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Review

Bacterial Contamination of Antiseptics, Disinfectants and Hand Hygiene Products in Healthcare Facilities in High-Income Countries: A Scoping Review

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Abstract: This scoping review addresses bacterial contamination of antiseptics, low-level disinfectants, and hand hygiene products in healthcare settings in high-income countries. Over 70 years, 114 articles were found: 68 outbreaks, 13 pseudo-outbreaks and 33 cross-sectional surveys. Outbreaks affected median 29 (1–151) patients, extended for 26 (1–156) weeks and had a case fatality of 0.0% (0.0–60.0%). Most (72.8%) (pseudo-)outbreaks were caused by water-based chlorhexidine (CHG), quaternary ammonium compounds (QUAT) and the combination CHG–QUAT. Contaminating bacteria were nonfermentative Gram-negative rods (87.6% (pseudo-)outbreaks), mainly *Burkholderia cepacia*, *Pseudomonas aeruginosa* and *Achromobacter* spp.) and Enterobacterales (29.6%, 24/81), mostly *Serratia* spp.). Risk factors were at the level of the bacteria (natural resistance to CHG and QUAT), containers (design and functioning, presence of cork and cotton, biofilm formation), preparation (nonsterile water, overdilution) and practices (too long expiry dates, inappropriate container reprocessing, topping up of containers and deviation from procedures). Transmission occurred through direct contact (antiseptics), contact with semicritical items (disinfectants) and were handborne (soaps). During recent decades, reports of soap contaminated with Enterobacterales emerged and nationwide outbreaks of intrinsically contaminated CHG occurred. Outstanding issues comprise intrinsic contamination, implementation of antiseptic stewardship, the role of unit doses and sterile products, transmission studies, biofilm control and understanding healthcare providers' perceptions.

Keywords: antiseptic; disinfectant; hand hygiene; intrinsic; in-use; outbreak; cross-sectional

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1. Introduction

Healthcare-associated infections cause a considerable burden of attributable deaths, prolonged hospital stay and economic loss [1]. Over the past decades, the healthcare environment (medical equipment and surfaces, commonly named "fomites") has been increasingly acknowledged as a reservoir of bacteria causing healthcare-associated infections [2–5]. These bacteria may be transmitted from fomites to patients by direct contact, by contact with (semi-)critical items and by the handborne route (i.e., through healthcare providers' hands) and, more rarely, by water, food and aerosols [6]. Once transmitted, the bacteria can colonize the skin and mucous membranes of patients and subsequently cause infections.

This chain of infection can be controlled by hand hygiene and asepsis (interrupting the transmission) and by environmental cleaning and disinfection (reducing the reservoir) [3,7].

Although designed to remove or inactivate microorganisms, antiseptics, disinfectants and hand hygiene products can be contaminated with bacteria and even constitute the reservoir of outbreaks of healthcare-associated infections [4,7,8]. Numerous reports date from as early as 1951 [9] and have incited several editorials and reviews [4,8,10–15]. Contaminated antiseptics and hand hygiene products also figured in a recent review about patient care items causing healthcare-associated infections [4].

2. Objective, Focus and Scope of this Review

In this scoping review, we assess bacterial contamination of antiseptics (AS), disinfectants (DI), and hand hygiene (HH) products (AS, DI and HH products) in healthcare facilities in high-income countries to give an update on the frequency, burden and microbiological spectrum of contamination events. Moreover, we assess factors associated with contamination, attribution and transmission and interventions and formulate outstanding issues, research questions and recommendations. This review addresses original papers assessing healthcare-associated outbreaks and pseudo-outbreaks caused by AS, DI and HH products as well as cross-sectional surveys assessing bacterial contamination of these products. It thereby focuses on products listed on the WHO Model List of Essential Medicines [16]; for disinfectants, low-level products used for environmental disinfection are targeted.

In line with the requirements of a scoping review [17], a priori protocol was developed comprising an exhaustive literature search, structured data extraction and steps to ensure internal reliability. The target audience of this review are healthcare providers and allied care professionals (maintenance, cleaning, management) working in the field of infection prevention and control (IPC), professional associations and academics working in IPC guideline development and education, as well as researchers working in development and implementation of IPC tools.

Although related, the following healthcare items are not assessed (references to reviews or key papers are added): automated and new technologies for decontamination [18,19], hospital water [7,20,21], sinks and hand-washing stations [22], products for mouth wash and hand lotions [23–25], cleaning products and equipment (buckets, mops and wipes) [3,5,18,26]. Studies from low- and middle-income countries are published in a separate systematic review paper [27]; the latter review also lists the "Best Practices" to minimize the risk of bacterial contamination of AS, DI and HH products.

