Antimicrobial Resistance and Infection Control

REVIEW

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Healthcare-associated bloodstream infections caused by bacterial and fungal contamination of intravenous fluids and medicines in healthcare facilities in low- and middle-income countries: a scoping review

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Abstract

Introduction We reviewed culture-confirmed healthcare-associated outbreaks linked to bacterial and fungal contamination of intravenous fluids and medicines (further "infusates") in low-income countries and lower and upper middle-income countries (LIC, Lower-MIC and Upper-MIC). We assessed the scope, impact, risks, and gaps in knowledge.

Methodology Literature search including PubMed, Web of Science, Worldwide Database for Nosocomial Outbreaks, Global Health, and Google Scholar. National essential medicine lists (NEMLs) of sub-Saharan countries were searched for listing of pediatric infusates.

Results Between 1975 and 2023, 50 articles were retrieved. Median (range) number of patients affected was 12 (3–185); 74.2% (761/1025) of all patients affected were children. All patients presented with bloodstream infections; median case fatality ratio was 21.1% (0.0–87.5%). Upper-MIC, Lower-MIC and LIC accounted for 21, 25 and 4 articles, respectively. Most frequently affected wards were neonatal and adult intensive care units (19 and 6 articles). The 50 articles revealed 59 contaminated infusates: IV fluids (n = 37), including TPN (n = 10, of which 8 were from Upper-MIC), and IV medicines (n = 22), comprising amongst others propofol (n = 4) and Water for Injection (n = 3). The 63 isolates included Enterobacterales (46.0% (29/63) of isolates), non-fermentative Gram-negative bacteria (NFGNB, 47.6% (30/63)), fungi (4.8%, 3/63)) and *Bacillus circulans* (1.6% (1/63)). Among the Enterobacterales, the genera *Serratia*, *Klebsiella*, and *Enterobacter* represented 82.8% (24/29) of isolates. *Burkholderia cepacia* was the most frequent NFGNB (53.3% (16/30) isolates). Excluding TPN, 18 IV fluids and 7 IV medicines (representing half (51.0%, (25/49) of these infusates) were incorrectly used as multidose vial. A third (33.9%, 20/59) of infusates in 40.0% (20/50) of articles was intrinsically contaminated. In LIC and LMIC, staff in neonatology units turned to in-ward preparation of infusates because of lack of access to pediatric IV formulations and sizes. Less than a third (31.8%, 18/44) of the NEMLs listed neonatal IV premixtures.

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Conclusion Infusate contamination is a serious, underreported risk especially for children in LICs and Lower-MIC. Outstanding issues are access to pediatric infusates and preventing in-ward preparation of IV medicines in LIC and Lower-MIC, and safe preparation and administration of TPN in Upper-MIC.

Keywords Low- and middle-income countries, Healthcare-associated infections, Outbreaks, Infusates, Bacterial contamination

Introduction

Healthcare-associated infections (HAI) are acquired while receiving treatment in a healthcare facility (HCF) [1]. In acute-care hospitals, for every 100 patients, 7 patients in high-income countries (HIC) and 15 in low- and middle-income countries (LMIC) will acquire at least one HAI. Among patients admitted to the intensive care unit, 30% can be affected by HAIs, with the incidence being 2–20 times higher in LMIC compared to HIC, especially among neonates [2].

The HCF environment contains multiple reservoirs of bacteria and fungi that can cause HAIs. Reservoirs include medical devices, patient care devices and water. They function as sources for pathogens, which can be transmitted to the patient's mucous membranes and skin, and subsequently colonize and infect the patient [3–6].

Patients admitted to HCF may require intravenous (IV) fluid for rehydration, medication, and parenteral nutrition. Children require pediatric doses of IV medicines and fluids, and neonates in addition require specific IV formulations (Box 1) [7, 8]. Like other fomites, infusates can be contaminated with bacteria and fungi and be reservoirs of pathogens that may cause HAI [3].

Despite the heavy burden of HAIs and the challenges of IV therapy, bacterial and fungal infusate contamination and its contribution to HAI are not known and have rarely been reported from LMIC. A review published in 2007, focusing on viral, bacterial, and fungal contamination of infusates and blood products, included almost twice as many articles from HIC compared to LMIC [3]. Based on our field observations and inspired by conversations during a course on Antimicrobial Resistance [9], we conducted a scoping review about HAI caused by bacterial and fungal contamination of IV fluids and medicines in HCF in LMIC. The purpose of this study was to identify the scope and impact of these contaminations, highlight potential gaps in knowledge, and inform strategies for prevention and control in LMIC.

The research questions of this review are as follows:

1. What were the known frequency and burden of outbreaks caused by bacterial and fungal infusate contamination in HCF in LMIC?
2. Which products and pathogens were involved?
3. Which were the risk factors for contamination and transmission?
4. Which interventions were made to contain these outbreaks and to mitigate the risks of infusate contamination?
5. What are the outstanding issues about contamination of infusates in LMIC?

Materials and Methods

Terms and Definitions of Infusates

Box 1 explains the terms and definitions used in the present review. In brief, the term infusates refers to both IV fluids and IV medicines. IV fluids are grouped as dextrose, saline and total parenteral nutrition (TPN), and IV medicines also include Water for Injection used for reconstitution. Single dose vials (SDV) are designed for a single injection, whereas multidose vials (MDV) are designed to deliver more than one dose; the latter contain antibacterial substances (preservatives). Premixtures are commercially prepared products; admixtures are mixtures of IV fluids and/or IV medicines which are prepared in the HCF, either in the pharmacy or in the ward. The term multiple-use single dose vial (mSDV) was coined for this review: mSDV comprise single dose IV medicines and IV fluids which are—against the manufacturer's instructions—used for administration of multiple doses. Intrinsic (primary) contamination refers to contamination during the manufacturing process, while extrinsic (secondary) contamination refers to contamination during transport, storage, preparation, and administration of infusates.

Eligibility Criteria

The inclusion criteria were original articles addressing culture-confirmed HAI (outbreaks and single patient cases) related to bacterial and fungal contamination of infusates in HCF in LMIC. Reports from HIC, reports that conducted only a clinical-epidemiological investigation with no environmental cultures, experimental studies, veterinary studies, and reviews were excluded. Studies that reported the contamination of medicine vials with nebulizing solutions, intraocular solutions, intra-articular injections, and intramuscular injections were

Box 1 Terms and definitions related to intravenous fluids and medicines used in this review

1. Infusates and Infusion

   The term infusates in this review denotes all solutions administered intravenously, including intravenous (IV) fluids and intravenous medicines [113]
   The term infusion in this review comprises both injection and infusion, whereby injection stands for the IV administration of a limited volume of fluid usually from a syringe and infusion stands for the parenteral administration of a larger volume of infusion fluid over a period of time [93]

2. Intravenous fluids include:

   Glucose (dextrose) -containing solutions at concentrations of 5%, 10%, and 50% as listed on the World Health Organization Model List of Essential Medicines 2023 (WHO EML) [8, 122]. In this review, infusates of dextrose and glucose are both referred to as dextrose
   Solutions of sodium chloride 0.9% also termed as saline 0.9%, normal saline, and sodium chloride. In this review they are referred to as saline and are also included in the WHO EML 2023 [122]
   Neonates and children have unique fluid requirements. The World Health Organization (WHO) recommends 10% dextrose infusions during the first 2 days of life. On day 3 of life, sodium should be added; the recommended infusate is 5% glucose (dextrose) with 0.45% sodium chloride ("half-normal saline–dextrose 5%"), [7] which is listed on the WHO EML for children [8]. For neonates who need IV fluids, the total fluid intake per day ranges between 60 and 100 ml/kg/day [7]. In addition, normal saline–dextrose 5% and Ringer's lactate—5% dextrose are options for IV therapy in children, e.g. during surgery and resuscitation of burns [7, 8]
   Ringer's lactate (Hartmann's solution) mentioned in the reference [27] contains sodium, chloride, potassium, calcium, and lactate [7, 93]
   Total parental nutrition (TPN) is a temporary means of providing intravenous nutritional support to patients whose dietary requirements cannot be met enterally. TPN comprises dextrose, proteins, fatty acids, amino acids, electrolytes, and vitamins [132, 133]

3. Premixtures and Admixtures:

   Premixtures are commercially prepared infusates (including mixtures of IV fluids and/or medicines) that are ready to use and do not require reconstitution [134]. They have a fixed composition and a fixed volume
   Admixtures are made in the hospital by mixing two or more IV fluids, or IV fluids and intravenous medicines [135–138]. They are prepared in the pharmacy or in the clinical area; the risk of contamination is higher in the clinical area [93]

4. Intravenous medicines: vials and ampoules, Water for Injection:

   Intravenous medicines are mostly contained in vials which are sealed by an elastomeric stopper locked in place by means of an aluminum overcap crumped over the stopper and neck of the vial while ampoules are closed by heat sealing (mostly glass fused by heat) [93]. In this review, the term "vial" is used except when referring to articles mentioning ampoule
   Water for Injection is sterile water prepared by distillation or a method of purification equivalent to distillation. It is used to reconstitute IV medicines especially when the active ingredient is poorly soluble in water and other solvents [93, 139]. It is manufactured in 2 ml, 5 ml, and 10 ml quantities [122]
   Reconstitution is the dissolving of powder or the dilution of a concentrate from a vial and withdrawing it in a syringe for administration (in preparation of injection [93]

5. Single dose vials or multi-dose vials:

   Single dose vials (SDV) are designed for a single patient/procedure/injection [106]. They do not have antibacterial substances ("preservatives")
   Multi-dose or multiple-dose vials (MDV) contain more than one dose of medication and may be used more than once as per manufacturer's recommendation. They have antibacterial preservatives (antibacterial substances) added [93, 106]
   The term "multiple-use single-dose vials (mSDV)" is used in this review to refer to medicine vials designed and manufactured as SDV, which are (incorrectly) used more than once and/or for more than one patient. The term mSDV in this review also applies to IV fluids which are—against the instructions of the manufacturer—used for administration of multiple doses, such as heparinized saline fluid in bags used to flush peripheral intravascular catheters [87]

6. Type of contamination

   Intrinsic or primary contamination occurs during the manufacturing process [113, 140]
   Extrinsic, secondary, or in-use contamination occurs during transport or storage of the infusates, or during the preparation or administration of the infusate [113, 135, 140]

7. Open and closed infusions systems

   Open IV infusion systems include containers that are rigid (glass, burette) or semi-rigid plastic containers that need to be vented during infusion, i.e. ambient air must be entered through needle or air filter to empty the bottle [88, 135, 141]
   Closed IV infusion systems include containers that are fully collapsible plastic containers that do not require or use any form of an external vent (air filter or needle) to empty the fluid. In addition, the injection ports are self-sealing [88, 135, 141]. The closed IV infusion system is associated with a lower frequency of catheter-related bloodstream infections [88, 91, 142]

also excluded, as was the bacterial or fungal contamination of blood products.

Search Strategy

Peer-reviewed studies were searched via PubMed, Web of Science, Global Health, Google Scholar, and via the Worldwide Database for Nosocomial Outbreaks [10]. The PubMed search terms used were: (nosocomial infection OR hospital-acquired infection OR HAI OR bacterial contamination OR fungal contamination) AND (admixtures OR intravenous fluid OR multidose vial OR single-dose vial). These keywords were adapted for the other databases. Additionally, we conducted a search without Boolean operators, using the following terms: 'intravenous fluid contamination,' 'intravenous medication contamination,' 'saline contamination,' and 'dextrose contamination.' A snowball search was performed by examining the reference list and the "cited

by" lists of the retrieved papers. Additional libraries and grey literature databases like ProQuest Dissertation were searched. Publications in English, French, Spanish, or German were considered, and no publication date limit was set.

The country's income level was retrieved from the World Bank website [11] based on the article's publication year. The categories used in the review include low-income countries (LIC), lower middle-income countries (Lower-MIC), and upper middle-income countries (Upper-MIC).

Data Extraction

The articles retrieved were screened first by title and abstract using Rayyan systematic review screening software [12]. Next, full-text screening of the articles that were retrieved in the first step was performed to determine eligibility. Data extraction was done by the first author (JN) and verified by the second author (PH); discrepancies were resolved by discussion with the fourth author (JJ). General data extracted for LMIC were year of publication, country, income level, and HCF level. Outbreak-related data extracted for review question 1 (frequency and burden) were clinical ward, number of patients and case fatalities, age and sex, clinical presentation and co-morbidities, and outbreak duration. For review question 2 (products and pathogens), the genus and species of clinical and environmental pathogens, their clonal relatedness and (if available) antimicrobial susceptibility data were extracted. For question 3 (risk factors for contamination and transmission), results of the clinical-epidemiological and microbiological investigations, procedure review, interviews with staff and observations were extracted. For question 4 (interventions), interventions were extracted. The bacterial and fungal nomenclature was verified [13]. Further in this manuscript, the updated genus and species names are used, with the superseded names used in the articles written in Table 1.

