


Prevalence of medication administration errors in hospitalized adults: A systematic review and meta-analysis up to 2017 to explore sources of heterogeneity

Christine Azar^{1,2,3,4}  | Paul Raffoul³ | Rana Rizk^{5,6} | Celina Boutros^{7,8} | Nadine Saleh^{3,4,6} | Patrick Maison^{1,2,9}

¹French National Agency for Medicines and Health Products Safety (ANSM), Saint-Denis, France

²EA 7379 EpiDermE, Paris-Est Creteil University, Creteil, France

³Department of Epidemiology and Biostatistics, Faculty of Public Health, Lebanese University, Fanar, Lebanon

⁴CERIPH, Center for Research in Public Health, Pharmacoepidemiology Surveillance Unit, Faculty of Public Health, Lebanese University, Fanar, Lebanon

⁵Department of Natural Sciences, School of Arts and Sciences, Lebanese American University, Byblos, Lebanon

⁶INSPECT-LB: Institut National de Santé Publique, Epidémiologie Clinique et Toxicologie, Beirut, Lebanon

⁷Institut Mondor de Recherche Biomédicale (IMRB)- Inserm U955, Ecole doctorale Sciences de la Vie et de la Santé, Université Paris Est Créteil, Creteil, France

⁸Department of Pediatrics and Adolescent Medicine, Center for Infectious Diseases Research, American University of Beirut Medical Center, Beirut, Lebanon

⁹Creteil Intercommunal Hospital Center (CHI Creteil), Creteil, France

Correspondence

Patrick Maison, French National Agency for Medicines and Health Products Safety (ANSM), 143-147 boulevard Anatole France, F-93285 Saint-Denis, France.
Email: patrick.maison@ansm.sante.fr

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Abstract

Previous estimates to meta-analyze administration error rates were limited by the high statistical heterogeneity, restricting their use. This study aimed to investigate sources of heterogeneity in pooled administration error rates in hospitalized adults. We systematically searched scientific databases up to November 2017 for studies presenting error rates/relevant numerical data in hospitalized adults. We conducted separate meta-analyses for the numerators: One Medication Error (OME) (each dose can be correct or incorrect) and Total Number of Errors (TNE) (more than one error per dose could be counted), using the generic inverse variance with a 95% confidence interval. Heterogeneity was assessed using the I^2 and Cochran's Q test. We meta-analyzed 33 studies. The global pooled analyses based on the OME and TNE numerators showed very high heterogeneity ($I^2 = 100%$; $p < 0.00001$). For each meta-analysis, subgroup analyses based on study characteristics (countries, wards, population, routes of administration, error detection methods, and medications) yielded results with consistently elevated heterogeneity. Beyond these characteristics, we stratified the studies according to the mean error prevalence level as the threshold. Based on the OME numerator, we identified two subgroups of low (0.15[0.13–0.17]; $I^2 = 0%$; $p = 0.43$) and high (0.26[0.24–0.27]; $I^2 = 38%$; $p = 0.17$) pooled prevalence rates, with controlled heterogeneity. Similarly, for the TNE

Abbreviations: CI, confidence interval; CINAHL, Cumulative Index to Nursing & Allied Health Literature; OME, One Medication Error; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; PRISMA-S, Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TNE, Total Number of Errors; TOE, total opportunities for errors.

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numerator, we identified two subgroups of low (0.10[0.09–0.10]; $I^2 = 0\%$; $p = 0.76$) and high (0.28[0.27–0.29]; $I^2 = 0\%$; $p = 0.89$) pooled prevalence rates, with controlled heterogeneity. These subgroups differed regarding the denominators used: Total opportunities for errors versus others (doses, observations, administrations). Calculation methods, specifically the denominator, seem a primary factor in explaining heterogeneity in error rates. Standardizing numerators, denominators, and definitions is necessary.

KEYWORDS

adults, hospital, medication administration error, medication errors, meta-analysis, statistical heterogeneity

1 | INTRODUCTION

Medication errors are common in hospital setting and can result in adverse drug events and a prolonged hospital stay [1]. The greater impact of medication errors in the hospital compared with the ambulatory setting may be related to the more acute and serious nature of clinical cases and the complexity of treatment regimens [2].

Medication errors can occur at any stage of the medication use process, including prescribing, dispensing, administration, and monitoring [3]. Nevertheless, more than half of hospital medication errors occur during the administration stage [4–6]. Administration error is a deviation from the physician's medication order as written on the patient's chart [7]. This error stage is of particular importance, as it constitutes the last step to implement an ultimate interception barrier [3]. In addition, according to medication incident reports in the United Kingdom, the majority of incidents resulting in severe harm or patient deaths are related to the administration stage [8]. Therefore, the prevention of administration errors is a priority for enhancing patient safety.

Several attempts were taken to understand and meta-analyze administration error rates. A systematic review of the prevalence of these errors in healthcare settings reported a median error rate of 19.6% of total opportunities for errors (TOE) [9]. Another systematic review in hospitalized patients showed a median error rate of 25.2% of TOE for cross-sectional studies [10]. However, these two reviews were limited by the high statistical heterogeneity, hindering the meta-analysis of included studies [9,10]. Other meta-analyses focused on specific countries, such as those by Taghizadeh et al [11] in Iran and Almalki et al [12] in Saudi Arabia, have also shown highly statistically heterogeneous administration error rates.

Although high heterogeneity in error rates has been highlighted [9,10,12], there is scarcity in studies attempting to explore heterogeneity in pooled error rates. This heterogeneity was suggested to be related to study design and error detection methods, among others [10].

So far, statistical heterogeneity is a main limitation for meta-analyzing administration error rates [10]; high heterogeneity questions the validity and reliability of the results of a meta-analysis [13] posing restrictions on their use [12]. The quantification of administration error rates with control of heterogeneity provides a valuable safety indicator to guide control measures in hospitals [14]. Our work is of exploratory nature, aiming to investigate the sources of heterogeneity in the prevalence of medication administration errors in hospitalized adults, through a systematic review of the literature and a meta-analysis.