3. Materials and Methods

3.1. Terms and Definitions

Antiseptics and disinfectants inactivate microorganisms or inhibit their growth (Box 1) [7,28–32]. Disinfectants act on surfaces and objects whereas antiseptics act on the skin and mucous membranes. Disinfectants are categorized according to their effectiveness into high-level disinfectants used for disinfection of endoscopes and low-level disinfectants for hospital environmental cleaning and disinfection [8,30].

The WHO Model List of Essential Medicines (EML) 2021 [16] lists the following products as disinfectants: chlorine-based compounds, chloroxylenol and alcohol-based handrub. Antiseptics listed comprise chlorhexidine (CHG), ethanol, isopropyl alcohol, iodine, and povidone iodine (Table 1). Additionally, many other products are used; as an example, according to the WHO EML 2021, 7 high-income countries have included cetrimide (a quaternary ammonium compound (QUAT)) in their national EML and 1 (Nauru) has also included chloramine. In addition, some products are marketed both as a disinfectant and as product for hand hygiene (e.g., chloroxylenol) or as both antiseptic and disinfectant (e.g., QUAT used as antiseptic and disinfectant ("spray and wipe")) [7].

According to the WHO [7], for hand hygiene in the healthcare setting, alcohol-based handrub or soap and water can be used. Alcohol-based handrub consists of a mixture of alcohol in water. Soaps are detergents that facilitate the removal of dirt and lipids. Antiseptic (medicated) soaps contain an antiseptic whereas plain soap does not; soaps

also contain preservatives, i.e., agents inhibiting growth of microorganisms. They are mostly available as liquid or bar soap. As for hand hygiene, alcohol-based handrub is the most effective, followed by antiseptic soap and plain soap [33]. For hand hygiene in clinical situations in the healthcare setting (except for a few situations), the WHO recommends alcohol-based handrub over water and soap. Given that storage of bar soap in wet conditions is associated with contamination, the WHO advises against the multiple-use of bar soap in the healthcare setting [7].

Containers are bottles or reservoirs for products, while dispensers consist of a container with a dispensing system, e.g., a wrist-operated pump. Containers and dispensers are designed and marketed as disposable or reusable; in the latter case, a procedure for reprocessing must be in place [7]. Figure 1A,B show an example of a refillable table-top dispenser with disposable pump and a gravitational dispenser, respectively. Dispensers can be wall-mounted or self-standing (table-top); in addition, pocket-size clip-on dispensers for individual use are available (Figure 1C).

The life cycle of AS, DI and HH products includes procurement, supply and registration, storage, preparation (mostly in a central place e.g., the pharmacy) and distribution, and labeling, as well as reprocessing and maintenance of dispensers and containers. Ready-to-use products are intended to be used by the end-user at the workplace and in their manufactured formulation and concentration. Disinfectants may be diluted at the workplace to a working concentration for use.

The shelf life refers to the unopened product and its expiry date, whereas the period after opening (in-use stability) refers to the period the product can be safely used after first opening. Refilling refers to filling the container after adequate reprocessing, whereas topping up refers to replenishing an in-use container (which may be empty or contain residual product) without reprocessing.

Contamination in the present review is defined as the presence of bacteria in the products. Contamination can be present in the original product as procured (intrinsic) or be introduced during preparation and use (extrinsic, in-use contamination).

The term outbreak in this review was adopted from the articles themselves, providing the same bacterial species was cultured from both clinical samples and samples from AS, DI and HH products and irrespective of the number of patients affected [4]. For clinical samples, both infection and colonization (i.e., presence of organisms without signs of infection) were considered and grouped together. The term pseudo-outbreak refers to false-positive cultures of clinical specimens caused by contaminated products in the absence of patient colonization, infection, and exposure [34,35]. The term cross-sectional survey in this review referred to series of sampling and culturing of products at a given point of time, unrelated to an ongoing outbreak.

Generic product and product class names (Table 1) were used in this review: in cases where the studies provided only brand names, the corresponding generic names were looked-up, if possible, by retrieving the product's Material Safety Data Sheet. The term "aqueous" and "tincture" were consistently replaced by "water-based" and "alcohol-based", respectively. Given the wide period of source references, bacterial taxonomy and nomenclature were verified according to the List of Prokaryotic names with Standing in Nomenclature and updated species names were used [36]. In line with other outbreak articles [37,38], we grouped species within the *Alcaligenes–Achromobacter* genera together and did the same for the species belonging to *Burkholderia cepacia* complex. Both groups were difficult to identify phenotypically; the *Alcaligenes–Achromobacter* genera had considerable taxonomic overlaps during the past year; and the *Burkholderia cepacia* complex represented at least 20 species, of which *Burkholderia cenocepacia* is the most virulent [39,40]. Antibiotic resistance data were assessed for acquired resistance on top of the wild-type resistance phenotype of bacterial species [41].