Data Analysis

The extracted data were compiled in an Excel spreadsheet (Microsoft, Redmond, WA, USA). Gram-negative bacteria were grouped as Enterobacterales and non-fermentative Gram-negative bacteria (NFGNB). Unless otherwise specified, results were presented for outbreaks and case reports combined (commonly "outbreak reports"). Most results were presented with the number of outbreak reports as the denominator; where appropriate, numbers of different infusate products or pathogens were used as the denominator. Medians were expressed with ranges.

Additional Search of National Model List of Essential Medicines

Given the problem of access to age appropriate IV infusate formulations and sizes for children and neonates reported from sub-Saharan Africa, we searched the national lists of essential medicines (NEML) of sub-Saharan countries. These NEML should reflect the WHO Model List of Essential Medicines for Children (9th Edition, 2023), with adaptations according to national needs [8]. The purpose of the NEML is to guide country-wide prioritization, procurement, and supply of medicines. In addition, NEML can serve as a foundation for national treatment guidelines [14]. We reviewed the NEMLs of sub-Saharan African countries to determine whether premixtures of combined saline-dextrose IV fluids (Box 1) were included. The NEML were retrieved by a desktop search from online resources and through professional contacts of the Institute of Tropical Medicine network [15].

Results

Overview of the Articles Retrieved

A total of 50 articles were included, comprising 48 outbreaks and 2 case reports; 17 were retrieved by snowball search (Fig. 1). Upper-MIC, Lower-MIC and LIC represented 21, 25 and 4 articles respectively (Fig. 2). The articles originated from a total of 17 countries (Fig. 3), including 2 articles from South Africa, which were published before the country shifted from the Lower-MIC to the Upper-MIC category [16, 17].

Frequency and Burden of the Outbreaks

More than half (28/50, 56.0%) of the outbreaks occurred in tertiary care hospitals, and 9 occurred in >1 HCF (Supplementary Table 1). The main clinical wards affected (information available for 48 articles, Table 1) were neonatal intensive care units (n = 19), adult intensive care units (n = 6), and hematology—oncology (n = 5); 32 and 20 outbreaks affected children and adults respectively, for a total of 1025 patients, 761/1025 (74.2%) of whom were children. The median number of patients affected (case reports excluded, data for 44 outbreaks) was 12 (3–185); 9 outbreaks reported >30 patients. All outbreaks presented as bloodstream infections, and clinical isolates were obtained from blood cultures. The median case-fatality ratio (case reports excluded, data for 33 outbreaks) was 21.1% (range of 0.0–87.5%). The median duration (data from 43 outbreaks) was 8 weeks (1 day–156 weeks), and 27 (62.8%) outbreaks had a duration of >1 month, of which 16 (34.8% (15/43) of all outbreaks) extended beyond 3 months.

Table 1 Synthetic overview of the outbreaks of bacterial and fungal contamination of infusates in healthcare facilities in low- and middle-income countries

	Intravenous fluids (n = 37)		Intravenous medicines (n = 22)		Total articles (n = 50)	Comments
	TPN (n = 10)	Saline, dextrose, other (n = 27)*	Water for Injection (n = 3)	Medicines (n = 19)**		
Country income level						
Low-income (LIC)	–	7	–	2	4	In total, reports originated from 17 countries, representing 2 LIC, 9 Lower-MIC and 6 Upper-MIC
Lower middle-income (lower-MIC)	2	12	2	6	25	
Upper middle-income (upper-MIC)	9	5	1	8	21	
Patients–wards–duration of outbreak **Median (range) duration: 8 weeks (1 day–156 weeks) (data: n = 43 articles)**						
Adults (A) and/or children (C) affected	1A/8C	6A/22C	1A/2C	8A/7C	16A/31C	Articles providing information about ward: n = 48 Articles providing information about duration: n = 45 Total number of patients affected: 1025 Total number of children affected: 761 Median (range) number of patients affected per outbreak: 12 [3] (3 - 185) Median (range) case fatality ratio: 21.1% (0.0–87.5%) (data: n = 33 articles)
Neonatal Intensive care unit	6	16	1	5	19	
Adult intensive care unit	–	2	–	3	7	
Hematology/oncology	–	2	1	2	4	
Other wards	3	10	2	9	23	
Duration > 1 month	5	17	3	11	27	
Duration > 3 months	3	13	2	7	16	
Pathogens **Gram-negative bacteria (n = 59 isolates)**						
Enterobacterales (n = 29 isolates)	8	15	0	6	26	In 4 articles, more than 1 species was identified from the infusates [26, 35, 40, 66] Where appropriate, the original (superseded) names of the bacteria are included in the comments to reflect taxonomic changes. They include: *Burkholderia cepacia*—(*Pseudomonas cepacia*) [44] *Saprochaete capitata*—(*Blastoschizomyces capitatus*) [42] *Pluralibacter gergoviae*—(*Enterobacter gergoviae*) [54] *Elizabethkingia meningoseptica*—(*Chryseobacterium meningosepticum*) [46] *Klebsiella aerogenes*—(*Enterobacter aerogenes*) [61] *Rhizobium radiobacter*—(*Agrobacterium tumefaciens*) [66]
Serratia sp.	2	3	–	2	7	
Klebsiella sp.	1	9	–	3	10	
Enterobacter sp.	2	1	–	1	4	
Leclercia decarboxylata	1	–	–	–	1	
Pantoea sp.	1	–	–	–	1	
Phytobacter diazotrophicus	1	–	–	–	1	
Pluralibacter gergoviae	–	1	–	–	1	
Proteus mirabilis	–	1	–	–	1	
NFGNB (n = 30 isolates)	2	11	5	11	25	
Burkholderia cepacia complex	–	7	2	7	12	
Ralstonia sp.	–	1	2	1	4	
Acinetobacter baumannii	2	1	–	–	3	
Achromobacter sp.	–	–	–	1	1	
Elizabethkingia meningoseptica	–	1	–	–	1	
Myroides odoratus	–	–	1	–	1	
Pseudomonas sp.	–	1	–	1	2	
Rhizobium radiobacter	–	–	–	1	1	

Table 1 (continued)

	Intravenous fluids (n = 37)		Intravenous medicines (n = 22)		Total articles (n = 50)	Comments
	TPN (n = 10)	Saline, dextrose, other (n = 27)*	Water for Injection (n = 3)	Medicines (n = 19)**		
Fungi (n = 3 isolates)						
Candida albicans	1	–	–	–	1	
Saprochaete capitata	–	1	–	–	1	
Sarocladium kiliense	–	–	–	1	1	
Gram-positive bacteria (n = 1 isolate)						
Bacillus circulans	–	–	–	1	1	
Contamination route						
Intrinsic contamination	4	2	3	11	19	Articles providing information about intrinsic contamination: n = 19 Articles providing information or hypothesis about extrinsic contamination: n = 30
Extrinsic contamination	6	23	–	8	30	
Used as mSDV	–	18	–	7	20	
Used as admixture	–	6	–	–	5	
Unsafe or deficient IPC practices	7	25	–	8	40	

For a total of 50 articles, 59 infusates and 63 microorganisms were described. The abbreviation mSDV refers to medicine vials designed and manufactured as SDV, which are incorrectly used more than once and/or for more than one patient and IV fluids which are used for administration of multiple doses against the instructions of the manufacturer (see Box 1)

IPC infection prevention and control; *NFGNB* non-fermentative gram-negative bacteria; *TPN* total parenteral nutrition. Data represent numbers of isolates, except if otherwise indicated

*Saline (n = 10, including 2 heparinized saline admixtures), other IV fluid admixtures (n = 3), dextrose (n = 7), IV premixtures (n = 4), Ringer's lactate (n = 1) and unspecified IV fluids (n = 2)

**Propofol (n = 4), calcium gluconate (n = 2), diltiazem (n = 2), bromopride, caffeine citrate, fentanyl, furosemide, gentamicin, granisetron, heparin, immunoglobulin, metronidazole, ondansetron, and a steroid (1 product each)

Epidemiological and Microbiological Methods Used

A clinical-epidemiological investigation was mentioned in 33/50 (66.0%) outbreaks. In another 12 (24.0%) outbreaks, the presumed reservoir and transmission were obvious from the start, *e.g.* by close in time clusters of bloodstream infections after administration of a particular infusate [17, 19–24] or by the distinct presence of an IV catheter among the affected patients [25–31]. Eleven (22.0%) investigations conducted a formal exposure analysis, 4 of them in a case–control design [22, 32–41] (Supplementary Table 1).

Selection of samples for environmental microbiology investigation (data available for 45 outbreaks) was limited to IV infusates in 13 investigations [22, 24–26, 30, 34, 35, 37, 40, 42–45]. In 19 other investigations, infusate analysis was part of a broader environmental investigation comprising high touch surfaces, shared equipment and surfaces, liquids, and instruments close to the patient. In 16 investigations, healthcare workers' hands were sampled. Other human samples were throat and nose swabs from healthcare workers [17, 46, 47], and urine [24, 48] and rectal swabs or stool samples from both patients and health care workers [32, 33, 49, 50]. In 3 investigations of contaminated TPN, the preparation area in the pharmacy including equipment and TPN compounds were assessed [19, 33, 51].

Microbiological methods varied widely but mostly consisted of direct plating on agar media sometimes combined with enrichment broths (Supplementary Table 1; for an overview of microbiological methods, see Supplementary Box 1). In 8 investigations, only enrichment broths were used [17, 27, 37, 40, 41, 48, 52, 53]; filtration was done in 6 investigations [16, 34, 35, 41, 51, 54]. Quantitative cultures of infusates were performed in 2 studies, reporting viable bacterial counts of 10^3/ml for *Burkholderia cepacia* in Water for Injection [26] and $>25*10^5$/ml of *Serratia liquefaciens* in saline [55]. Identification was done by conventional biochemical testing; in recent studies MALDI-TOF analysis was used [21, 31, 38, 41, 47, 56]. If performed, methods of antimicrobial susceptibility testing were not fully detailed and, in some articles, only partial information about antimicrobial resistance was available [24, 39, 41, 57].

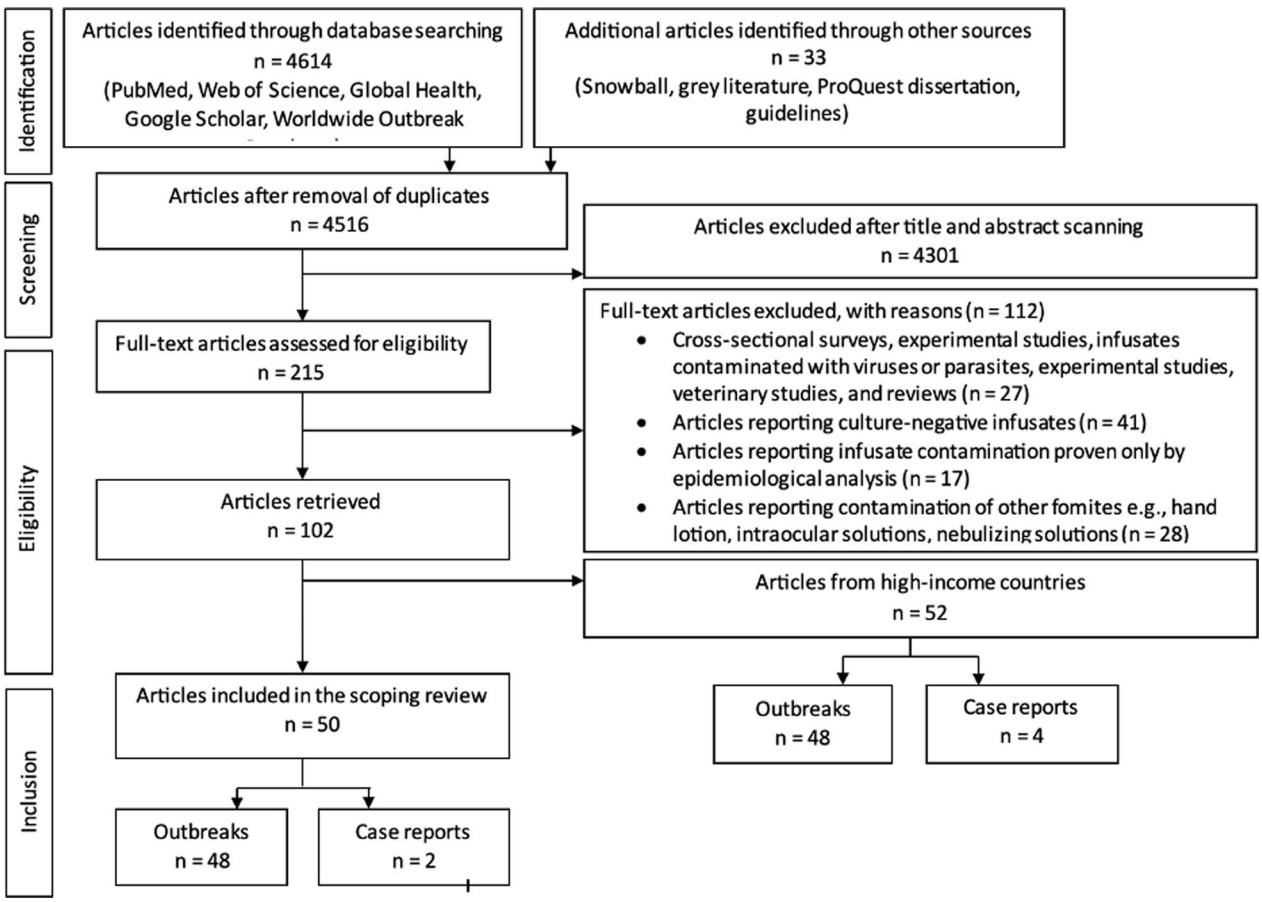

Fig. 1 Flow chart of the literature search for outbreaks related to bacterial and fungal contamination of intravenous fluids and medicines in healthcare facilities in low-and middle-income countries