2 | MATERIALS AND METHODS

2.1 | Search strategy

We searched MEDLINE via Ovid, PubMed, Embase via Ovid, and the Cumulative Index to Nursing & Allied Health Literature (CINAHL) via EBSCO up to November 21, 2017. The search was performed using keywords and controlled vocabulary, combining two concepts: “errors” and “hospital setting.” The search strategy was validated by a medical information specialist and is available in Appendix 1. We also conducted a manual search of bibliographies of included studies and relevant systematic reviews for potentially eligible studies. This systematic review was not registered a priori.

2.2 | Inclusion and exclusion criteria

Included studies had to present a medication administration error rate or provide numerical data to calculate a medication administration error rate, be conducted in hospital setting, on adult patients over 18 years of age, and published in English or French, between January 1, 2000, and November 21, 2017. We included cross-sectional studies, prospective studies, and interventional studies for which only pre-intervention data were retained. We excluded retrospective studies, studies that are not original articles (editorials, letters,

comments, opinions, narrative, and systematic reviews), as well as qualitative studies, case reports, and case series, and studies that are only available as a conference abstract. We excluded studies that only target errors related to a specific medication, and studies that rely only on reporting systems to detect errors, because of the underreporting [15,16]. We also excluded studies that did not provide numerical data regarding errors, or if the presented data were pooled with those of the pediatric population.

For the meta-analysis, we further excluded studies that presented the error rate pooled with error risk, and studies that presented rates only for errors with potential or actual adverse events.

2.3 | Selection of studies

Two reviewers (CA/PR) reviewed the titles and abstracts retrieved to identify potentially eligible studies, using EndNote X6 software. Then, three pairs of reviewers (CA/PR; CA/CB; PR/CB) reviewed independently and in duplicate the full texts of these studies against the inclusion criteria.

A calibration exercise was performed before starting the selection process. Discrepancies were resolved by consensus between the two reviewers after discussion. If no consensus was reached, a third reviewer was consulted.

2.4 | Data extraction

An extraction form was developed and used to collect data, including study's characteristics, methodology, and error rates. The authors of included studies were contacted in case of missing or inaccurate information and to clarify ambiguities such as the population studied, the definition of errors, the classifications used, the calculation methods, etc. Data extraction was performed by same three pairs of reviewers independently and in duplicate following a calibration exercise. Discrepancies were resolved through discussions or with the assistance of a third reviewer.

2.5 | Data synthesis

Author-reported study characteristics were summarized narratively in textual and tabular forms. The numerators were presented based on: number of doses (or administrations) with at least One Medication Error (OME) (i.e., each dose may be either correct or incorrect) and the Total Number of Errors (TNE) (i.e., more than one error per dose could be counted). We contacted authors of studies where the numerators were unclear regarding whether they represented the

numerator as OME or TNE. In case they did not respond, we considered the numerator as OME [17–19], since no information on whether one or more errors were counted per dose. The prevalence was calculated by dividing the numerator by the denominator. The denominators were used, as reported in the studies, including the number of doses, administrations, observations, and the TOE.

2.6 | Statistical analysis

Meta-analyses of medication administration error prevalence were performed separately for the OME and TNE numerators, following the generic inverse variance method, using a random-effects model with a 95% confidence interval (95% CI). Heterogeneity in pooled error prevalence rates was our outcome. It was assessed using the I^2 statistic and the Cochran's Q test [20,21]. An I^2 statistic of 0% indicates no observed heterogeneity, and higher values indicate increasing heterogeneity [20]. A P -value <0.05 of the Cochran's Q test indicates heterogeneity [21]. Sources of heterogeneity were first explored by performing subgroup analyses based on the study characteristics, including countries, wards, population, medications, routes of administration, and error detection methods. The analyses were performed on Cochrane Review Manager software (RevMan Version 5.4). Results of meta-analyses were presented visually through forest plots.

2.7 | Quality of reporting of included studies

The quality of reporting of included studies was assessed independently and in duplicate by the same three pairs of reviewers. The assessment was based on a combination of the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) checklist consisting of 22 items [22] and four additional criteria adopted by Alsulami et al [23], three of which are error specific (definition of medication error, categories of errors specified, and categories of errors defined), in addition to the ethical agreement criterion. The quality of reporting was assessed for each item as yes, no, or not applicable. The percentage of applicable items satisfied was calculated ($[\text{number of items satisfied}/\text{total number of applicable items}] \times 100$). The respective thresholds of 0%–25%, 26%–50%, 51%–75% and 76%–100% indicated low, medium, good, and excellent quality of reporting.

Finally, the reporting of the systematic review followed the recommendations of the "Preferred Reporting Items for Systematic reviews and Meta-Analyses" (PRISMA) [24], including those for the literature search extension (PRISMA-S) [25].

3 | RESULTS

3.1 | Selection of studies

The initial search yielded 32 650 references, of which 37 were included in the systematic review and 33 in the meta-analysis (Figure 1). The characteristics of the four studies included only in the systematic review [26–29] are described in Appendix 2.

3.2 | Characteristics of studies included in the meta-analysis

The characteristics of the 33 studies included in the meta-analysis are described in Tables 1 and 2.

3.2.1 | Country

The included studies ($n = 33$) were mainly conducted in the United States ($n = 6$) [17,30,35,41,51,56], France ($n = 5$) [36,38,42,45,53], the United-Kingdom ($n = 5$) [19,31,32,34,46], the Netherlands ($n = 2$) [33,47], and Denmark ($n = 2$) [52,55].

3.2.2 | Hospitals and wards

Most of the studies ($n = 23$) took place in teaching hospitals [17,18,32,37–46,49–58]. Regarding the wards, studies were carried out in medical and/or surgical

wards [19,33,37,38,40,42,43,45,46,48,50,55,58], geriatric wards [32,36,57], mental health wards [31,34,52], intensive care wards [17,39,41,47,51,53,54], emergency department [44], or mixed wards [18,30,35,49,56,59].

3.2.3 | Population

The mean age of the participants varied between 46 [52] and 84 years [36]. The studies by Jheeta and Franklin [32], Cousein et al [36], Kelly et al [46], and Ernawati et al [57] included geriatric patients only.

3.2.4 | Medications and routes of administration

No specific medications were selected in included studies, except in the study by Calabrese et al [17], which targeted high-alert medications, comprising different classes of medications, and the study by Foo et al [18], which included all medications except chemotherapy.