Box 1. Terms, definitions and applications of antiseptics and disinfectants and products for hand hygiene discussed in this review

1. **Antiseptics:** Antiseptics are used to prepare the skin or mucosa for invasive procedures and surgery, surgical hand preparation, oral care for intubated patients and (in community settings with high neonatal mortality) umbilical care in newborns and topical wound care [7,28–32], e.g., alcohol, chlorhexidine and iodine compounds.
2. **Disinfectants:** products that inactivate microorganisms or inhibit their growth and are applied to inanimate **objects and surfaces** [42]
   - Disinfectants with high-level effectiveness inactivate all microorganisms except bacterial spores. Examples are glutaraldehyde and ortho-phthalaldehyde, used for disinfection of endoscopes [30]; they are not subject to this review.
   - **Low-level disinfectants** act on most bacteria and some viruses and fungi, but most have no activity on mycobacteria and spores (Table 1). Examples are sodium hypochlorite, quaternary ammonium compounds and chloroxylenol. They are used for:
     - environmental cleaning: removal of body materials, dust or foreign material [42];
     - decontamination: removal of soil and pathogenic microorganisms [43].
3. **Products used for Hand Hygiene:**
   - 3.1. **Alcohol-based handrub:** an alcohol-containing product that inactivates microorganisms or inhibits their growth. It is applied to the hands without use of water; after application, hands are rubbed until they are dry. Water and towels to dry the hands are not needed [7].
     - Alcohol-based handrub consists of **ethanol or isopropyl alcohol** mixed with water (Table 1) to the recommended concentration of 60–90% [7,44].
     - Alcohol-based handrub is available as a **liquid** (solution), **gel** or **foam** [7].
     - Alcohol-based handrub can be **combined with antiseptics** such as chlorhexidine (0.5–1%) [7].
     - Alcohol is industrially produced by fermenting sugar or starch (cane, beet, manioc starch, mahogany or walnut) [45,46]. "**Denaturation**" means adding agents which corrupt the taste and make the products unsuitable for consumption as a beverage.
     - The term **Hand Sanitizer** is a general term referring to alcohol-based handrub used in the community setting [47]. It is not used in this review.
   - 3.2. **Soaps:** although soaps, strictly defined, are naturally occurring (anionic) detergents, the term "soap" in this review indicates both natural and synthetic detergents.
     - **Detergents** are surfactants i.e., products that allow suspension of fats in water. Detergents may be anionic, cationic, amphoteric or nonionic, i.e., having positive, negative, both positive and negative, or no electrical charge [48].
     - Cationic detergents have antimicrobial activity (e.g., **quaternary ammonium compounds**).
     - Soaps can contain antiseptic agents (**antiseptic soap**, antimicrobial soap, medicated soap) or not (**plain soap**, unmedicated or nonmedicated soap).
     - Soaps are available in various forms, including **liquid**, foam and solid (**bar**, powder). In healthcare settings, liquid soap is preferred over bar soap, as liquid soap was less contaminated in several studies [49,50].
     - Soap may contain **preservatives**, i.e., agents that destroy or inhibit growth of microorganisms (e.g., benzyl alcohol, methyl-chloroisothiazolinone and methylisothiazolinone) [7,48].
     - Some soaps contain antiseptics with a **sustained activity** (synonym: residual, remnant) effect, i.e., they have an effect that extends beyond the application, e.g., chlorhexidine.

Table 1. Overview of antiseptics, disinfectants and products for hand hygiene discussed in this review, based on references [16,28,32,42,43,51–55]. Products listed on the 21st WHO Model List of Essential Medicines (EML) are marked with *. Product characteristics listed are selected in relation to the risk of bacterial contamination; extensive product characteristics can be found in references [56,57].

