search strategies and data extraction forms are available from the corresponding author upon reasonable request.

Code availability No custom code was developed for this systematic review. All analyses were conducted using standard functions in Review Manager 5.

Author contributions *Hanan Khalil* was involved in the conception of this review, the drafting of the initial protocol and providing critical feedback on drafts of the review. Hanan Khalil selected the studies for inclusion/exclusion and critically appraised the included studies. Hanan Khalil undertook the analysis described in the review and wrote the review. She approved the final version of the review. *Anthony Avery* was involved in the conception of the initial review, the drafting of the initial protocol and providing critical feedback on drafts of the review. Anthony Avery helped with editing the review. He approved the final version of the review. Brian G Bell selected the studies for inclusion/exclusion and critically appraised the included studies and helped with editing the review. He approved the final version of the review. *Richard N Keers, Penny Lewis, Megan Foreman, Amelia Taylor and Barbara Iyen* critically appraised the included studies during screening, helped with editing the review, and approved the final version. *Darren Ashcroft* was involved in securing funding for the review, review of the protocol and providing critical feedback on drafts of the review and approved the final version. Aziz Sheikh was involved in the conception of this review, the drafting of the initial protocol and providing critical feedback on drafts of the review. He approved the final version of the review.

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