Regarding routes of administration, only one study considered all routes [18], 13 studies considered multiple routes [19,33,37,39,40,45,47,49,50,52,54,55,58], and five studies targeted specific routes, such as the intravenous route [48,59], the oral route [36], the oral/enteral routes [46], and the intravenous and oral routes [17]. In 12 studies, the routes of administration were not reported [31,34,35,38,41–44,51,53,56,57], and in two other studies, the routes were unclear [30,32].

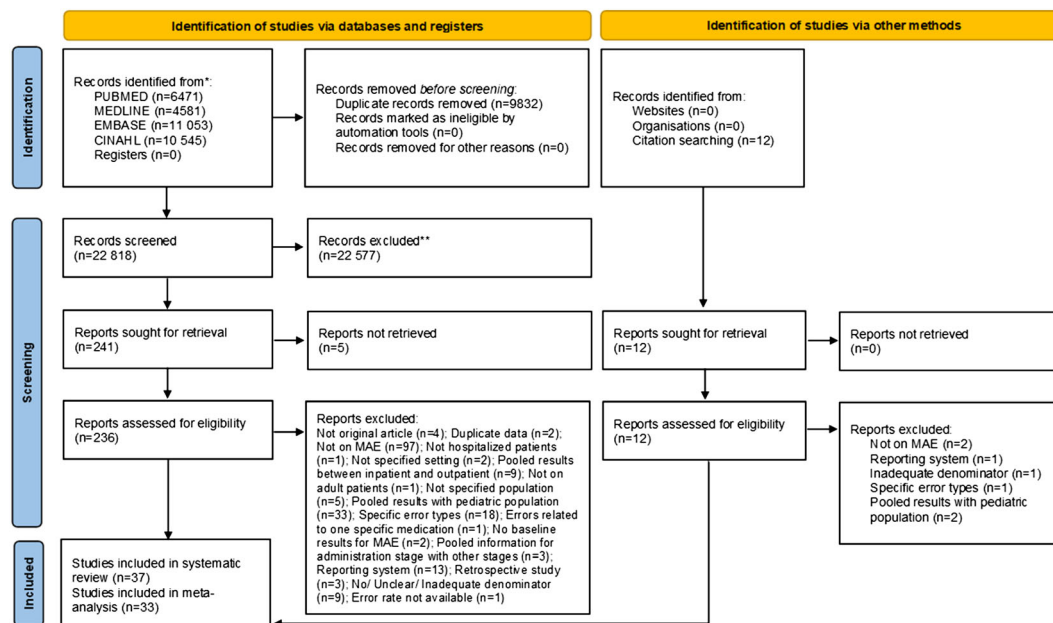


FIGURE 1 PRISMA flow diagram.

TABLE 1 Characteristics of studies included in the meta-analysis, based on the OME numerator (studies are classified by ascending order of prevalence).

Author, year	Setting(country, hospital, ward)	Population(mean ± SD range)	Medication/routes of administration	Design	Error detection method	Numerator (OME)	Denominator	Prevalence
Donaldson et al, 2014 [30]	United States H (43); 107 medical/surgical wards, 26 step down, 24 critical care	Adult Mean age: 59.3 years	No selection Unclear routes (exclusion of medications administered by infusion)	Cross-sectional	Direct observation	OME = 665	Doses = 33 325	0.02
Calabrese et al, 2001 [17]	United States UH: 5 ICU (surgical, medical or mixed)	Adult (age ≥ 18 years) Mean NS	IV and oral high-alert medications	Cross-sectional	Direct observation	OME = 187	Observations = 5744	0.03
Cottney and Innes, 2015 [31]	United Kingdom Mental health hospital: 41 mental health wards: 15 acute adult mental health wards, 15 forensic mental health wards, 7 mental health care of older people wards, 4 adult psychiatric ICU	Adult Mean NS	No selection Routes not reported	Cross-sectional	Direct observation	OME = 139	TOE = 4167	0.03
McLeod et al, 2015 [19]	United Kingdom National Health Service (NHS) hospital trust (3): 1 vascular/cardiology ward, 1 surgical ward, 1 neurological rehabilitation ward	Adult Mean NS	No selection IV Non-IV	Cross-sectional	Direct observation	OME = 16	TOE = 458	0.03
Jheeta and Franklin, 2017 [32]	United Kingdom UH: geriatric medicine ward	Geriatric Mean NS	No selection Unclear routes (exclusion of the IV route)	Pre-post intervention	Direct observation	OME = 18	TOE = 428	0.04
van der Veen et al, 2018 [33]	Netherlands H (4): Internal medicine (including cardiology, pulmonary diseases, and geriatrics), neurological	Adult (age ≥18 years) Mean NS	No selection Oral Others	Cross-sectional	Direct observation	OME = 312	Administrations = 5793	0.05

(Continues)



TABLE 1 (Continued)

Author, year	Setting (country, hospital, ward)	Population (mean \pm SD range)	Medication/routes of administration	Design	Error detection method	Numerator (OME)	Denominator	Prevalence
Foo et al, 2017 [18]	diseases, surgical wards Singapore UH: 26 general wards, 7 ICU	Adult Mean NS	All medications except chemotherapy All routes	Cross-sectional	Direct observation	OME = 273	TOE = 3675	0.07
Cottney, 2014 [34]	United Kingdom Mental health hospital: mental health ward	Adult Mean NS	No selection Routes not reported	Pre-post intervention	Direct observation	OME = 138	TOE = 1542	0.09
Seibert et al, 2014 [35]	United States NUH (2): 2 medical-surgical wards, 2 telemetry wards, 2 rehabilitation wards, oncology ward, ICU	Adult Mean NS	No selection Routes not reported	Pre-post intervention	Direct observation	OME = 417	TOE = 3746	0.11
Cousein et al, 2014 [36]	France General hospital: short stay geriatric ward	Geriatric Mean age: 84 years	No selection Oral	Pre-post intervention	Direct observation	OME = 74	TOE = 615	0.12
Härkänen et al, 2015 [37]	Finland UH: 2 medical wards (cardiology, internal medicine and nephrology), 2 surgical wards (gastroenterology, traumatology)	Adult Mean age: 66.5 years Range: 23–88 years	No selection Oral IV SC Others	Cross-sectional	Direct observation	OME = 149	Observations = 1058	0.14
Tissot et al, 2003 [38]	France UH: 1 geriatric ward, 1 cardiovascular-thoracic surgery ward	Adult Mean NS	No selection Routes not reported	Cross-sectional	Direct observation	OME = 78	TOE = 523	0.15
Romero et al, 2013 [39]	Chile UH: medical-surgical ICU	Adult Mean age: 51.1 \pm 17.8 years	No selection Enteral Parenteral (exclusion of medications administered by inhalation or by continuous infusion)	Pre-post intervention	Direct observation	OME = 33	Observations = 194	0.17
Sweden UH: 3 surgical wards	Adult Mean NS	No selection/ Oral	Cross-sectional	Direct observation	OME = 54	Doses = 306	0.18	(Continues)