Product	Characteristics and Indications
Products for hand hygiene	
Alcohol-based handrub Ethanol 80% vol/vol * Isopropyl alcohol 75% vol/vol *	Procured as ready-to-use products or diluted with water (from a 96% solution) See also Box 1 Formulations combined with chlorhexidine or quaternary ammonium compounds are available
Antiseptic soap	Examples of antiseptics added to soap are (concentrations according to reference (WHO, 2009): ○ Chlorhexidine (see Antiseptics) 0.5–4% ○ Chloroxylenol (see Disinfectants) 0.5–4% ○ Triclosan (mostly added to bar soap, 0.1–2%) ○ Iodophors (see Antiseptics) 0.5–10% ○ Quaternary Ammonium compounds (see Disinfectants) ○ Hexachlorophene 3%, no longer used because of neurotoxicity for infants
Antiseptics	
Chlorhexidine (Chlorhexidine digluconate: CHG) 5% digluconate solution for dilution * Class: biguanides Examples: Hibiclens, Hibiscrub, Hibitane	Dilutions made in water or alcohol: 0.5% up to 4% Has detergent activity and residual activity (4–6 h) Good activity against Gram-positives Gram-negatives may be intrinsically resistant Vulnerable to contamination with Gram-negative bacteria
Ethanol and Isopropyl-alcohol (60–90%)	Ethanol 70% (denatured) solution *
Povidone iodine 7.5–10% * solution (water-based) Class: iodophors Example: Betadine	10% povidone iodine is equivalent to 1% available iodine Procured as ready-to-use product, water-based Can be applied on intact skin but also on mucosa and wounds Note: Iodophors have largely replaced 1% iodine in alcohol (iodine tincture) (Weber et al., 2007; WHO, 2018a)
Cetrimide, cetrimonium Class: Quaternary Ammonium Compounds	Used as antiseptic soap or as water-based solution Procured as ready-to-use product or product for dilution See disinfectants
Chloramine Class: Chlorine compounds Example: Dakin, a stabilized chlorine product	Product which provides slow release of chlorine Less irritating and longer acting than chlorine compounds (see Disinfectants) Mostly used in French-speaking countries

Table 1. *Cont.*

Product	Characteristics and Indications
Low-level disinfectants (note chlorine is sometimes categorized as an intermediate-level disinfectant)	
Chlorine (sodium hypochlorite) Powder 0.1% concentration of available chlorine * Household Bleach (concentration 5%) Eau de Javel (concentration 8–15°) Sodium dichloroisocyanurate granules Calcium hypochlorite tabs Chloramine-T tablets Class: Chlorine compounds	Chlorine solutions are made in water by dilution up to 0.5% or 1.0% final concentration of hypochloric acid (HOCl) Household bleach contains 5.25–6.15% sodium hypochlorite Eau de Javel mostly used in French speaking countries (1° ("degree chlorométrique") equals 0.317% HOCl) Chloramine-T releases chlorine very slowly, resulting in a more prolonged effect, is (also) used as antiseptic
Chloroxylenol * Therapeutic alternatives: 4th level ATC chemical subgroup (D08AE Phenol and derivatives) PCMX (para-chloro-meta-xylenol) solution 4.8% DCMX (Dichloro-meta-xylenol) solution 2.5% Class: PhenolicsExample: Dettol	Ready-to-use product, water-based Residual activity Products are diluted in water Also marketed as product for hand hygiene (water-based) and antiseptic (wound cleansing)
Cetrimide (Cetrimonium bromide) Didecyl dimethyl ammonium bromide Dioctyl dimethyl ammonium bromide Benzalkonium chloride Class: Quaternary Ammonium Compounds (QUAT) Example: Zephiran	Water-based, procured ready-to-use or product for dilution Detergent activity High water hardness, cotton and gauze diminish activity Most active against Gram-positives. Some Gram-negatives (e.g., Pseudomonas aeruginosa) are intrinsically resistant Vulnerable to contamination with Gram-negatives, in particular Benzalkonium chloride Formulations combining QUAT and chlorhexidine: Examples: Savlon, HAC (hospital antiseptic concentrate)