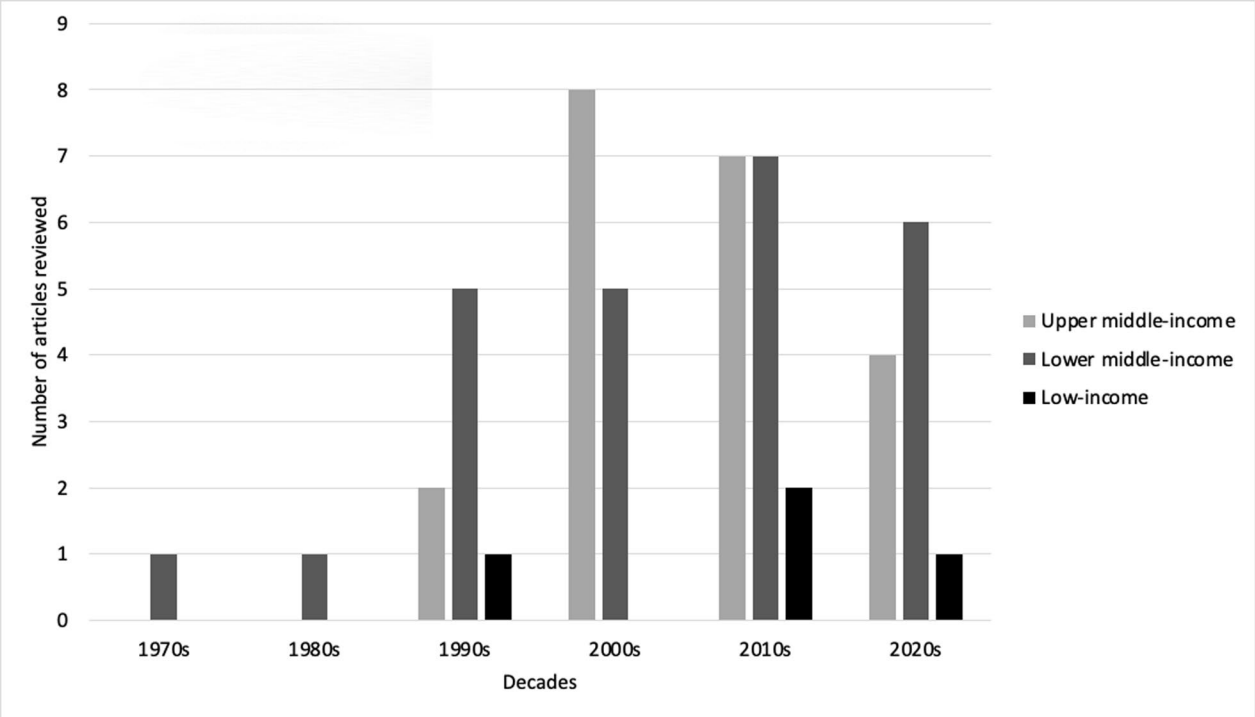

Fig. 2 The number and timeline of reviewed articles reporting outbreaks related to bacterial and fungal contamination of intravenous fluids and medicines in healthcare facilities in upper middle-income countries (n = 21), lower middle-income countries (n = 25) and low-income countries (n = 4)

In one third (17/50, 34.0%) of the articles, assessment of relatedness between environmental and clinical isolates was based on identification and the antimicrobial susceptibility results only [22, 23, 25, 26, 30, 33, 36, 41, 42, 44, 46, 52, 53, 55, 57–59]. Clonal relatedness was further assessed by phenotypic testing (biotyping) [17, 19, 28, 32, 49, 60], Pulsed Field Gel Electrophoresis [29, 34, 35, 43, 45, 47, 49, 54, 60–63], nucleic acid amplification-based typing tests [19, 27, 28, 37, 38, 50, 64], and whole genome sequencing [21, 31, 39, 40, 65]. More than three-quarters (37/50, 74.0%) of outbreak investigation teams also conducted a review of procedures, site observations and interviews of the healthcare workers (Supplementary Table 1).

Products and Pathogens

In the 50 articles, 59 infusate products were involved; 4 articles reported >1 contaminated infusate [34, 39, 52, 66] (Table 1). Overall, 37 IV fluids were involved, including TPN (n = 10), saline (n = 10, including 2 heparinized saline admixtures), other IV fluid admixtures (n = 3), dextrose (n = 7), IV premixtures (n = 4), Ringer's lactate (n = 1) and unspecified IV fluids (n = 2). Contaminated TPN products were reported from Brazil, Türkiye, Venezuela, Malaysia, Mexico, and South Africa [17, 19, 21, 33, 43, 50, 63, 64, 66], *i.e.* all but 2 were from upper-MIC at the time of reporting.

Two out of 3 admixtures were made in the ward by mixing saline with dextrose and saline with dextrose and potassium chloride as an IV fluid admixture for neonates; they were contaminated with *Klebsiella pneumoniae* and *Klebsiella oxytoca* respectively [25, 58]. Saline-heparin admixtures were used in 2 outbreaks (contaminated with *Acinetobacter baumannii* and *Serratia marcescens* respectively) [28, 29]; the remaining admixture was made in a cardiology unit and contaminated with *Pseudomonas fulva* [62].

Twenty-two IV medicines were counted, including propofol (n = 4), Water for Injection (n = 3), calcium gluconate (n = 2), diltiazem (n = 2), bromopride, caffeine citrate, fentanyl, furosemide, gentamicin, granisetron, heparin, immunoglobulin, metronidazole, ondansetron, and a steroid (1 product each).

Excluding TPN, 18 IV fluids and 7 IV medicines (in total half (51.0%, (25/49) of infusates) were incorrectly used as multidose vial: the IV fluid products were used amongst others for flushing intravascular catheters (n = 6) and reconstituting antibiotics (n = 5); another (n = 6) were used in pediatrics and neonatology, though their specific use was not specified (Table 2). The IV

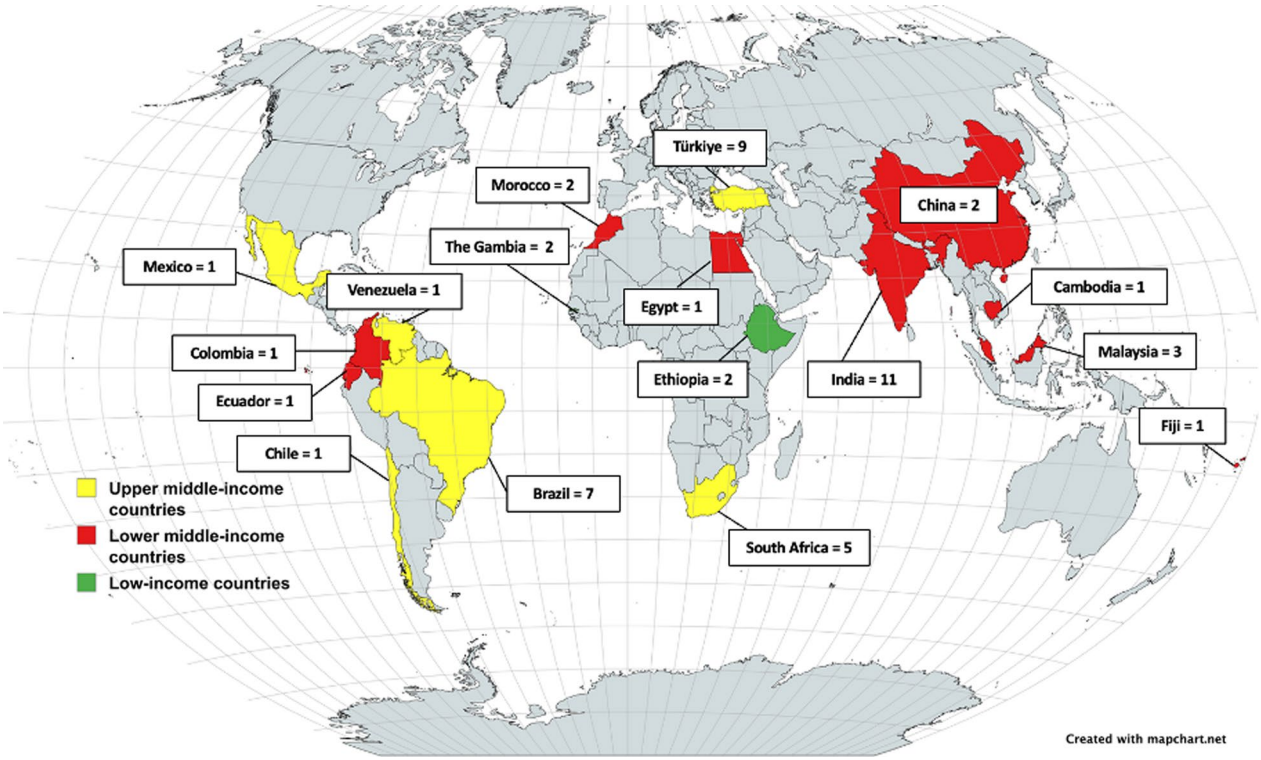

Fig. 3 Geographic distribution of the reviewed articles (n = 50) reporting outbreaks and case reports of bacterial and fungal contamination of intravenous fluids and medicines in healthcare facilities in low- and middle-income countries (lower- and upper middle-income countries) according to the UN Geoscheme [18] and by the World Bank Classification by income level at the year of publication [11]. Numbers represent the number of reviewed articles. In South Africa, 2 articles [16, 17] were published before it shifted from the lower middle-income category to the upper middle-income category

medicines which were used as mSDV comprised immunoglobulin, propofol and the antibiotics (gentamicin and metronidazole).

A total of 63 microorganisms were cultured; in 4 infusates, more than one species was cultured [26, 35, 40, 66]. Enterobacterales and NFGNB accounted for 46.0% (29/63) and 47.6% (30/63) isolates, respectively (Table 1). The remaining isolates were fungi (n = 3), *i.e.*, *Candida albicans* associated with TPN, *Saprochaete capitata* associated with a non-specified fluid and *Sarocladium kiliense* associated with ondansetron [42, 50, 65] and Gram-positive bacteria (n = 1) *i.e., Bacillus circulans* associated with intrinsically contaminated calcium gluconate [32].

The 29 Enterobacterales isolates grew in 29 infusates: TPN (n = 8), other IV fluids (n = 15), and IV medicines (n = 6, immunoglobulins, propofol and steroids); 16 of them were used as mSDV including the IV medicine immunoglobulin and propofol. The genera *Serratia*, *Klebsiella*, and *Enterobacter* species accounted for 82.7% (24/29) of the infusates contaminated by Enterobacterales. The 30 Non fermentative Gram-negative bacteria (NFGNB) isolates were cultured from 29 infusates: 11 IV fluids (2 admixtures and 7 IV fluids used as mSDV, 2 premixtures of 5% saline dextrose and IV lipid), TPN (n = 2), and 16 out of 22 medicine vials including Water for Injection, and 3 TPN infusates. The most frequent bacteria among the NFGNB were *Burkholderia cepacia* complex (among which *Burkholderia contaminans*); they grew from 16 infusates. Of note, among the 16 outbreaks with a duration > 3 months, 12 were associated with 18 NFGNB isolates (*B. cepacia* (n = 10), *Acinetobacter* sp. (n = 3), *Ralstonia pickettii* (n = 2), *Ralstonia solanacearum*, *Phytobacter diazotrophicus, Rhizobium radiobacter* [16, 19, 31, 35, 37, 39, 41, 44, 45, 52, 62, 66] with 2 outbreaks having growth of more than one organism from the infusates [35, 66].