TABLE 1 (Continued)

Author, year	Setting (country, hospital, ward)	Population (mean ± SD range)	Medication/routes of administration	Design	Error detection method	Numerator (OME)	Denominator	Prevalence
Gunningberg et al, 2014 [40]			Rectal SC IM IV Eye drops (exclusion of medication administered by infusion)					
Ford et al, 2010 [41]	United States UH: medical ICU, coronary critical care unit	Adult (age > 18 years) Mean NS	No selection Routes not reported	Parallel controlled study	Direct observation	OME = 75 ^a	Doses = 315	0.24
Le Grogneq et al, 2005 [42]	France UH: internal medicine ward	Adult Mean age: 69 years Range: 57–81 years	No selection Routes not reported	Cross-sectional	Direct observation	OME = 52	TOE = 217	0.24
Westbrook et al, 2010 [43]	Australia UH (2): geriatrics, respiratory medicine, renal/vascular medicine, orthopedics and neurology wards	Adult Mean age: Hospital A: 72.6 years Hospital B: 67.5 years	No selection Routes not reported	Cross-sectional	Direct observation	OME = 1067	Administrations = 4271	0.25
Acheampong et al, 2016 [44]	Ghana UH: emergency department	Adult Mean NS	No selection Routes not reported	Cross-sectional	Direct observation	OME = 362	TOE = 1332	0.27
Berdot et al, 2012 [45]	France UH: 1 immunology-cardiology ward, 1 nephrology ward, 1 vascular medical ward, 1 cardiovascular surgical ward	Adult Mean NS	No selection Oral Injectable Other	Cross-sectional	Direct observation	OME = 415	TOE = 1501	0.28
Kelly et al, 2011 [46]	United Kingdom UH (2) and NUH (2): 4 care-of-the-elderly wards, 4 stroke wards	Geriatric Mean NS	No selection Oral Enteral	Cross-sectional	Direct observation	OME = 817	TOE = 2129	0.38
	Netherlands	Adult Mean age: 67 years	No selection Enteral	Cross-sectional	Direct observation	OME = 104	TOE = 233	0.45

(Continues)

TABLE 1 (Continued)

Author, year	Setting (country, hospital, ward)	Population (mean \pm SD range)	Medication/routes of administration	Design	Error detection method	Numerator (OME)	Denominator	Prevalence
van den Bemt et al, 2002 [47]	H (2): 2 medical-surgical ICU	Range: 26–87 years	IV Rectal Inhalation Local					
Sumithra et al, 2017 [48]	India Tertiary care hospital: general medicine ward	Adult Mean NS	No selection IV	Cross-sectional	Direct observation	OME = 180	Administrations = 329	0.55
Feleke et al, 2015 [49]	Ethiopia UH: 1 medical ward, 1 gynecology ward, 1 surgical ward, 1 ICU, 1 emergency ward, 1 recovery ward	Adult (age \geq 18 years) Mean NS	No selection IV IM SC Oral	Cross-sectional	Direct observation	OME = 168	Administrations = 288	0.58
al Teheyw et al, 2016 [50]	Egypt UH: 5 medical wards: 1 geriatric, 1 nephrology, 1 gastroenterology, 1 chest, 1 rheumatology	Adult Mean NS	No selection IV IM Infusion Oral Syrup	Cross-sectional	Direct observation	OME = 2053	Observations = 2090	0.98

Abbreviations: H, hospital; ICU, intensive care unit; IM, intramuscular; IV, intravenous; NS, not specified; NUH, non-university hospital; OME, One Medication Error; SC, subcutaneous; SD, standard deviation; TOE, Total Opportunities for Errors; UH, university hospital.

^aRecalculated excluding prescription errors.

TABLE 2 Characteristics of studies included in the meta-analysis, based on the TNE numerator (studies are classified by ascending order of prevalence).

Author, year	Setting (country, hospital, ward)	Population (mean \pm SD median range)	Medication/routes of administration	Design	Error detection method	Numerator (TNE)	Denominator	Prevalence
Carayon et al, 2014 [51]	United States UH: 1 medical/surgical ICU, 1 cardiac ICU	Adult (age \geq 18 years) Mean age: 61 \pm 16 years	No selection Routes not reported	Cross-sectional	Chart review, reporting system	TNE = 763	Prescriptions = 45 658	0.02
van der Veen et al, 2018 [33]	Netherlands H (4): Internal medicine (including cardiology, pulmonary diseases, and geriatrics), neurological diseases, surgical wards	Adult (age \geq 18 years) Mean NS	No selection Oral Others	Cross-sectional	Direct observation	TNE = 315	Administrations = 5793	0.05
Soerensen et al, 2013 [52]	Denmark UH: 3 psychiatric wards	Adult Mean age: 46 years Range: 20–79 years	No selection Injections Tablets Capsules Suppositories Mixture	Cross-sectional	Direct observation	TNE = 19 ^a	TOE = 340	0.06
Chapuis et al, 2010 [53]	France UH: 2 medical ICU	Adult Median age: 63 years	No selection Routes not reported	Pre-post intervention	Direct observation	TNE = 59	TOE = 668	0.09
Vazin and Delfani, 2012 [54]	Iran UH: internal ICU	Adult Mean age: 50.63 \pm 19.63 years Range: 19–80 years	No selection Oral IV (bolus, continuous infusion) SC IM Inhalation Rectal Intraocular	Cross-sectional	Direct observation	TNE = 265	TOE = 2766	0.10
Lisby et al, 2005 [55]	Denmark UH: 1 medical ward, 1 surgical ward	Adult (age \geq 18 years) Mean age: Medical ward = 55 years/surgical ward = 62 years	No selection IV IM SC Tablets Suppositories Mixtures	Cross-sectional	Direct observation	TNE = 40 ^a	TOE = 412	0.10
Ching et al, 2013 [56]	United States UH: 10 acute care wards, 1 ICU, 1	Adult Mean NS	No selection Routes not reported	Pre-post intervention	Direct observation	TNE = 132	Doses = 1282	0.10