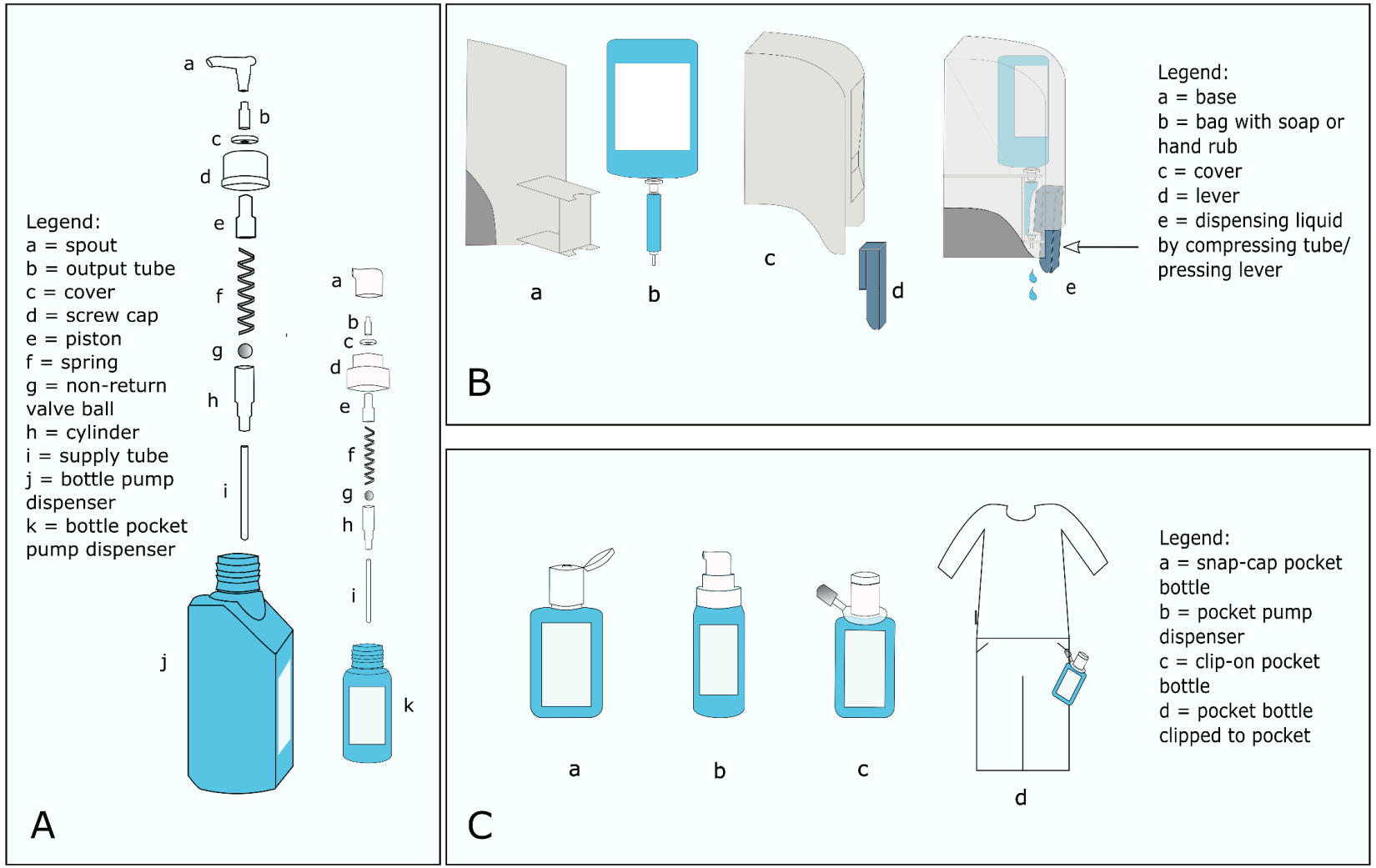

Figure 1. (**A**–**C**). Exploded view drawing of different types of dispensers. (**A**) = a refillable table-top and pocket pump dispenser with associated disposable regular pump system, (**B**) = a wall-mounted gravitational dispenser and a rechargeable cartridge, and (**C**) = a pocket and clip-on container. For other models of regular pumps, see Bánsághi et al. [58].

3.2. Search Strategy

The aforementioned reviews and editorials about outbreaks related to contaminated AS, DI and HH products were used as a starting point to define search terms and strategy [4,8,12–15]. Next, the Worldwide Database for Nosocomial Outbreaks [59], which compiles over 3600 structured reports of healthcare-associated outbreaks, was searched. To complement the previous outbreak reviews and to find cross-sectional surveys, the databases of PubMed, Google Scholar, and Scopus were screened. Articles in English, French, Spanish, Portuguese, and German were included. The search was last updated on 31 May 2022.

The literature search strings used in the PubMed database were structured in the following 4 concept groups: (1) antiseptic, disinfectant and soap, (2) bacteria, (3) contamination and (4) nosocomial infection. These concepts were combined with terms as described in Supplementary Table S1. In addition, for the other databases (Worldwide Database for Nosocomial Outbreaks as well as in Google scholar and Scopus), the main key words (Antiseptic OR disinfectant OR soap OR detergent AND contamination OR contaminated AND bacterial infection hospital) were used. To run a snowball search, reference lists were hand-searched upstream (reference list of the papers) and downstream ("cited by" lists).

All original research studies were included, including (pseudo-)outbreak investigations and cross-sectional surveys conducted in healthcare facilities (hospitals, health centers including inpatient and outpatient departments). Excluded were nonhuman studies, experimental studies, studies in which AS, DI and HH products were assessed as potential reservoirs of healthcare-acquired infections but were cultured negative, and reviews. Focus was put on the product (content); studies and results describing only contamination of the outer surfaces of containers and dispensers were not considered.