In all articles clonal identity between clinical isolates and those of the environmental reservoir was demonstrated; coexisting clones were observed for *Klebsiella pneumoniae* and *Burkholderia cepacia* [39]. Among the articles with well-described antibiotic susceptibility results, there were third-generation cephalosporin-resistant Enterobacterales (*Klebsiella* spp. n = 5, *Enterobacter hormaechei*, n = 1, *Proteus mirabilis* n = 1) and New Delhi

Table 2 Outbreaks related to bacterial and fungal contamination of infusates in healthcare facilities in low- and middle-income countries: products involved, and pathogens isolated

Author, year, country (n = 50)	Type and use of the infusate involved	Pathogens isolated (n = 56)
Thong 1975 [2] Malaysia (lower-MIC)	5% dextrose-saline used in pediatrics	*Burkholderia cepacia*
Koopman 1980 [3] Colombia (lower-MIC)	Saline-dextrose-potassium admixture used in pediatrics	*Klebsiella pneumoniae*
Lacey 1991 [4] South Africa (lower-MIC)	Intrinsically contaminated sterile distilled water used to reconstitute heparin for flushing central venous catheters in pediatrics	*Ralstonia pickettii*
Frean 1994* [5] South Africa (lower-MIC)	Intrinsically contaminated TPN used in pediatrics	*Serratia odorifera*
Worku 1997* [6] Ethiopia (LIC)	Saline-dextrose admixture used in pediatrics	*Klebsiella oxytoca*
Kapil 1998* [7] India (Lower-MIC)	mSDV of saline-heparin admixture used to flush intravascular catheters used in adults	*Acinetobacter baumannii*
Mathews 1998 [8] India (lower-MIC)	Case report of a neonate who received an IV fluid	*Saprochaete capitata*
Thuler 1998* [9] Brazil (upper-MIC)	Intrinsically contaminated IV calcium gluconate used in adults	*Bacillus circulans*
Van Nierop 1998 [11] South Africa (upper-MIC)	mSDV of IV amino acid premixture used in neonates	*Enterobacter cloacae*
Lalitha 1999 [11] India (lower-MIC)	Intrinsically contaminated dextrose used in neonates	*Klebsiella pneumoniae*
Tresoldi 2000* [12] Brazil (upper-MIC)	TPN used in neonates	*Enterobacter cloacae*
Ganeswire 2003 [13] Malaysia (lower-MIC)	mSDV of dextrose used to reconstitute antibiotics in neonates	*Pluralibacter gergoviae*
Güngör 2003* [14] Türkiye (upper-MIC)	mSDV of IV lipid premixture added to TPN solution, used in neonates	*Elizabethkingia meningoseptica*
Habsah 2005* [15] Malaysia (lower-MIC)	TPN used in neonates	*Pantoea* sp.
Moodley 2005 [16] South Africa (upper-MIC)	mSDV of dextrose-amino acid premixture used in neonates	*Klebsiella pneumoniae*
Moore 2005 [17] Egypt (lower-MIC)	mSDV of dextrose, MDV of a steroid and mSDV of an immunoglobulin solution used in neonates	*Klebsiella pneumoniae*
Moreira 2005* [18] Brazil (upper-MIC)	Intrinsically contaminated Water for Injection used in adults and neonates	*Burkholderia cepacia* *Ralstonia pickettii*
Marais 2006 [19] South Africa (upper-MIC)	TPN used in neonates	*Klebsiella pneumoniae*
Vegas 2006 [20] Venezuela (upper-MIC)	TPN used in neonates	*Acinetobacter* sp.
Campos 2007 [21] Brazil (upper-MIC)	Intrinsically contaminated TPN used in neonates	*Enterobacter hormaechei*
Dias 2008 [22] Brazil (upper-MIC)	Intrinsically contaminated heparin used in adults and pediatrics	*Pseudomonas putida*
Douce 2008 [23] Ecuador (lower-MIC)	Intrinsically contaminated Water for Injection used to dilute antibiotics	*Burkholderia cepacia* *Myroides odoratus*
Narayan 2009 [24] Fiji (lower-MIC)	mSDV of saline used to flush intravascular catheters and dilute antibiotics used in neonates	*Klebsiella aerogenes*
Arslan 2010 [25] Türkiye (upper-MIC)	TPN used in neonates	*Serratia marcescens*
Martins 2010 [26] Brazil (upper-MIC)	Intrinsically contaminated IV bromopride medication used in adults	*Burkholderia cepacia*
Liu 2011 [27] China (lower-MIC)	mSDV of heparinized saline used to flush intravascular catheters in adults	*Serratia marcescens*
DeSmet 2013 [28] Cambodia (lower-MIC)	mSDV of Ringer's lactate used to flush intravascular catheters in adults	*Burkholderia cepacia*
Liu 2014 [29] China (lower-MIC)	Dextrose-saline-isosorbide dinitrate-potassium aspartate admixture used in adults	*Pseudomonas fulva*

Table 2 (continued)

Author, year, country (n = 50)	Type and use of the infusate involved	Pathogens isolated (n = 56)
Singhal 2015 [30] India (lower-MIC)	Intrinsically contaminated IV granisetron medicine vials used in adults	*Burkholderia cepacia*
Guducuoglu 2016 [31] Türkiye (upper-MIC)	TPN used in pediatrics	*Candida albicans*
Ikumapayi 2016 [32] The Gambia (LIC)	mSDV of saline used in pediatrics	*Serratia liquefaciens*
Jain 2016 [33] India (lower-MIC)	mSDV of dextrose used to flush intravascular catheters used in neonates	*Proteus mirabilis*
Paul 2016 [34] India (lower-MIC)	mSDV of saline and dextrose used in neonates	*Burkholderia cepacia*
Shrivastava 2016 [35] India (lower-MIC)	Intrinsically contaminated IV caffeine citrate medicine vials used in neonates	*Burkholderia cepacia*
Ari 2017 [36] Türkiye (upper-MIC)	mSDV of saline used to dilute contrast agent used in myocardial scintigraphy in adults	*Serratia liquefaciens*
Orsini 2018 [37] Chile (upper-MIC)	Intrinsically contaminated ondansetron used in adults and pediatrics	*Sarocladium kiliense*
Pillonetto 2018 [38] Brazil (upper-MIC)	Intrinsically contaminated TPN	*Acinetobacter baumannii* *Phytobacter diazotrophicus*
	Intrinsically contaminated calcium gluconate	*Rhizobium radiobacter*
Cilli 2019 [39] Türkiye (upper-MIC)	mSDV of IV propofol used in adults	*Serratia marcescens*
Eshetu 2019 [40] Ethiopia (LIC)	mSDV of IV fluid used in a neonate	*Klebsiella oxytoca*
Okomo 2020 [41] The Gambia (LIC)	mSDV of saline and dextrose used to reconstitute antibiotics mSDV of gentamicin and metronidazole used in neonates	*Burkholderia cepacia* *Klebsiella pneumoniae*
Arjun 2021 [42] Türkiye (upper-MIC)	Intrinsically contaminated IV furosemide medicine ampoules used in adults	*Achromobacter denitrificans* *Achromobacter xylosoxidans*
Garza-Gonzalez 2021 [43] Mexico (upper-MIC)	Intrinsically contaminated TPN used in neonates	*Leclercia decarboxylata*
Jaber 2021 [44] Morocco (lower-MIC)	mSDV of propofol used in adults	*Klebsiella oxytoca*
Murugesan 2021 [45] India (lower-MIC)	Intrinsically contaminated IV diltiazem medicine used in adults	*Burkholderia contaminans*
Tunccan 2021 [46] Türkiye (upper-MIC)	Intrinsically contaminated IV saline bottles used in pediatrics and adults	*Ralstonia solanacearum*
Ergenc 2022 [47] Türkiye (upper MIC)	mSDV of propofol used in adults	*Serratia marcescens*
Moukafih 2022 [48] Morocco (lower-MIC)	mSDV of propofol used in pediatrics	*Enterobacter cloacae*
Rajachandaran 2022 [49] India (lower-MIC)	Intrinsically contaminated IV fentanyl medicine vials used in adults	*Ralstonia pickettii*
Sridharan 2022 [50] India (lower-MIC)	Intrinsically contaminated diltiazem vials used in adults	*Burkholderia cepacia*
Fomda 2023 [51] India (lower-MIC)	mSDV saline used to flush intravascular catheters used in adults	*Burkholderia cepacia*

The numbers of pathogens and products exceed the number of articles because in some articles more than one pathogen was isolated and/or more than one product was reported

IV intravenous, *LIC* low-income country, *Lower-MIC* lower middle-income country, *Upper-MIC* upper middle-income country, *mSDV* multiple-use single-dose vials, *i.e.* medicine vials designed and manufactured as SDV, which are incorrectly used more than once and/or for more than one patient and IV fluids which are used for administration of multiple doses against the instructions of the manufacturer; *TPN* total parenteral nutrition

The symbol * refers to articles included in a previous review [3]. Infusates of dextrose and glucose IV fluids are both referred to as "dextrose." The table mentions "intrinsic" in case of culture-proven contamination of sealed unopened products; the remaining products were extrinsically contaminated or had no specified information about the contamination pathway. The ward and patients involved, and age group of the patients were mentioned whenever information was provided

producing carbapenem-resistant *Leclercia adecarboxylata* (n = 1) [21, 34, 36, 43, 48, 61, 63, 67].

Risk factors for Contamination and Transmission (Tables 1, 2, Supplementary Table 1)

In 40.0% (20/50) outbreaks representing a third (33.9%, 20/59) infusates, were intrinsically contaminated; they included one saline and one 5% saline-dextrose premixture, 4 TPN infusates, as well as 14 IV medicines. Seven products (TPN (n = 4), bromopride, calcium gluconate and ondansetron) were implicated in multi-institutional outbreaks involving 3–15 hospitals in Brazil, Mexico, and South Africa [17, 21, 35, 37, 43, 65, 66]. One investigation of intrinsically contaminated TPN assessed the compounding facility: air leaks in the compounding chamber were noted, as well as errors in cleaning and hand hygiene practices [17]. In another outbreak caused by *Ralstonia solanacearum* associated with intrinsically contaminated saline bottles, the packaging of the infusates in the stock room had air bubbles, water drops, and leaks suggestive for contamination [31].

For the 30 remaining outbreaks, one had no detailed data about environmental sampling and 9 articles did not address nor discuss the potential pathway of the contamination of the infusate. Ten reports explicitly mentioned handborne transmission as the probable transmission pathway, and in 4 investigations, hands of healthcare workers grew Gram-negative bacteria matching the index organisms, *i.e., Enterobacter cloacae*, *Pluralibacter gergoviae*, *K. pneumoniae* and *P. mirabilis* respectively [36, 48, 49, 54]. Of note, in 2 other investigations, Gram-negative bacteria unrelated to the index pathogen were found on the healthcare workers' hands [17, 58]. In 13 articles, potential handborne transmission was mentioned indirectly ("handling", "preparation of TPN", "breaches in asepsis").

A third (34.0%, 17/50 of the articles, mostly from LIC and Lower-MIC, mentioned unsafe practices such as the use of infusates as mSDV [20, 23, 24, 34, 36, 39, 55, 57, 63, 68], not respecting the period after opening [20, 54, 68], cloth tape used to cover the tops of single-use, preservative-free ampoules between uses [34], not disinfecting the IV rubber ports on fluid bags and lines [61, 68], withdrawing medication from medicine vials using a previously used syringe with a new needle [23–25, 39, 55, 57], air venting (inserting a needle in semirigid containers (Box 1)) [25], pooling of residual volumes of admixed antibiotics [39], and not reprocessing the infusion pump after use [68]. Further, infusates were prepared and stored in the clinical ward and at room temperature, even close to the sink [34, 39, 47, 58, 64]. In several cases, these unsafe practices were caused by non-compliance with HCF procedures or manufacturer's instructions [36, 41, 47]. Further, several articles reported poor hand hygiene [34, 36, 39, 41, 47, 48, 61, 64] and environmental cleaning [17, 41, 64] as well as sharing equipment [55] and use of IV catheters without clinical indication [41].

Factors cited as root-causes of the IPC failures included economical constraints, understaffing, high workload, and time pressure related to a performance-based payment system [47, 48, 58, 62, 64]. The main reason behind the practices of making admixtures and using mSDV in neonatal wards (mentioned in 6 articles) was the lack of access to pediatric IV fluid formulations (including premixtures) and volumes [30, 34, 36, 39, 46, 58].

Interventions

Forty-three (86.0%) out of 50 articles reported interventions. For the intrinsic contamination of the infusates, recall and withdrawal of the products controlled the outbreak. Interventions made to prevent contamination of TPN included the provision of a biosafety cabinet in the pharmacy, installing a medicines' preparation room [64], installing automated TPN preparation [50], and increasing the frequency of sterility testing of prepared TPN [33]. For IV fluids and medicines, mSDV were replaced by single-use medicine vials [20, 24, 28, 46, 56, 68]. Where this was not possible, risk mitigation was sought by adequate disinfection of the sample port of the mSDV and reducing the period-after-opening [27, 54, 61]. Further, storage of infusates in the refrigerator and keeping the medication preparation trolley away from the sink was implemented [39].

Cohorting of the infected neonates was done in 5 outbreaks, caused respectively by *Burkholderia contaminans*, *P. mirabilis, P. gergoviae*, *Klebsiella aerogenes* and *Serratia marcescens* ([38, 48, 54, 61, 64]. Many articles reported reinforcement of hand hygiene practices and/or environmental cleaning [29, 33, 34, 36, 38, 48, 49, 55, 58, 61, 62]. Education and in-service training of healthcare workers were implemented in 8 articles [34, 39, 46–48, 61, 62, 64].