(Continues)

TABLE 2 (Continued)

Author, year	Setting (country, hospital, ward)	Population (mean \pm SD median range)	Medication/routes of administration	Design	Error detection method	Numerator (TNE)	Denominator	Prevalence
Ermawati et al, 2014 [57]	rehabilitation ward, 1 emergency department Indonesia UH: geriatric ward	Geriatric (age \geq 60 years) Mean age: 71.4 \pm 7.5 years	No selection Routes not reported	Cross-sectional	Chart review Interviews with patients/carers, review of medications dispensed from the central pharmacy, checking stock levels in patients' medication drawers	TNE = 927	Doses = 7662	0.12
Gunningberg et al, 2014 [40]	Sweden UH: 3 surgical wards	Adult Mean NS	No selection Oral Rectal SC IM IV Eye drops (exclusion of medication administered by infusion)	Cross-sectional	Direct observation	TNE = 58	Doses = 306	0.19
Sulaiman et al, 2017 [58]	Jordan UH: internal medicine ward	Adult Mean age: 54.2 \pm 17.59 years Range: 51–60 years	No selection Oral IV bolus IV Infusion SC IM Inhalation Intraocular Rectal Others	Cross-sectional	Direct observation Chart review	TNE = 739	TOE = 3667	0.20
Westbrook et al, 2010 [43]	Australia UH (2): geriatrics, respiratory medicine, renal/vascular medicine, orthopedics and neurology wards	Adult Mean age: Hospital A: 72.6 years Hospital B: 67.5 years	No selection Routes not reported	Cross-sectional	Direct observation	TNE = 1196	Administrations = 4271	0.28
	France	Adult	No selection		Direct observation	TNE = 430	TOE = 1501	0.29 (Continues)

TABLE 2 (Continued)

Author, year	Setting (country, hospital, ward)	Population (mean ± SD median range)	Medication/routes of administration	Design	Error detection method	Numerator (TNE)	Denominator	Prevalence
Berdot et al, 2012 [45]	UH: 1 immunology-cardiology ward, 1 nephrology ward, 1 vascular medical ward, 1 cardiovascular surgical ward	Mean NS	Oral Injectable Other	Cross-sectional				
Taxis and Barber, 2004 [59]	Germany NUH: 1 surgical ward, 1 surgical ICU	Adult Mean NS	No selection IV	Cross-sectional	Direct observation	TNE = 35	Doses = 122	0.29
al Tehewy et al, 2016 [50]	Egypt UH: 5 medical wards: 1 geriatric, 1 nephrology, 1 gastroenterology, 1 chest, 1 rheumatology	Adult Mean NS	No selection IV IM Infusion Oral Syrup	Cross-sectional	Direct observation	TNE = 5531	TOE = 14 630	0.38
van den Bent et al, 2002 [47]	Netherlands H (2): 2 medical-surgical ICU	Adult Mean age: 67 years Range: 26–87 years	No selection Enteral IV Rectal Inhalation Local	Cross-sectional	Direct observation	TNE = 131	TOE = 233	0.56

Abbreviations: H, hospital; ICU, intensive care unit; IM, intramuscular; IV, intravenous; NS, not specified; NUH, non-university hospital; SC, subcutaneous; SD, standard deviation; TNE, Total Number of Errors; TOE, Total Opportunities for Errors; UH, university hospital.

^aRecalculated excluding the error type "lack of identity control" as it was considered a risk of error.

3.2.5 | Study design

Most of the studies were cross-sectional ($n = 25$) [17–19,30,31,33,37,38,40,42–52,54,55,57–59]. The others were pre–post implementation studies ($n = 7$) [32,34–36,39,53,56], and one parallel-controlled study [41].

3.2.6 | Error detection method

In most studies, medication errors were detected through direct observation, whether disguised or not [17–19,30–50,52–56,58,59]. Other detection methods used included chart review [51,57,58], reporting system [51], interviews with patients/carers [57], review of medications dispensed from the central pharmacy [57], and checking stock levels in patients' medication drawers [57].

3.3 | Administration error rate

The error rates were expressed either as incidence, that is, error rate taking into account the unit of time, for example, patient-day, or as prevalence, that is, error rate according to different denominators, for example, observations, administrations, and TOE. The results of this meta-analysis were expressed in terms of prevalence, since only one study [51] expressed one of its error rates in terms of incidence.

3.3.1 | Denominator

Various denominators were used in included studies, the definitions of which were not always sufficiently detailed or precise. Furthermore, the same term sometimes corresponded to different definitions. The denominators used included number of observations [17,37,39,50], doses [30,40,41,56,57,59], administrations [33,43,48,49], and TOE. The definitions of the latter varied between the total number of ordered doses and unordered doses administered to patients [34,38,44,45], or the total number of doses administered and doses omitted [31,32,35,36,42,46,47,53–55,58]; in some studies, the authors elaborated their own definition of the TOE [18,19,50,52].

3.3.2 | Numerator

Eighteen studies presented error rates based only on the OME numerator [17–19,30–32,34–39,41,42,44,46,48,49], while nine studies used only the TNE numerator [51–59]. Six studies presented the error rate based on OME and TNE [33,40,43,45,47,50]. To

estimate the global rate of medication administration errors, two analyses were performed: one analysis for studies using the OME numerator and one for those using the TNE numerator.

3.3.3 | Global rate of medication administration errors, based on the OME numerator

Twenty-four studies based on the OME numerator were included in the meta-analysis, the characteristics of which are detailed in Table 1.