3.3. Data Extraction

Titles and abstracts were screened using Rayyan online articles' screening software [60] and data were extracted by the first author (PL) and verified by a second author (JJ); discrepancies were resolved by discussion. Extracted data included study setting (healthcare facility level, ward), year of publication, investigated products and product category, product concentration, sampling methods (selection, use of neutralizer, laboratory methods), contaminating bacteria and their antibiotic resistance profile. In addition, risk factors for bacterial contamination (either demonstrated or assumed) were recorded as well as investigations to trace the source of contamination (e.g., analysis of tap water used for product dilution, analysis of sealed un-used products at reception). Extra information added was the income level of the country at the year of publication (or the closest to this year) according to the World Bank classification [61].

For (pseudo-)outbreaks, demographic and clinical data of affected patients were extracted, including wards and numbers of patients affected, infected or colonized body sites, and results of microbiological analysis of the products. When performed and available, data supporting attribution of the contaminating flora were recorded including molecular methods assessing relatedness between clinical and environmental isolates. In addition, potential routes of transmission (assumed or demonstrated) were recorded. As a minimum for causality, AS, DI and HH products were considered as reservoirs when the same bacterial species was retrieved from both human infections and suspected products [4]. Finally, we also extracted interventions applied for outbreak control.

Data were compiled in an Excel database (Microsoft, Redmond, WA, USA). The data extraction form was piloted for a starting set of approximately 20 articles and then adapted according to the initial experience. Supplementary Document S1 lists the articles included; Supplementary Document S2 contains the validated database of extracted information.

4. Results and Discussion

4.1. (Pseudo-) Outbreak Reports and Cross-Sectional Surveys: Overview

For all countries combined, 154 retrieved original articles were selected (Figure 2), of which three-quarters (74.0%, 114/154) originated from high-income countries, and 26.0% (40/154) from low- and middle-income countries; the latter (published elsewhere) [27] were excluded from the present review. The underrepresentation of articles from low- and middle-income countries is in line with general healthcare-associated outbreak reporting and it is striking given the higher frequency of healthcare-associated infections in low-resource settings [1,43,62–64]. The 114 articles included comprised 68 outbreaks, 13 pseudo-outbreaks and 33 cross-sectional surveys. Nearly one-third (32.4%, 37/114) of the articles were retrieved by hand search, and 70.3% (26/37) had been published earlier than 1990.

Outbreaks and pseudo-outbreaks were reported from all global regions (Table 2). They were consistently reported over the past 70 years; although a decreasing trend was noted in a review from 2007 (ascribed to improved products and new guidelines [8]) and 13/68 (19.1%) outbreaks were reported during the past 2 decades (Table 3). Two geographic clusters of articles were noted: 1 related to iodophors in the US (5 articles from 3 different products) [65–69] and another related to chlorhexidine in Spain (6 articles) [70–74].

Apart from the clusters mentioned above, 5 other outbreaks occurred in more than 1 center [75–79]; the remaining outbreaks (73.5%, 50/68) occurred in a single ward. Wards most frequently affected were the adult intensive care unit (n = 8), neonatology (n = 6), adult surgery (n = 11), adult oncology and hematology (n = 5), and pediatric wards (n = 11, including pediatric oncology and surgery). Six articles mentioned invasive procedures (e.g., cardiac catheterization, intra-articular injection, bronchoscopy, and cystoscopy). The median (range) number of patients affected (information for 64 outbreaks) was 29 (1–151); 10 outbreaks counted more than 50 patients.

Most frequently described body sites infected and specimens submitted (for 65 outbreak investigations reporting information) were blood (70.8% (57/65) of investigations), followed by cerebrospinal fluid and peritoneal fluid (6 and 5 investigations respectively). The median duration (for 60 outbreaks) was 26 (1–156) weeks, with 55% (33/60) and 30.0% (18/60) of outbreaks extending more than 3 months and 1 year, respectively. The median case-fatality rate (for 45 outbreak investigations) was 0.0% (0.0–60.0%), with aggregated case-fatality ratio of 6.1%; 25 articles reported no case fatalities, whereas 6 reported case fatality rates $\geq$ 20%, 3 of them occurring in hematology wards and 1 in a neonatology ward. Among the outbreaks with case fatalities (n = 20), the median number of associated deaths was 4 (1–21), varying according to patients' comorbidities. For some low-virulence organisms (*Burkholderia cepacia*, *Achromobacter* spp.), however, the authors reported it was doubtful to attribute mortality to the infection itself [37,80,81].