Additional Search of National Model List of Essential Medicines

In the Sect. 26 about "Solutions containing water, electrolyte and acid–base disturbance", the WHO Model List of Essential Medicines for Children mentions the premixtures of half-normal saline—5% dextrose and normal saline—5% dextrose IV fluids. Sizes (volumes) are not mentioned (Box 1) [8]. The NEML list of 44/48 sub-Saharan countries was retrieved. Less than a third (14/44, 31.8%) of these NEML mentioned one of both saline—dextrose premixtures, and only 8 among them (18.8% of all 44 countries) mentioned the half-saline—5% dextrose recommended for neonates (Supplementary Table 2).

Discussion

Frequency and Burden

The present review aggregated 50 culture-confirmed infusate-related outbreak and case reports which occurred in HCF in LMIC. All outbreaks presented as bloodstream infections, over long durations, and with high case-fatality ratios. The neonatology ranked first among the affected wards, in line with the high burden of HAI in neonatology wards in LMIC [69, 70]. The long duration of outbreaks reflects the typical insidious course and difficult detection of HAI outbreaks [6, 71, 72]. The risk of overlooking outbreaks is even larger in the case of "endemic" organisms, such as *Klebsiella* sp. [69].

The 50 retrieved articles probably represent an underrepresentation from LMIC, as noted previously [3]. It points to a substantial under-reporting and under-detection [69, 73]. For the LIC and Lower-MIC, a main problem for detection and monitoring is the low availability of clinical bacteriology: in a recent survey across 14 countries in sub-Saharan Africa, only 1.3% of diagnostic laboratories declared to perform bacteriology analysis [74]. Further, more than half of the outbreaks were described from tertiary care and referral hospitals. The frequency and burden of infusate-related HAI is probably much higher in remote and rural areas in LMIC, where Water, Sanitation and Hygiene (WASH) standards are low [75], and where the poor storage and distribution practices along the supply system may create conditions for product contamination or accelerated degradation [76].

Products and Pathogens

Among the infusate products, IV fluids were most represented, and most of them were used as mSDV. TPN (10 outbreaks) is well-known for its risk of contamination. Among the contaminated IV medicines, contaminated propofol and fentanyl were previously reported from HIC [3, 77]. In line with their nutrient requirements, Enterobacterales and yeasts were the most frequent organisms found in contaminated TPN; similarly, the 3 saline-dextrose admixtures reported from the neonatal wards were contaminated with *Klebsiella* spp. [25, 39, 58]. In a review of neonatal outbreaks in Africa, half of the 20 outbreaks were due to *Klebsiella pneumoniae* [78]. Among the IV fluids (n = 37), both NFGNB and Enterobacterales were isolated, the latter most probably reflecting hand contact during their preparation or manipulation of admixtures and mSDV [79]. *P. gergoviae* (isolated from dextrose IV fluid in a neonatology unit [54]) is naturally resistant to preservatives and a well-known contaminant of cosmetics and soaps [80].

NFGNB have very low nutrient requirements. *B. cepacia* complex (reported from 16 infusates) is naturally resistant to preservatives and is the most frequent bacterial species found in contaminated water-based pharmaceuticals [81, 82]. *Ralstonia* species (5 infusates) are slender rods capable of bypassing sterilization filters used in pharmaceutical filling processes [83]. Third-generation cephalosporin and carbapenem-resistant Enterobacterales (reported from 8 outbreaks) are listed as Critical Group Pathogens on the WHO Bacterial Priority Pathogens List for the containment of antimicrobial resistance [84].

Risk Factors for Contamination and Transmission

Preparation and administration of IV medication are error prone [85, 86]. Use of mSDV is a major risk for infusate contamination [3]. In the articles reviewed, half of the infusates (TPN extracted) were used as mSDV, for IV catheter flushing, medicine reconstitution, and pediatric IV fluid administration. The heparin-saline solution used for peripheral IV catheter flushing [28, 29] ranked first among the outbreaks listed in the previous review [3] and the WHO explicitly warns against mSDV for IV catheter flushing [87]. In addition, multiple unsafe practices during preparation and administration were reported, also in recent studies [39, 41]. Some of the observed practices occur frequently in LMIC, such as air-venting of rigid infusion containers (Box 1) [88–91].

The saline–dextrose IV fluid admixtures for neonates (Box 1) were prepared in the ward, where they also were divided in into smaller bag sizes [30, 39, 58]. In HICs, preparing IV medicines in the ward is more at risk for contamination than compounding in the pharmacy [92, 93], even if compounding pharmacies themselves are not exempt from risk of contamination [94]. This risk is probably much higher in HCF in LMIC, given the high environmental contamination [95]. Likewise, storage in the ward and in the vicinity of sinks are also risks for contamination [3, 96, 97]. The general IPC deficiencies contribute to the risk of infusate contamination, either directly (hand hygiene) or indirectly (recontamination of hands due to poor environmental cleaning). The above-mentioned risk factors were also reported from other LMIC articles related to infusate outbreaks and contamination [34, 89, 90, 98–101]. Many of these studies also revealed nursing care challenges [34, 102], in part related to overcrowding and understaffing [103, 104].

Interventions

Most interventions listed in the selected articles were in line with recommendations and good practice statement issued by healthcare associations [87, 91, 97, 105–107]. They should be implemented according to the WHO multimodal improvement strategy [108] and in pace with implementation of standard IPC practices and quality patient care. Key elements of these recommendations are

not using mSDV [29], strictly using SDV for one patient and one injection [34, 36, 46, 55, 61], limiting MDV to single-patient use [34], creating dedicated medicine preparation areas [34, 39], and transitioning to closed IV infusion systems [89]. Access to age-appropriate formulations (premixtures) and sizes, syringe and infusion pumps will eliminate the need for admixing and aliquoting infusates in neonatology and pediatrics. Unnecessary infusates should be banned [109] and the IV route must be reserved for selected clinical conditions and for periods as short as possible [87, 89, 93].

Outbreak Investigation Methods

Most of the outbreak reports used clinical-epidemiological information to orient the environmental sampling. Broad sampling (done in 19/45 of the documented outbreak investigation) may detect co-existing reservoirs and provide clues to transmission. Sampling healthcare workers' hands (done in outbreaks) has low priority in the context of high environmental contamination and suboptimal handwash facilities; it is most effective if focused on onychomycosis, artificial fingernails, or rings [69, 110]. In the outbreak setting caused by Gram-negative bacteria, microbiological testing of healthcare workers' or patients' throat and nose samples (done in 3 outbreaks) has no place. Likewise, assessing patients' stool samples for the index organisms (done in 4 outbreaks) has little additional value in the context of an ongoing outbreak; it can be considered in the case of screening for carriage of multidrug resistant organisms when the possibility of isolating or cohorting patients is present [69, 111]. However, it entails a risk of stigma and cultural offensiveness and must be balanced against the required expertise, means and costs [111].

The spread plate culture method is within reach of the standard microbiology laboratory and provides information about bacterial counts (Supplementary Box 1). In the case of Enterobacterales and nutrient-rich infusates, counts can be very high (exceeding 10^5/ml) [55, 98, 112] and even such high contaminations are not detectable by the naked eye [113]. Species identification and antibiotic resistance pattern provide instant clues to the relatedness of clinical and environmental isolates [6] but ideally should be further studied by molecular analysis. *Burkholderia cepacia* is frequently polyclonal [37, 114], and distinct clones of *Klebsiella*, *Serratia* and *Enterobacter* may coexist [67, 115–117]. Given its high resolution and the database libraries, Whole Genome Sequencing provides sub-species identification, resistome analysis and information about in-hospital epidemiology, as presently shown for the *Klebsiella* and *B. cepacia* outbreaks in a neonatology unit in The Gambia [39].

Outstanding Issues and Research Questions

As discussed above, the underrepresentation of reports from LMIC—in particular LIC and Lower-MIC—despite anecdotal reports is a main issue. A recent review highlighted a significant publication gap between LMIC and HIC, revealing that HIC produce nearly 9 times more publications than LMIC [118]. Strengthening the capacity of researchers and healthcare professionals in LMICs to document and publish their findings can be achieved through mentorship opportunities [119], fostering networks and collaborations), engaging policymakers, funders, and hospital management [120].

Further, despite the overall low number of outbreak reports, a variation according to country income was noted. The 4 outbreaks reported from LIC occurred in pediatrics and were related to in-ward prepared and administered admixtures and mSDV fluids [30, 39, 55, 58]. In addition, LIC and many Lower-MIC reported serious shortcomings in standard IPC practices. By contrast, Upper-MIC reported all but one of the contaminated TPN infusates and were also experiencing large multi-institutional outbreaks of intrinsically contaminated IV medicines, in line from what was also seen in outbreaks related to contaminated antiseptics and disinfectants in HIC [72]. Further, they could afford high-cost interventions to assure safe TPN preparation [33, 50, 64]. Upper-MIC countries also scored consistently higher as to the implementation of IPC and WASH compared to Lower-MIC and LIC [2]. Further studies should explore these differences as they can orient and prioritize IPC interventions.

It is probably unknown to many in the global health community, including policymakers, that contaminated infusates represented the cause of a quarter (5/20) of neonatal outbreaks in sub-Saharan Africa [69]. The need for pediatric IV infusates has been raised 20 years ago based on microbiological and observational studies in Mexico and Egypt [34, 99, 121] and it was still expressed very recently by the presently assessed outbreak reports from sub-Saharan Africa [30, 39]. This situation is not unique to infusates. The NEML serve as a basis for the procurement and supply of medicines in public HCF. Ideally, these medicines should be available in the appropriate quality, quantity, and dosage forms to meet the needs of the population including children [122]. Some positive initiatives are underway: for instance, a priority list of antibiotics for pediatric medicines optimization was published in 2023 [123].

Given the probable underreporting but heavy burden of the neonatal outbreaks, the extent of the scarcity of pediatric formulations in LIC should be explored. The low adoption of the saline–dextrose 5% IV fluid premixtures in the NEML of the sub-Saharan countries

and the low access to these products may explain the frequent practice of in-ward preparation of infusates. Large-scale access to pediatric IV infusates will require commitment of numerous (inter)national stakeholders, a stable supply chain and a healthy market, with local production enabled by transfer of technology and quality know-how through public–private partnerships [89, 124]. Moreover, suspicion or evidence of intrinsic contamination should be accompanied by timely communication to the supplier, the National Regulatory Authority (NRA), and the national Pharmacovigilance (PV) Centre. The supplier and NRA may assess if the concerned product batch presents and organize a national batch recall if indicated. The PV center can identify poor dispensing practices consistently resulting in safety incidents and support the update of guidelines at national level.

To guide interventions, a better understanding of the errors during the IV infusate preparation and administration is needed. Simulation and video-based teaching settings have been successfully used to study errors of infusate preparation and administration [125–127]. Further, the human factors behind the unsafe practices should be explored. Recent IPC surveys in sub-Saharan Africa pointed to gaps in IPC risk knowledge and awareness, such as ignorance of the period-after-opening of antiseptics, underestimation of the dangers of tap water and overestimation of the bactericidal power of a refrigerator [128, 129]. An unexpected barrier noted in Mexico was the outspoken preference of pediatricians for calculator-based admixtures over premixtures, as the former were perceived as more scientific [99]. Although not mentioned in the articles, training materials and procedural support for aseptic reconstitution and admixing of infusates is rare. In view of the absence of generic training material, a Spanish team developed practical trainings for medication preparation in the neonatal ward with video demonstrations [125]. At the HCF level, education will rely on in-service training, whereby task-based, bedside and simulation trainings are preferred [130]. Examples of information leaflets and workplace reminders about safe injection practices are available [106]. Further, the risks and risk mitigation of infusate contaminations should be addressed in medical curricula and textbooks [99].

Limitations and Strengths

Most outbreak reports did not fully comply with outbreak reporting guidelines [131]. Part of them were brief reports [23, 29, 43, 60, 63] or focused on molecular analysis [21, 38, 39, 66]. This may have caused a retrieval and selection bias. However, even if the search retrieval reflected only part of the real-life incidence and burden, we believe that—apart from the obviously higher burden—the main findings of the review we believe that would still hold true if more articles had been retrieved. Further, only culture-proven outbreaks were included. As to the strengths, the present review has an additional 41 culture-confirmed reports from LMIC compared to a previous review (nearly 20 years ago) [3]. Further, a detailed inventory of products and products wase made and risk factors and interventions were explored.

Conclusion

Bacterial and fungal contamination of infusates in LMIC is a serious but an underreported and overlooked risk for patients, with—in LIC and Lower-MIC a possible disproportionate impact on young children and neonates. Awareness among healthcare workers and policymakers can prepare for risk-mitigating measures along the production and supply and at the HCF level. HCF in LMIC face different challenges related to the country's income level, with an outstanding need for pediatric infusate formulations (premixtures) and sizes in LIC and Lower-MIC and a better understanding of the human factors behind unsafe practices. Improvement of local practices should be framed and supported by global efforts to correct the current imbalances in availability of adequate resources including appropriate infusates for children.