The rate of administration errors varied between 0.02 [30] and 0.98 [50]. The global pooled rate based on the OME numerator was 0.23 (95% CI: 0.11–0.35) with a very high heterogeneity ($I^2 = 100%$; Cochran's Q test $p < 0.00001$). Since, as expected, the heterogeneity of the pooled rate was high ($I^2 = 100%$), different subgroup analyses based on study characteristics including countries, wards, population, medications, and routes of administration were performed to explain and control this heterogeneity. In each of these analyses, heterogeneity remained consistently high (Appendix 3). Therefore, we explored the sources of heterogeneity beyond the study characteristics. Since the prevalence of errors in the different studies varied between low and high rates, we stratified the studies according to the error prevalence level: low versus high, taking the pooled mean of the meta-analysis (0.23) as the threshold. Accordingly, 14 studies had a low prevalence level (i.e., ≤ 0.23) [17–19,30–40] and 10 studies had a high prevalence level (i.e., >0.23) [41–50]. In each side of this threshold, we tested incrementally the heterogeneity to obtain the combination with the least heterogeneity (Figure 2).

The two subgroups, for which the heterogeneity was controlled, showed a low pooled prevalence rate of 0.15 (95% CI: 0.13–0.17; $I^2 = 0%$) and a high rate of 0.26 (95% CI: 0.24–0.27; $I^2 = 38%$) (Figure 3).

After exploring these two subgroups, we noticed that they differed regarding the denominators used: In the subgroup of studies with a low pooled error rate, the majority of denominators were based on doses and observations, while in the subgroup that presented the high pooled error rate, the denominators tended toward the TOE. These two subgroups consisted of sets of studies closely located from either side of the pooled mean of the meta-analysis.

3.3.4 | Global rate of medication administration errors, based on the TNE numerator

Fifteen studies based on the TNE numerator were included in the meta-analysis, the characteristics of which are detailed in Table 2.

FIGURE 2 Forest plot of the global prevalence of medication administration errors, based on the OME numerator and the two subgroups of low and high prevalence with control of heterogeneity. The dotted line represents the pooled mean of the meta-analysis. The low prevalence subgroup is visualized in green, and the high prevalence subgroup is visualized in red.

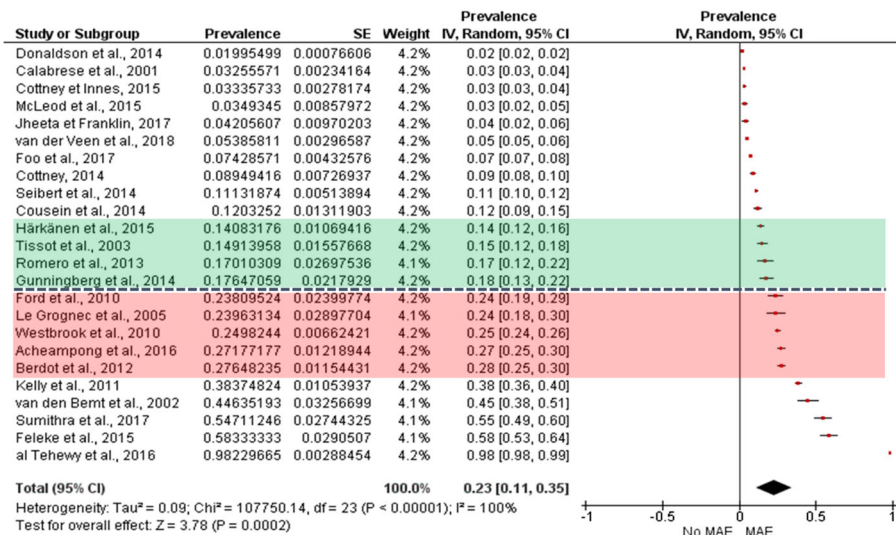
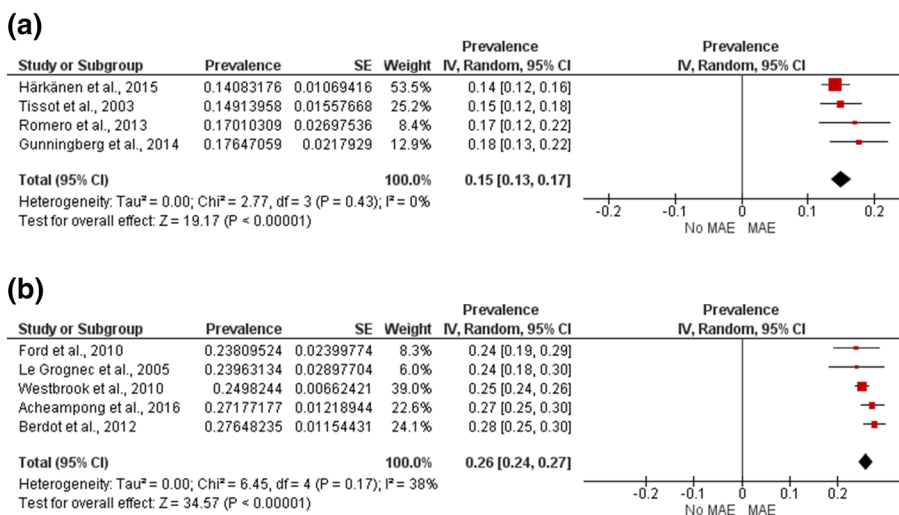


FIGURE 3 (a) Forest plot presenting the low pooled prevalence of medication administration errors, based on the OME numerator. (b) Forest plot presenting the high pooled prevalence of medication administration errors, based on the OME numerator.



The rate of administration errors varied between 0.02 [51] and 0.56 [47]. The global pooled error rate based on the TNE numerator was 0.19 (95% CI: 0.12–0.25) with a very high heterogeneity ($I^2 = 100\%$; Cochran's Q test $p < 0.00001$). Given that the heterogeneity for the global result was high ($I^2 = 100\%$), the same approach described above was adopted to reduce heterogeneity. We conducted different subgroup analyses based on the characteristics of the studies, including countries, wards, population, routes of administration, and error detection methods, for all of which the heterogeneity remained high (Appendix 4). To better explore heterogeneity, we also stratified the studies according to the level of prevalence of errors, taking the pooled mean of the meta-analysis (0.19) as a threshold: Nine studies had a low prevalence level (i.e., ≤ 0.19) [33,40,51–57], and six studies had a high prevalence level

(i.e., >0.19) [43,45,47,50,58,59]. In each side of this threshold, we tested incrementally the heterogeneity to obtain the combination with the least heterogeneity (Figure 4).