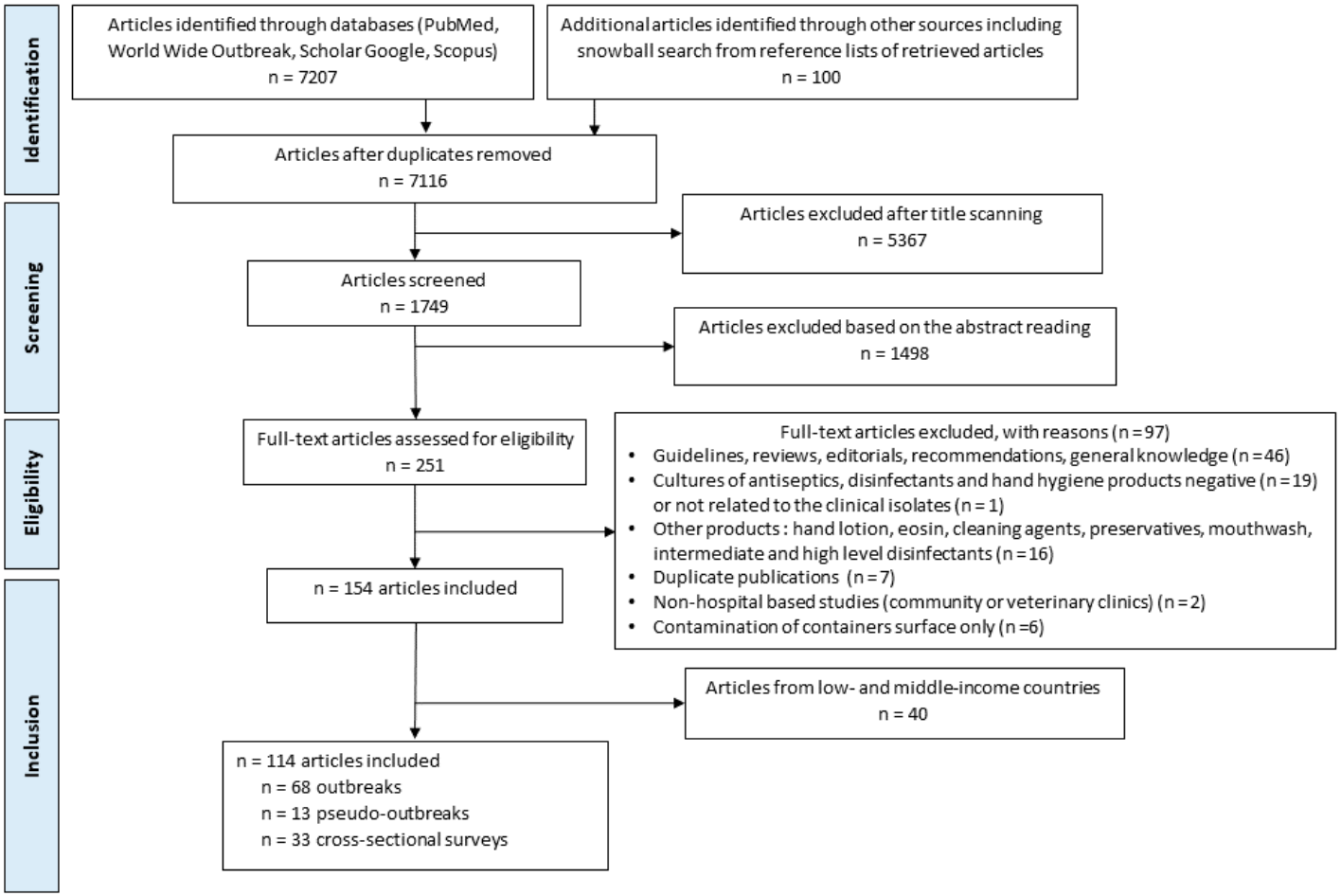

Figure 2. Flow chart presenting the literature search strategy for bacterial contamination of antiseptics, disinfectants and hand hygiene products in healthcare facilities in high income countries.

Pseudo-outbreaks (12/13 investigations providing information) involved a median number of 19 (2–178) patients. Ten mentioned the ward, among which 1 was reported in 4 wards. The affected wards included intensive care (n = 3), hematology–oncology and pediatrics (n = 2 each), and surgery and the related wards of dialysis, emergency, obstetrics and gynecology, and blood transfusion (n = 1 each). Blood cultures were the most frequent specimen (11/13 reports). The median (range) duration was 11 (1–104) weeks, with 1 pseudo-outbreak extending for >1 year.

Apart from the clinical presentation, triggers for outbreak investigations included unusually high numbers of organisms, which generally occurred only rarely in the healthcare facility (e.g., *Burkholderia cepacia* [82], *Achromobacter* spp. [83,84] and *Ralstonia pickettii* [85], "usual" organisms occurring in a short time frame (e.g., *Serratia marcescens*) [86], alerts by the hospital laboratory [87] or by national health authorities [70,71], or incidental findings of contaminated products [77]. The characteristics above (long duration, insidious course, sometimes common hospital pathogens) are typical for healthcare-associated outbreaks in general [88]. Furthermore, the nonspecific alerts (in some outbreaks triggered by serendipitous findings) suggest that many (pseudo-)outbreaks may be overlooked or not investigated.