Abbreviations

AST	Antimicrobial susceptibility testing
BSI	Bloodstream infection
CLABSI	Central line-associated bloodstream infection
EML	Essential medicines for children
HAI	Healthcare-associated infections
HCF	Healthcare facilities
HIC	High-income countries
IPC	Infection and prevention control
IV	Intravenous
LIC	Low-income countries
LMIC	Low- and middle-income countries
Lower-MIC	Lower middle-income countries
MALDI-TOF	Matrix-assisted laser desorption/ionization
MIC	Middle-income countries
mSDV	Multiple-use single dose vials
NFGNB	Non-fermentative gram-negative bacteria
NEMLs	National essential medicines lists
OPPP	Opportunistic pathogens of premise plumbing
SDV	Single-dose vials
TPN	Total parenteral nutrition
Upper-MIC	Upper middle-income countries
WGS	Whole genome sequencing
WHO	World health organization

Supplementary Information

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Additional file 1.

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Author contributions
Conceptualization was done by J.N. and J.J.; methodology by J.N., P.H., and J.J.; database screening and extraction by J.N., P.H., and J.J.; data analysis by J.N., P.H., and J.J.; writing—original draft preparation by J.N. and J.J.; writing—review and editing by J.N., P.H., R.R., and J.J.; and supervision by J.J.

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References

1. World Health Organization. Report on the Burden of Endemic Health Care-Associated Infection Worldwide Clean Care is Safer Care. 2011. https://www.who.int/publications/i/item/report-on-the-burden-of-endemic-health-care-associated-infection-worldwide. Accessed on 15th May 2024.
2. World Health Organization. Global report on infection prevention and control. 2022. https://www.who.int/publications/i/item/9789240051164. Accessed on 2nd June 2024.
3. Vonberg RP, Gastmeier P. Hospital-acquired infections related to contaminated substances. J Hosp Infect. 2007;65(1):15–23.
4. Kanamori H, Weber DJ, Rutala WA. Healthcare outbreaks associated with a water reservoir and infection prevention strategies. Clin Infect Dis. 2016;62(11):1423–35. https://doi.org/10.1093/cid/ciw122. Accessed on 20th May 2024.
5. Kanamori H, Rutala WA, Weber DJ. The role of patient care items as a fomite in healthcare-associated outbreaks and infection prevention. Clin Infect Dis. 2017;65(8):1412–9.
6. Lompo P, Agbobli E, Heroes AS, Van den Poel B, Kühne V, Kpossou CMG, et al. Bacterial contamination of antiseptics, disinfectants, and hand hygiene products used in healthcare settings in low-and middle-income countries—a systematic review. Hygiene. 2023;3(2):93–124.
7. World Health Organization. WHO Pocketbook of Hospital Care for children 2013. https://www.who.int/publications/i/item/9789241548373. Accessed on 29th August 2024.
8. World Health Organization. WHO-MHP-HPS-EML-2023 Children. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.03. Accessed on 10th January 2024.
9. Institute of Tropical Medicine (ITM) A. Hospital-Based Interventions to Contain Antibiotic Resistance. https://www.itg.be/en/study/courses/hospital-based-interventions-to-contain-antibiotic-resistance/2024-2025?tab=about-the-course. Accessed on 12th October 2024.
10. The Worldwide Database for Nosocomial Outbreaks. Institute for Hygiene and Environmental Medicine Charité—University Medicine Berlin. https://www.outbreak-database.com/Home.aspx. Accessed 7 Feb 2024.
11. The World Bank Group. World Bank Country Classifications by Income Level. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.2024. Accessed 10 Feb 2024.
12. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. System Rev. 2016. https://doi.org/10.1186/s13643-016-0384-4.
13. Parte AC. LPSN—list of prokaryotic names with standing in nomenclature. Nucleic Acids Res. 2014;42(D1):D613–6. https://doi.org/10.1093/nar/gkt1111. Accessed on 8th April 2024.
14. World Health Organization. Selection of essential medicines at country level: using the WHO model list of essential medicines to update a national essential medicines list. World Health Organization; 2018 Nov 7. https://www.who.int/publications/i/item/9789241515443. Accessed 10 Feb 2025.
15. Institute of Tropical Medicine Library. https://lib.itg.be. Accessed on 11th October 2024.
16. Lacey S, Want SV. Pseudomonas pickettii infections in a paediatric oncology unit. J Hosp Infect. 1991;17(1):45–51.
17. Frean JA, Arntzen L, Rosekilly I, Isaäcson M. Investigation of contaminated parenteral nutrition fluids associated with an outbreak of *Serratia odorifera* septicaemia. J Hosp Infect. 1994;27(4):263–73. https://doi.org/10.1016/0195-6701(94)90114-7.
18. United Nations Statistics Division. Standard Country or Area Codes for Statistical Use (M49). 2024. https://unstats.un.org/unsd/methodology/m49/. Accessed on 12th February 2024.
19. Vegas EZS De, Nieves B, Araque M, Velasco E, Ruíz J, Vila J. Outbreak of infection with acinetobacter strain RUH 1139 in an intensive care unit. Infect Control Hosp Epidemiol. 2006;27(4):397–403.
20. Arı A, Olut AI, Ay B, Tosun S, Zencir M, Çayıröz MU. A small outbreak of serratia liquefaciens bacteremia due to use of contaminated saline infusion solution for myocardial perfusion scintigraphy. Infect Dis. 2017;49(8):639–40. https://doi.org/10.1080/23744235.2017.1308550.
21. Garza-González E, Bocanegra-Ibarias P, Rodríguez-Noriega E, González-Díaz E, Silva-Sanchez J, Garza-Ramos U, Contreras-Coronado-Tovar IF, Santos-Hernández JE, Gutiérrez-Bañuelos D, Mena-Ramirez JP, Ramírez-De-los-Santos S, Camacho-Ortiz A, Morfín-Otero R. Molecular investigation of an outbreak associated with total parenteral nutrition contaminated with NDM-producing Leclercia adecarboxylata. BMC Infect Dis. 2021. https://doi.org/10.1186/s12879-021-05923-0.
22. Rajachandran K, Varghese GS, Vinoth Kumar J, Mathew KT. Outbreak of nosocomial infection from an unusual source. Indian J Crit Care Med. 2022;26(9):1042–4.
23. Jaber EK, Amine EM, Hicham K, Ahmed HM, Jaouad L. Propofol related infections: short case series description. Rev Esp Anestesiol Reanim. 2021;68(4):240–1.
24. Moukafih B, El Marrakchi S, Bennani I, Lakhdar-Idrissi M, Hida M, El Kartouti A, et al. Complications infectieuses liées à l'utilisation du propofol: une nouvelle série de cas et revue de la littérature. Therapies. 2023;78(4):375–83.
25. Koopman JS, de Fighetti Olave A. An extensive outbreak of *Klebsiella pneumoniae* bacteremias from in-use contamination of IV bottles. Bull Pan Am Health Organ (PAHO). 1980;14(2):1980.
26. Douce RW, Zurita J, Sanchez O, Aldaz PC. Investigation of an outbreak of central venous catheter-associated bloodstream infection due to contaminated water. Infect Control Hosp Epidemiol. 2008;29(4):364–6.

27. De Smet B, Veng C, Kruy L, Kham C, van Griensven J, Peeters C, Ieng S, Phe T, Vlieghe E, Vandamme P, Jacobs J. Outbreak of *Burkholderia cepacia* bloodstream infections traced to the use of Ringer lactate solution as multiple-dose vial for catheter flushing, Phnom Penh, Cambodia. Clin Microbiol Infect. 2013;19(9):832–7. https://doi.org/10.1111/1469-0691.12047.
28. Kapil A, Gulati S, Goel V, Kumar L, Krishnan R, Kochupillai V. Outbreak of nosocomial *Acinetobacter baumannii* bacteremia in a high-risk ward. Med Oncol. 1998;15:270–4.
29. Liu D, Zhang LP, Huang SF, Wang Z, Chen P, Wang H, et al. Outbreak of *Serratia marcescens* infection due to contamination of multiple-dose vial of heparin–saline solution used to flush deep venous catheters or peripheral trocars. J Hosp Infect. 2011;77(2):175–6.
30. Eshetu B, Gashaw M, Berhane M, Abdissa A, McClure EM, Goldenberg RL, et al. Intravenous fluid contaminated with *Klebsiella oxytoca* as a source of sepsis in a preterm newborn: case report. Am J Infect Control. 2019;47(7):840–2.
31. Güzel Tunçcan Ö, Dizbay M, Özger HS, Erganiş S, Aksakal FN, Yalinay M, et al. Monoclonal outbreak of *Ralstonia solanacearum* catheter-related bloodstream infection associated with contaminated package of normal saline solution in a tertiary care hospital. Turk J Med Sci. 2021;51(3):1027–32.
32. Claudio Santos Thuler L, Velasco E, de Souza A, Martins C. An outbreak of *Bacillus* species in a cancer hospital. Infect Control Hosp Epidemiol. 1998;19:856.
33. Habsah H, Zeehaida M, Van Rostenberghe H, Noraida R, Wan Pauzi WI, Fatimah I, Rosliza AR, Nik Sharimah NY, Maimunah H. An outbreak of *Pantoea spp.* in a neonatal intensive care unit secondary to contaminated parenteral nutrition. J Hosp Infect. 2005;61(3):213–8. https://doi.org/10.1016/j.jhin.2005.01.004.
34. Moore KL, Kainer MA, Badrawi N, Afifi S, Wasfy M, Bashir M, et al. Neonatal sepsis in Egypt associated with bacterial contamination of glucose-containing intravenous fluids. Pediatr Infect Dis J. 2005;24(7):590–4.
35. Moreira BM, Leobons MBGP, Pellegrino FLPC, Santos M, Teixeira LM, de Andrade ME, et al. *Ralstonia pickettii* and *Burkholderia cepacia* complex bloodstream infections related to infusion of contaminated water for injection. J Hosp Infect. 2005;60(1):51–5.
36. Moodley P, Coovadia YM, Sturm AW. Intravenous glucose preparation as the source of an outbreak of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* infections in the neonatal unit of a regional hospital in KwaZulu-Natal. S Afr Med J. 2005;95(11):861–4.
37. Martins IS, Pellegrino FLPC, d'Avila FA, da Santos MS, d'Alemeida FGI, Vasques MRG, et al. Case-crossover study of *Burkholderia cepacia* complex bloodstream infection associated with contaminated intravenous bromopride. Infect Control Hosp Epidemiol. 2010;31(5):516–21.
38. Murugesan M, Ranjan J, Devanga Ragupathi NK, Michael JS, Viggeswarpu S, Wilson BP, et al. Diagnostic methods and identification challenges experienced in a Burkholderia contaminans outbreak occurred in a tertiary care centre. Indian J Med Microbiol. 2021;39(2):192–5.
39. Okomo U, Senghore M, Darboe S, Bojang E, Zaman SMA, Hossain MJ, et al. Investigation of sequential outbreaks of *Burkholderia cepacia* and multidrug-resistant extended spectrum β-lactamase producing Klebsiella species in a West African tertiary hospital neonatal unit: a retrospective genomic analysis. Lancet Microbe. 2020;1(3):e119–29.
40. Arjun R, John KE, Niyas VKM, Nair SR, Mohan V, Ratheesh RS. Achromobacter spp. Bacteremia outbreak related to contaminated furosemide ampoules. Infez Med. 2021;29(3):427–33.
41. Fomda B, Velayudhan A, Siromany VA, Bashir G, Nazir S, Ali A, et al. An outbreak of *Burkholderia cepacia* bloodstream infections in a tertiary-care facility in northern India detected by a healthcare-associated infection surveillance network. Infect Control Hosp Epidemiol. 2023;44(3):467–73.
42. Mathews MS, Sen S. *Blastoschizomyces capitatus* infection after contamination of fluids for intravenous application. Mycoses. 1998;41(9–10):427–8.
43. Campos LC, Lobianco LF, Seki LM, Santos RMR, Asensi MD. Outbreak of *Enterobacter hormaechei* septicaemia in newborns caused by contaminated parenteral nutrition in Brazil. J Hosp Infect. 2007;66(1):95–7.
44. Thong ML, Tay LK. Septicaemia from prolonged intravenous infusions. Arch Dis Child. 1975;50(11):886–9.
45. Dias MBS, Habert AB, Borrasca V, Stempliuk V, Ciolli A, Araújo MRE, et al. Salvage of long-term central venous catheters during an outbreak of *Pseudomonas putida* and *Stenotrophomonas maltophilia* infections associated with contaminated heparin catheter-lock solution. Infect Control Hosp Epidemiol. 2008;29(2):125–30.
46. Güngör S, Özen M, Akinci A, Durmaz R. A *Chryseobacterium meningosepticum* outbreak in a neonatal ward. Infect Control Hosp Epidemiol. 2003;24(8):613–7.
47. Cilli F, Nazli-Zeka A, Arda B, Sipahi OR, Aksit-Barik S, Kepeli N, et al. *Serratia marcescens* sepsis outbreak caused by contaminated propofol. Am J Infect Control. 2019;47(5):582–4.
48. Jain S, Gaind R, Kothari C, Rachna Sehgal A, Shamweel SS, Thukral HK, Chellani,. VEB-1 extended-spectrum β-lactamase-producing multidrug-resistant Proteus mirabilis sepsis outbreak in a neonatal intensive care unit in India: clinical and diagnostic implications. JMM Case Rep. 2016. https://doi.org/10.1099/jmmcr.0.005056.
49. van Nierop WH, Duse AG, Stewart RG, Bilgeri YR, Koornhof HJ. Molecular epidemiology of an outbreak of *Enterobacter cloacae* in the neonatal intensive care unit of a Provincial Hospital in Gauteng, South Africa. J Clin Microbiol. 1998;36(10):3085–7. https://doi.org/10.1128/JCM.36.10.3085-3087.1998.
50. Guducuoglu H, Gultepe B, Otlu B, Bektas A, Yildirim O, Tuncer O, et al. *Candida albicans* outbreak associated with total parenteral nutrition in the neonatal unit. Indian J Med Microbiol. 2016;34(2):202–7.
51. Tresoldi AT, Padoveze MC, Trabasso P, Veiga JFS, Marba STM, von Nowakonski A, et al. *Enterobacter cloacae* sepsis outbreak in a newborn unit caused by contaminated total parenteral nutrition solution. Am J Infect Control. 2000;28(3):258–61.
52. Paul LM, Hegde A, Pai T, Shetty S, Baliga S, Shenoy S. An outbreak of *Burkholderia cepacia* Bacteremia in a neonatal intensive care unit. Indian J Pediatr. 2016;83(4):285–8.
53. Shrivastava B, Sriram A, Shetty S, Doshi R, Varior R. An unusual source of *Burkholderia cepacia* outbreak in a neonatal intensive care unit. J Hosp Infect. 2016;94(4):358–60.
54. Ganeswire R, Thong KL, Puthucheary SD. Nosocomial outbreak of *Enterobacter gergoviae* bacteraemia in a neonatal intensive care unit. J Hosp Infect. 2003;53(4):292–6.
55. Ikumapayi UN, Kanteh A, Manneh J, Lamin M, Mackenzie GA. An outbreak of Serratia liquefaciens at a rural health center in the Gambia. J Infect Dev Ctries. 2016;10(8):791–8.
56. Sridharan S, Yamunadevi R, Senthur Nambi P, Ramasubramanian V. Outbreak of *B. cepacia* bacteremia following use of contaminated drug vials in a tertiary care centre. Indian J Med Microbiol. 2022;40(1):119–21. https://doi.org/10.1016/j.ijmmb.2021.12.003.
57. Ergenc Z, Ergenç H, Bostancı F, Ekiz F, Baycelebi G, Gökosmanoğlu F. Bacterial contamination of propofol vials: the second report from Turkey. Med Sci Discov. 2022;9(11):639–42.
58. Worku B. *Klebsiella oxytoca* outbreak at the Ethio-Swedish Children's Hospital (ESCH). Ethiop Med J. 1997;35(3):177–83.
59. Singhal T, Shah S, Naik R. Outbreak of *Burkholderia cepacia* complex bacteremia in a chemotherapy day care unit due to intrinsic contamination of an antiemetic drug. Indian J Med Microbiol. 2015;33(1):117–9.
60. Lalitha MK, Kenneth J, Jana AK, Jesudason MV, Kuruvilla KA, Jacobson K, et al. Identification of an IV-dextrose solution as the source of an outbreak of *Klebsiella pneumoniae* sepsis in a newborn nursery. 1999.
61. Narayan SA, Kool JL, Vakololoma M, Steer AC, Mejia A, Drake A, et al. Investigation and control of an outbreak of enterobacter aerogenes bloodstream infection in a neonatal intensive care unit in Fiji. Infect Control Hosp Epidemiol. 2009;30(8):797–800.
62. Liu Y, Liu K, Xiaomin Yu, Li B, Cao B. Identification and control of a Pseudomonas spp. (*P. fulva* and *P. putida*) bloodstream infection outbreak in a teaching hospital in Beijing, China. Int J Infect Dis. 2014;23:105–8. https://doi.org/10.1016/j.ijid.2014.02.013.
63. Marais E, Moodley A, Govender N, Kularatne R, Thomas J, Duse A. Clusters of *Klebsiella pneumoniae* infection in neonatal intensive care units in Gauteng. S Afr Med J. 2006;96(9):813.
64. Arslan U, Erayman I, Kirdar S, Yuksekkaya S, Cimen O, Tuncer I, et al. Serratia marcescens sepsis outbreak in a neonatal intensive care unit. Pediatr Int. 2010;52(2):208–12.
65. Orsini M, Otaíza F, Vega P, Hederra LM, Pidal P, Salas V, et al. Brote de fungemias por Sarocladium kiliense en ocho hospitales públicos por