The two subgroups for which heterogeneity was null had respectively a low pooled prevalence rate of 0.10 (95% CI: 0.09–0.10; $I^2 = 0\%$) and a high rate of 0.28 (95% CI: 0.27–0.29; $I^2 = 0\%$) (Figure 5).

These subgroups differed regarding their denominators. The subgroup of studies that presented the low pooled error rate was mostly oriented toward the TOE denominator, while the subgroup that presented the high pooled error rate was mostly oriented toward the denominators doses/administrations. Having two groups of denominators (TOE vs. other denominators: doses, administrations, or observations) on each side of the mean prevalence was also noticed in the analysis based on the OME numerator.

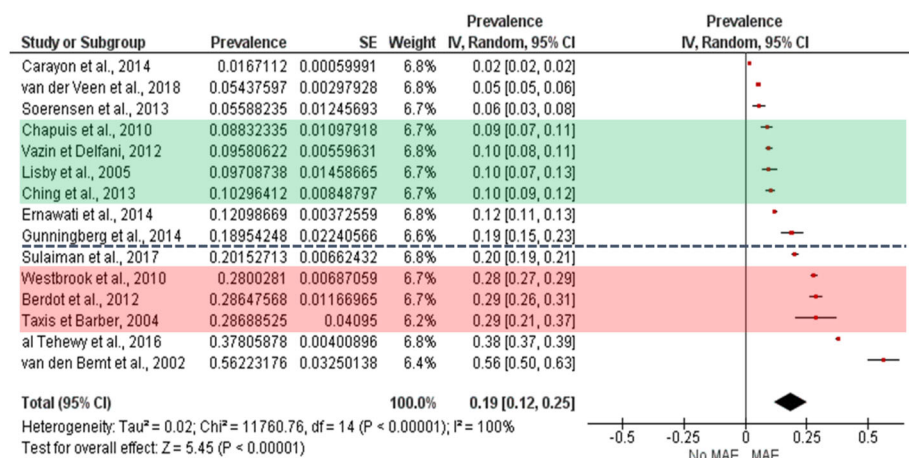


FIGURE 4 Forest plot of the global prevalence of medication administration errors, based on the TNE numerator and the two subgroups of low and high prevalence with control of heterogeneity. The dotted line represents the pooled mean of the meta-analysis. The low prevalence subgroup is visualized in green, and the high prevalence subgroup is visualized in red.

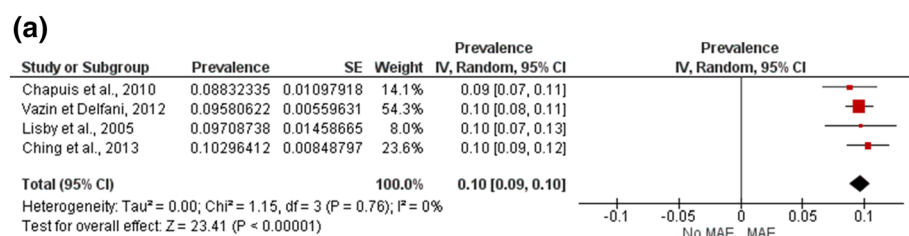
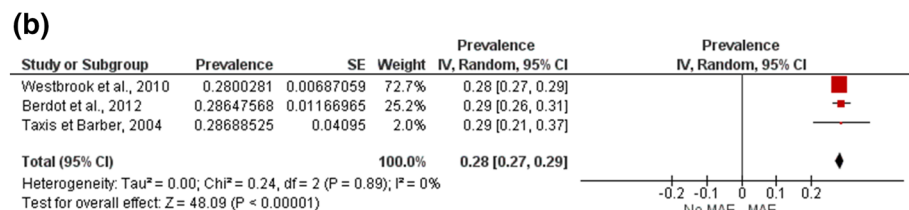


FIGURE 5 (a) Forest plot presenting the low pooled prevalence of medication administration errors, based on the TNE numerator. (b) Forest plot presenting the high pooled prevalence of medication administration errors, based on the TNE numerator.



3.4 | Quality of reporting of the studies

Nine studies had a good quality of reporting [17,18,34,35,42,47,48,54,59], and 24 studies had an excellent quality [19,30–33,36–41,43–46,49–53,55–58].

4 | DISCUSSION

This meta-analysis confirms that medication administration errors are common in hospitalized adult patients. However, estimating exact prevalence rates remains a great challenge, as shown by the substantial heterogeneity in previous meta-analyses [9,10,12]. In this meta-analysis, we sought to investigate factors affecting heterogeneity to improve error prevalence assessment. Our extensive analyses indicated that error calculation methods, specifically the denominator, are a crucial factor in explaining heterogeneity in pooled error rates. This hypothesis allowed for the first time to assess a

pooled prevalence of medication errors without heterogeneity.

The high heterogeneity in our meta-analyses was expected. Indeed, this heterogeneity is highlighted in the literature [9,10,12], and it could be attributed to many factors, including study design and error detection methods, etc. [10].

Our results suggest that these factors as well as other study characteristics (country, ward studied, population, medications, routes of administration), isolated, are not sufficient to explain heterogeneity. Similar observations were reported by other researchers. Taking the country as an example, despite being focused on specific countries, several meta-analyses presented heterogeneous results such as the work of Taghizadeh et al [11] in Iran and Almalki et al [12] in Saudi Arabia.

Following these analyses, we tested the hypothesis of heterogeneity being linked to the error calculation method. We identified two subgroups of studies for which heterogeneity was controlled, one with a low

pooled prevalence of 15% and one with a high pooled prevalence of 26%, based on the OME numerator. These subgroups differed mainly by their denominators: other denominators (doses/observations) versus TOE. The same approach applied for the analysis based on the TNE numerator resulted in two subgroups without heterogeneity with low and high pooled prevalence rates of 10% and 28%, respectively. These subgroups also differed by their denominators (TOE vs. other denominators: doses/administrations).