contaminación intrínseca de ondansetrón intravenoso. Rev Chil Infectol. 2018;35(4):363–70.
66. Pillonetto M, Arend L, Gomes SMT, Oliveira MAA, Timm LN, Martins AF, Barth AL, Mazzetti A, Hersemann L, Smits THM, Mira MT, Rezzonico F. Molecular investigation of isolates from a multistate polymicrobial outbreak associated with contaminated total parenteral nutrition in Brazil. BMC Infect Dis. 2018. https://doi.org/10.1186/s12879-018-3287-2.
67. Okomo UA, Darboe S, Bah SY, Ayorinde A, Jarju S, Sesay AK, et al. Maternal colonization and early-onset neonatal bacterial sepsis in the Gambia, West Africa: a genomic analysis of vertical transmission. Clin Microbiol Infect. 2023;29(3):386-e1.
68. Sardan YC, Zarakolu P, Altun B, Yildirim A, Yildirim G, Hascelik G, et al. A cluster of nosocomial *Klebsiella oxytoca* bloodstream infections in a university hospital. Infect Control. 2004;25(10):878–82.
69. Dramowski A, Aucamp M, Bekker A, Mehtar S. Infectious disease exposures and outbreaks at a South African neonatal unit with review of neonatal outbreak epidemiology in Africa. Int J Infect Dis. 2017;1(57):79–85.
70. Dramowski A, Aucamp M, Beales E, Bekker A, Cotton MF, Fitzgerald FC, et al. Healthcare-associated infection prevention interventions for neonates in resource-limited settings. Front Pediatr. 2022;10:919403.
71. Gastmeier P, Loui A, Stamm-Balderjahn S, Hansen S, Zuschneid I, Sohr D, et al. Outbreaks in neonatal intensive care units-they are not like others. Am J Infect Control. 2007;35(3):172–6.
72. Lompo P, Heroes AS, Agbobli E, Kühne V, Tinto H, Affolabi D, et al. Bacterial contamination of antiseptics, disinfectants and hand hygiene products in healthcare facilities in high-income countries: a scoping review. Hygiene. 2023;3(2):136–75.
73. Fraser JL, Mwatondo A, Alimi YH, Varma JK, Vilas VJRD. Healthcare-associated outbreaks of bacterial infections in Africa, 2009–2018: a review. Int J Infect Dis. 2021;103:469–77. https://doi.org/10.1016/j.ijid.2020.12.030.
74. African Society for Laboratory Medicine. Mapping AMR and AMU Partnership. Incomplete Antimicrobial Resistance Data (AMR) Data in Africa: The Crisis with the Crisis. https://aslm.org/wp-content/uploads/2022/09/ASLM_MAAP-Policy-Brief_Embargoed-until-15-Sept-6AM-GMT.pdf?x69286. Accessed on 17th June 2024.
75. UNICEF. Strategy for Water, Sanitation and Hygiene 2016–2030. 2016. https://www.unicef.org/media/91266/file/UNICEF-Strategy-for-WASH-2016-2030.pdf. Accessed on 12th October 2024.
76. Giralt AN, Bourasseau A, White G, Pouget C, Tabernero P, Van Assche K, et al. Quality assurance systems of pharmaceutical distributors in low-income and middle-income countries: weaknesses and ways forward. BMJ Glob Health. 2020;5(10):e003147.
77. Zorrilla-Vaca A, Arevalo JJ, Escandón-Vargas K, Soltanifar D, Mirski MA. Infectious disease risk associated with contaminated propofol anesthesia, 1989–2014. Emerg Infect Dis. 2016;22(6):981–92.
78. Dramowski A, Velaphi S, Reubenson G, Bekker A, Perovic O, Finlayson H, Duse A, Rhoda NR, Govender NP. National neonatal sepsis task force launch: supporting infection prevention and surveillance, outbreak investigation and antimicrobial stewardship in neonatal units in South Africa. South Afr Med J. 2020;110(5):360. https://doi.org/10.7196/SAMJ.2020.v110i5.14564.
79. Buffet-Bataillon S, Rabier V, Bétrémieux P, Beuchée A, Bauer M, Pladys P, et al. Outbreak of *Serratia marcescens* in a neonatal intensive care unit: contaminated unmedicated liquid soap and risk factors. J Hosp Infect. 2009;72(1):17–22.
80. Lucassen R, van Leuven N, Bockmühl D. A loophole in soap dispensers mediates contamination with gram-negative bacteria. Microbiologyopen. 2023;12(5):e1384.
81. Shaban RZ, Sotomayor-Castillo C, Nahidi S, Li C, MacBeth D, Mitchell BG, et al. Global burden, point sources, and outbreak management of healthcare-associated *Burkholderia cepacia* infections: an integrative review. Infect Control Hosp Epidemiol. 2020;41(7):777–83.
82. Tavares M, Kozak M, Balola A, Sá-Correia I. *Burkholderia cepacia* complex bacteria: a feared contamination risk in water-based pharmaceutical products. Clin Microbiol Rev. 2020;33(3):10–1128.
83. Krone M, Rauschenberger V, Blaschke V, Claus H, Kurzai O, Kampmeier S. Ralstonia pickettii bloodstream infections with potential genomic link to internationally distributed contaminated saline solution, Germany, October 2023. Eurosurveillance. 2024. https://doi.org/10.2807/1560-7917.ES.2024.29.3.2400010.
84. World Health Organization. WHO Bacterial Priority Pathogens List 2024. https://www.who.int/publications/i/item/9789240093461. Accessed on 16th June 2024.
85. McDowell SE, Mt-Isa S, Ashby D, Ferner RE. Where errors occur in the preparation and administration of intravenous medicines: a systematic review and Bayesian analysis. Qual Saf Health Care. 2010;19(4):341–5. https://doi.org/10.1136/qshc.2008.029785.
86. Nguyen H-T, Nguyen T-D, van den Heuvel ER, Haaijer-Ruskamp FM, Taxis K. Medication errors in Vietnamese hospitals: prevalence, potential outcome and associated factors. PLoS ONE. 2015;10(9):e0138284. https://doi.org/10.1371/journal.pone.0138284.
87. World Health Organization. Guidelines for the prevention of bloodstream infections and other infections associated with the use of intravascular catheters Part 1: peripheral catheters. 2024. https://www.who.int/publications/i/item/9789240093829. Accessed on 8th June 2024.
88. Franzetti F, Borghi B, Raimondi F, Rosenthal VD. Impact on rates and time to first central vascular-associated bloodstream infection when switching from open to closed intravenous infusion containers in a hospital setting. Epidemiol Infect. 2009;137(7):1041–8.
89. Tack B, Vita D, Ntangu E, Ngina J, Mukoko P, Lutumba A, et al. Challenges of antibiotic formulations and administration in the treatment of bloodstream infections in children under five admitted to Kisantu Hospital, Democratic Republic of Congo. Am J Trop Med Hyg. 2023;109(6):1245–59.
90. Rosenthal VD. Central line-associated bloodstream infections in limited-resource countries: a review of the literature. Clin Infect Dis. 2009;49(12):1899–907.
91. Lutwick L, Al-Maani AS, Mehtar S, Memish Z, Rosenthal VD, Dramowski A, Lui G, Osman T, Bulabula A, Bearman G. Managing and preventing vascular catheter infections: a position paper of the international society for infectious diseases. Int J Infect Dis. 2019;84:22–9. https://doi.org/10.1016/j.ijid.2019.04.014.
92. Larmené-Beld KHM, Frijlink HW, Taxis K. A systematic review and meta-analysis of microbial contamination of parenteral medication prepared in a clinical versus pharmacy environment. Eur J Clin Pharmacol. 2019;75(5):609–17. https://doi.org/10.1007/s00228-019-02631-2.
93. Tubic-Grozdanis M, Krämer I. Parenteral. In: Le Brun P, Crauste-Manciet S, Krämer I, Smith J, Woerdenbag H, editors. Practical pharmaceutics: an international guideline for the preparation, care and use of medicinal products. Cham: Springer International Publishing; 2023. p. 473–519.
94. Minghetti P, Pantano D, Gennari CGM, Casiraghi A. Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe. Health Policy (New York). 2014;117(3):328–33.
95. Ogunsola FT, Mehtar S. Challenges regarding the control of environmental sources of contamination in healthcare settings in low-and middle-income countries—a narrative review. Vol. 9, Antimicrobial Resistance and Infection Control. BioMed Central. 2020.
96. Kotay SM, Donlan RM, Ganim C, Barry K, Christensen BE, Mathers AJ. Droplet- rather than aerosol-mediated dispersion is the primary mechanism of bacterial transmission from contaminated hand-washing sink traps. Appl Environ Microbiol. 2019. https://doi.org/10.1128/AEM.01997-18.
97. Glowicz JB, Landon E, Sickbert-Bennett EE, Aiello AE, Dekay K, Hoffmann KK, et al. SHEA/IDSA/APIC Practice Recommendation: Strategies to prevent healthcare-associated infections through hand hygiene: 2022 Update. Infect Control Hosp Epidemiol. 2023;44(3):355–76.
98. Macías AE, Muñoz JM, Herrera LE, Medina H, Hernández I, Alcántar D, et al. Nosocomial pediatric bacteremia: the role of intravenous set contamination in developing countries. Infect Control Hosp Epidemiol. 2004;25(3):226–30.
99. Macias AE, Munoz JM, Galvan A, Gonzalez JA, Medina H, Alpuche C, et al. Nosocomial bacteremia in neonates related to poor standards of care. Pediatr Infect Dis J. 2005;24(8):713–6.
100. Van Den Heever A, Scribante J, Perrie H, Lowman W. Microbial contamination and labelling of self-prepared, multi-dose phenylephrine solutions used at a teaching hospital. South Af J Anaesth Analg. 2016;22(6):18–22.
101. Baniasadi S, Dorudinia A, Mobarhan M, Karimi Gamishan M, Fahimi F. Microbial contamination of single- and multiple-dose vials

after opening in a pulmonary teaching hospital. Braz J Infect Dis. 2013;17(1):69–73.
102. Tabor A, Shalemariam Z, Alemu Y, Gorems K. Bacterial contamination of single and multiple-dose parenteral injection vials after opening and antibiotic susceptibility of isolates at Jimma Medical Center, Jimma, Southwest Ethiopia. Infect Prev Pract. 2023;5(3):100290. https://doi.org/10.1016/j.infpip.2023.100290.
103. Richards C, Alonso-Echanove J, Caicedo Y, Jarvis WR. Klebsiella pneumoniae bloodstream infections among neonates in a high-risk nursery in Cali, Colombia. Infect Control Hosp Epidemiol. 2004;25(3):221–5.
104. Garrett DO, McDonald LC, Wanderley A, Wanderley C, MillerCarr PJ, Arduino M, Sehulster L, Anderson R, Jarvis WR. An outbreak of neonatal deaths in Brazil associated with contaminated intravenous fluids. J Infect Dis. 2002;186(1):81–6. https://doi.org/10.1086/341083.
105. Dolan SA, Felizardo G, Barnes S, Cox TR, Patrick M, Ward KS, et al. APIC position paper: safe injection, infusion, and medication vial practices in health care. Am J Infect Control. 2010;38(3):167–72.
106. Centers for Disease Control and Prevention. Single-Dose or Multi-Dose? 2024. https://www.cdc.gov/injection-safety/media/pdfs/Injection-Safety-For-Healthcare-P.pdf. Accessed on 12th May 2024.
107. Gorski LA. Infusion nursing standards of practice. J Infus Nurs. 2007;30(3):151–2.
108. World Health Organization. Guidelines on Core Components of Infection Prevention and Control Programmes at the National and Acute Health Care Facility Level. 2016. https://www.who.int/publications/i/item/9789241549929. Accessed on 30th May 2024.
109. Damani N. Manual of infection prevention and control. USA: Oxford University Press; 2019.
110. Ulrich N, Gastmeier P, Vonberg RP. Effectiveness of healthcare worker screening in hospital outbreaks with gram-negative pathogens: a systematic review. Antimicrob Resist Infect Control. 2018;7:1–8.
111. World Health Organization. Improving Infection Prevention and Control at the Health Facility: an Interim Practical Manual. 2018. https://www.who.int/publications/i/item/WHO-HIS-SDS-2018.10. Accessed on 19th August 2024.
112. Macías AE, Muñoz JM, Bruckner DA, Galván A, Rodríguez AB, Guerrero FJ, Medina H, Gallaga JC, Cortés G. Parenteral infusions bacterial contamination in a multi-institutional survey in Mexico: considerations for nosocomial mortality. Am J Infect Control. 1999;27(3):285–90. https://doi.org/10.1053/ic.1999.v27.a92879.
113. Curran E. Intravenous drug preparation: the infection risks. Br J Nurs. 2011;20(Sup7):S4-8.
114. Wong SCY, Wong SC, Chen JHK, Poon RWS, Hung DLL, Chiu KHY, et al. Polyclonal burkholderia cepacia complex outbreak in peritoneal dialysis patients caused by contaminated aqueous chlorhexidine. Emerg Infect Dis. 2020;26(9):1987–97.
115. Rabier V, Bataillon S, Jolivet-Gougeon A, Chapplain J, Beuchée A, Bétrémieux P. Hand washing soap as a source of neonatal Serratia marcescens outbreak. Acta Paediatr. 2008;97(10):1381–5.
116. Stoesser N, Giess A, Batty EM, Sheppard AE, Walker AS, Wilson DJ, et al. Genome sequencing of an extended series of NDM-producing *Klebsiella pneumoniae* isolates from neonatal infections in a Nepali hospital characterizes the extent of community-versus hospital-associated transmission in an endemic setting. Antimicrob Agents Chemother. 2014;58(12):7347–57.
117. Hernandez-Alonso E, Bourgeois-Nicolaos N, Lepainteur M, Derouin V, Barreault S, Waalkes A, et al. Contaminated incubators: source of a multispecies enterobacter outbreak of neonatal sepsis. Microbiol Spectr. 2022;10(4):e00964-22.
118. Woods WA, Watson M, Ranaweera S, Tajuria G, Sumathipala A. Underrepresentation of low and middle income countries (LMIC) in the research literature: ethical issues arising from a survey of five leading medical journals: have the trends changed? Glob Public Health. 2023. https://doi.org/10.1080/17441692.2023.2229890.
119. Busse CE, Anderson EW, Endale T, Smith YR, Kaniecki M, Shannon C, et al. Strengthening research capacity: A systematic review of manuscript writing and publishing interventions for researchers in low-income and middle-income countries, vol. 7. BMJ Global Health: BMJ Publishing Group; 2022.
120. Bhati D, Deogade MS, Kanyal D. Improving patient outcomes through effective hospital administration: a comprehensive review. Cureus. 2023. https://doi.org/10.7759/cureus.47731.
121. Hernández-Ramos I, Gaitán-Meza J, García-Gaitán E, León-Ramírez AR, Justiniani-Cedeño N, Avila-Figueroa C. Extrinsic contamination of intravenous infusates administered to hospitalized children in Mexico. Pediatr Infect Dis J. 2000;19(9):888–90.
122. World Health Organization. World Health Organization Model List of Essential Medicine. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02. Accessed on 18th December 2023.
123. World Health Organization. Paediatric Drug Optimization for Antibiotics Meeting Report, 30 November, 5–7 December 2022. World Health Organization. 2023. https://www.who.int/publications/i/item/9789240068933. Accessed on 26th October 2024.
124. Tack B, Ravinetto R, Allegaert K. Collaborative partnerships as a solution for poor access to essential antimicrobial medicines: What can we learn from the chlorhexidine gel example?, vol. 6. BMJ Paediatrics Open: BMJ Publishing Group; 2022.
125. Campino A, Arranz C, Unceta M, Rueda M, Sordo B, Pascual P, et al. Medicine preparation errors in ten Spanish neonatal intensive care units. Eur J Pediatr. 2016;175:203–10.
126. Gargiulo DA, Sheridan J, Webster CS, Swift S, Torrie J, Weller J, et al. Anaesthetic drug administration as a potential contributor to healthcare-associated infections: a prospective simulation-based evaluation of aseptic techniques in the administration of anaesthetic drugs. BMJ Qual Saf. 2012;21(10):826–34.
127. Gargiulo DA, Mitchell SJ, Sheridan J, Short TG, Swift S, Torrie J, et al. Microbiological contamination of drugs during their administration for anesthesia in the operating room. Anesthesiology. 2016;124(4):785–94.
128. Lompo P, Heroes AS, Ouédraogo K, Okitale P, Wakpo A, Kalema J, et al. Knowledge, awareness, and risk practices related to bacterial contamination of antiseptics, disinfectants, and hand hygiene products among healthcare workers in sub-saharan Africa: a cross-sectional survey in three tertiary care hospitals (Benin, Burkina Faso, and DR Congo). Antimicrob Resist Infect Control. 2024;13(1):44.
129. Heroes AS, Kabamba P, Luyindula A, Bongenya B, Nzazi P, Nasali M, et al. Knowledge, attitude and practice survey of bacterial contamination of blood for transfusion in the Democratic Republic of the Congo. Blood Transfus. 2024;22(3):213–25.
130. World Health Organization. Infection prevention and control in-service education and training curriculum. 2024. https://www.who.int/publications/i/item/9789240094123. Accessed on 28th July 2024.
131. Stone SP, Cooper BS, Kibbler CC, Cookson BD, Roberts JA, Medley GF, et al. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. Lancet Infect Dis. 2007;7(4):282–8. https://doi.org/10.1016/S1473-3099(07)70082-8.
132. American Society for Parenteral and Enteral Nutrition. Safety in Parenteral Nutrition Compounding. 2024. https://www.nutritioncare.org. Accessed on 22nd July 2024.
133. British Association for Parenteral and Enteral Nutrition (BAPEN). Parenteral Nutrition Formulation. 2024. https://www.bapen.org.uk/education/nutrition-support/parenteral-nutrition/parenteral-nutrition-formulation/. Accessed on 22nd July 2024.
134. Ruble J. Impact safety, efficiency, and the bottom line with premixed IV products. Pharm Purch Prod. 2008;5(2):34–8.
135. Rosenthal VD, Maki DG. Prospective study of the impact of open and closed infusion systems on rates of central venous catheter-associated bacteremia. Am J Infect Control. 2004;32(3):135–41.
136. Macias AE, Huertas M, de Leon SP, Munoz JM, Chavez AR, Sifuentes-Osornio J, et al. Contamination of intravenous fluids: a continuing cause of hospital bacteremia. Am J Infect Control. 2010;38(3):217–21.
137. Gorski LA, Hadaway L, Hagle ME, Broadhurst D, Clare S, Kleidon T, et al. Infusion therapy standards of practice. J Infus Nurs. 2021;44(1S):S1-224.
138. Genatrika E, Puspitasari I, Kristina SA, Sulaiman TNS. Personnel knowledge of intravenous admixtures: a survey in a government hospital. Pan Afr Med J. 2021;1:40.
139. Medicines Agency E. Committee for Medicinal Products for Human Use (CHMP) Committee for Medicinal Products for Veterinary Use (CVMP) Guideline on the quality of water for pharmaceutical use. 2020. https://www.ema.europa.eu/en/documents/scientific-guideline/guide

line-quality-water-pharmaceutical-use_en.pdf. Accessed on 24th July 2024.
140. Roesti D, Staerk A. Microbiology. In: Le Brun P, Crauste-Manciet S, Krämer I, Smith J, Woerdenbag H, editors. Practical Pharmaceutics: an international guideline for the preparation, care and use of medicinal products. Cham: Springer International Publishing; 2023. p. 207–26.
141. Lyles CA, Bouza E, Rosenthal VD. Drug delivery systems' role in preventing central line-associated bacteraemia: An international perspective. https://www.researchgate.net/publication/237353193. Accessed on 27th July 2024.
142. Maki DG, Rosenthal VD, Salomao R, Franzetti F, Rangel-Frausto MS. Impact of switching from an open to a closed infusion system on rates of central line-associated bloodstream infection: a meta-analysis of time-sequence cohort studies in 4 countries. Infect Control Hosp Epidemiol. 2011;32(1):50–8.
143. World Health Organization. Assessment tool on infection prevention and control minimum requirements for tertiary health care facilities. 2023. https://www.who.int/publications/i/item/WHO-UHL-IHS-IPC-2023.5. Accessed 10 Feb 2024.
144. Bonnet M, Lagier JC, Raoult D, Khelaifia S. Bacterial culture through selective and non-selective conditions: the evolution of culture media in clinical microbiology. New Microbes New Infect. 2020;34:100622.
145. Lagier JC, Edouard S, Pagnier I, Mediannikov O, Drancourt M, Raoult D. Current and past strategies for bacterial culture in clinical microbiology. Clin Microbiol Rev. 2015;28(1):208–36.
146. Brugger SD, Baumberger C, Jost M, Jenni W, Brugger U, Mühlemann K. Automated counting of bacterial colony forming units on agar plates. PLoS ONE. 2012;7(3):e33695.
147. Forster B, Pinedo CA. Bacteriological examination of waters: membrane filtration protocol. American Society for Microbiology. 2015.
148. Zapka CA, Campbell EJ, Maxwell SL, Gerba CP, Dolan MJ, Arbogast JW, et al. Bacterial hand contamination and transfer after use of contaminated bulk-soap-refillable dispensers. Appl Environ Microbiol. 2011;77(9):2898–904.
149. Sanders ER. Aseptic laboratory techniques: plating methods. J Vis Exp. 2012. https://doi.org/10.3791/3064-v.

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