The approach to quantifying administration error rates based on different types of denominators was suggested by other authors [9,10]. Following a series of analyses, we induced that, indeed, denominator types play a primary role in explaining heterogeneity in the pooled error rates. However, this hypothesis is not without limitations, since the definitions of the denominators were limited by the details given in each publication. Furthermore, the robustness of this hypothesis must be confirmed by future studies.

The scientific literature encompasses a variety of denominators used in calculating medication error rates, including TOE, doses, prescriptions, and patients [60]. Furthermore, Ferner et al [61] found that often the denominator used to quantify error rates is both poorly defined and inconsistently measured. Although the use of the TOE as a denominator has been advocated to determine the rate of medication errors in general [62], McLeod et al [63] recommended the use of this denominator particularly for administration error rates. Moreover, McLeod et al [63] recommended using the proportion of opportunity of error with at least one administration error, as this approach is the most practical and easily interpreted. However, reaching a consensus on numerators and denominators is warranted.

The primary factor leading to heterogeneity seems to be the denominator. However, for each subgroup with heterogeneity controlled, there have been studies that, when introduced, led to an increase in heterogeneity. It is, therefore, plausible that beyond the denominator as primary factor, there are a combination of factors (characteristics of the studies) that further explain the heterogeneity. Nevertheless, we were unable to investigate this reasoning since studies with similar characteristics were limited in number.

Since the heterogeneity in pooled error rates is mainly related to calculation methods, we therefore recommend standardizing the numerators, denominators, and their definitions. Regarding this point, a systematic review of the literature found 45 generic definitions of medication errors, including 26 different forms of wordings confirming the inconsistency in the definitions of errors [60]. The authors of this review suggested that definitions and detection methods may be subject to individual researcher preferences rather than being reproducible and reliable [60]. Applying clear definitions and reliable methods could significantly improve the

quality and consistency of medication error studies [60]. Likewise, research on medication administration error rates must describe the methodology in a precise manner, specifically regarding the number of possible errors per dose, the number of doses with at least one error if more than one error is possible per dose, the total number of errors detected in the doses with error, the detailed definitions of numerators and denominators, and the method used to calculate the error rate. These recommendations echo those suggested by McLeod et al [63].

Targeted efforts should be deployed to enhance the methods and reporting of medication error studies. We suggest to bring together key stakeholders in the field of medication safety including national and international entities along with academicians and researchers to foster the work on standardizing study methods, especially denominators, numerators, and calculation methods. Practical steps include identifying inconsistencies across studies, issuing clear definitions and terminology, and reaching a consensus on valid, reliable, yet relatively simple, and easy reproducible denominators and numerators to track medication error rate in a consistent and systematic manner. Based on our work, we suggest the use of the OME numerator with the TOE denominator given their practicality. On the one hand, the OME numerator is widely used, is practical, and avoids the overestimation of error rates. On the other hand, it seems that the TOE denominator is better defined than the other denominators adopted by the studies included in this meta-analysis. For the TOE denominator, although the definitions may slightly vary, they are very precise, which makes it more practical and more reproducible. Nevertheless, it remains necessary to perform robust methodological studies that allow us to identify the best types of numerators and denominators in terms of validity, reliability, and practicality.

Calls for standardization in this research field would ultimately lead to issuing guidelines on study design, which should be disseminated among researchers, who should be also trained on using them while conducting pertaining research. Furthermore, we suggest to issue a set of reporting criteria or a checklist for authors to submit to journals along with their research findings.

4.1 | Strengths and limitations

Our study was first to provide quantitative evidence on the sources of heterogeneity in pooled medication administration error rates and induced that the calculation methods, specifically the denominator, constitute a primary factor in this regard. We used an exhaustive search strategy, conducted on several databases and validated by a medical information

specialist. Inclusion of studies and data extraction were done in duplicate. Finally, we followed best practices for reporting systematic reviews and used a validated checklist to assess the reporting quality of included studies [24,25].

However, our systematic review has certain limitations, specifically regarding the categorization of studies. The definitions of denominators used in included studies were not always sufficiently detailed or precise; also, in some studies, the same term corresponded to different definitions. These factors might have affected the assignment of the studies into the two groups of denominators. Similarly, we had to contact some authors to clarify the numerators used. In cases where they did not respond, the numerators were categorized by default as OME. However, this concerned only three studies, which is unlikely to affect our results. Although the metaregression is a suggested method to explore heterogeneity, we could have not used it. The analysis by the meta-regression method assumes a linear relationship between the dependent variable and the independent variables, which we could not ascertain in the current analysis. Other factors should be taken into account to further explain heterogeneity. Future studies can build on the work generated by this analysis to explore these factors. Finally, we acknowledge that recent literature was not included in this review. This systematic review is of exploratory nature, aiming to investigate the sources of heterogeneity in error rates using a pool of studies, rather than generating actualized prevalence rates, where including recent studies is required. Extending the study period may be of value; however, we argue that our work is still valid given that systematic reviews of recent literature still pinpoint heterogeneity of error rates as a major problem [12,64,65]. Lack of standardization of methods, numerators, and denominators definitions remains a main shortcoming in this field [66], especially that, to our knowledge, in recent years, no standardization of medication error methods was issued by national or international agencies. All of these factors highlight the relevance of our recommendation for standardization in medication error research.

5 | CONCLUSION

This work was first to meta-analyze medication administration error rates in hospitalized adult patients while controlling heterogeneity. Our analyses induce that the calculation methods, specifically the denominator, appear to be a primary factor in explaining heterogeneity in error rates. Standardization of numerators, denominators, and definitions is a necessity. Future studies could be conducted to validate our hypothesis and explore other factors contributing to heterogeneity in error rates.

AUTHOR CONTRIBUTIONS

Patrick Maison, Nadine Saleh, and Christine Azar were involved in the concept and design. Christine Azar and Rana Rizk performed the searches. Christine Azar and Paul Raffoul conducted the title and abstract screening. Christine Azar, Paul Raffoul, and Celina Boutros conducted the full-text screening and performed the data extraction and quality assessment. All the authors contributed to writing the draft manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Open Science Framework at <https://doi.org/10.17605/OSF.IO/QC7RX>.

ORCID

Christine Azar  <https://orcid.org/0000-0001-9224-8262>

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SUPPORTING INFORMATION

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