Cross-sectional surveys (27/33 articles providing information) assessed a median of 48 (1–492) samples per survey, mostly selected from surgery and related wards, intensive care unit and neonatology. The reasons and objectives in conducting the surveys included study of the process of contamination and its associated factors (17 surveys), description of an interesting observation (particular bacteria, product or process, n = 6), exploration triggered by ongoing (unrelated) or past healthcare-associated infections (n = 6), and quality assurance (monitoring) of the in-use products' contamination (n = 4). Examples of observations prompting a survey were suspicion of contamination of soap by the appearance of the containers (bulging, blown open seals and color change) [49], high numbers of bacteria detected by routine microbiological monitoring of the cleaning and disinfection process [89], and the unexpected culture of *Pseudomonas aeruginosa* obtained during validation of a new hand hygiene protocol [90].

In some of the articles, the terms antiseptics and disinfectants were sometimes used interchangeably or in a mixed form ("disinfectant soap") and products were sometimes used both as antiseptics and disinfectants, particularly, but not exclusively, in the earlier reports [76,79,81,91–96]. Some papers classified as outbreaks also reported a few cases of pseudo-infections [66,68,97] and vice versa [82]. The title of 1 paper incorrectly mentioned "pseudo-bacteremia" while describing infected and colonized patients [73].

Table 2. Geographic distribution of articles reporting bacterial contamination of antiseptics, disinfectants, and hand hygiene products in healthcare facilities in high-income countries. The values represent the numbers of articles published in the different areas worldwide according to United Nations geoscheme [98].

United Nations Geoscheme/Countries	Cross-Sectional	Outbreak	Pseudo-Outbreak	Total
Northern Europe	**9**	**7**	**-**	**16**
Iceland	1	-	-	1
Norway	1	-	-	1
United Kingdom of Great Britain and Northern Ireland	7	7	-	14
Western Europe	**8**	**8**	**4**	**20**
Belgium	1	-	1	2
France	-	8	2	10
Germany	6	-	1	7
Switzerland	1	-	-	1
Southern Europe	**2**	**13**	**-**	**15**
Italy	1	4	-	5
Spain [a]	1	9	-	10
North America	**7**	**26**	**3**	**36**
Canada	1	2	-	3
United States of America [a]	6	24	3	33
Latin America and the Caribbean	**-**	**1**	**-**	**1**
Chile	-	1	-	1
Oceania: Australia and New Zealand	**4**	**4**	**1**	**9**
Australia	3	3	1	7
New Zealand	1	1	-	2
Eastern Asia	**3**	**7**	**3**	**13**
Hong Kong, Special Administrative Region, China	-	1	-	1
Japan	3	3	1	7
Republic of Korea	-	3	2	5
Taiwan [b]	-	-	1	1
Western Asia	**-**	**2**	**1**	**3**
Cyprus	-	1	-	1
Israel	-	1	1	2
Total	**33**	**68**	**13**	**114**

[a] There were 2 geographical clusters of articles: 1 cluster reporting (pseudo-)outbreaks associated with contaminated iodophors (3 different products) in the United States of America (1980s and early 1990s) [65–69], and another reporting outbreaks associated with contaminated chlorhexidine in Spain (2010s) [70–74]. [b] The name Taiwan refers to the countries' income level classification by the World Bank; the United Nations geoscheme does not mention Taiwan.

Table 3. Articles reporting contamination of antiseptics, disinfectants, and hand hygiene products in healthcare facilities in high-income countries: outbreak and pseudo-outbreak reports (n = 81) and cross-sectional surveys (n = 33). Numbers represent outbreak and pseudo-outbreak reports, and surveys; CHG = chlorhexidine gluconate, PCMX = chloroxylenol, QUAT = quaternary ammonium compounds. For the (pseudo-)outbreaks, the total of each contaminated product is represented by the number of outbreak reports/number of pseudo-outbreak reports.

Decades	1950s	1960s	1970s	1980s	1990s	2000s	2010s	2020s	Total Outbreak/Pseudo-Outbreak
Outbreaks and pseudo-outbreaks (n = 81)	2/0	5/0	12/1	10/5	7/1	16/3	14/3	2/0	68/13
Alcohol	-	-	-	1	1	-	2	-	2/2
CHG	-	2	4	6	2	6	9	2	26/5
QUAT	2	3	4	3	2	6	4	-	20/4
CHG–QUAT	-	-	4	-	-	-	-	-	4/0
Iodophor	-	-	-	4	1	-	-	-	3/2
Phenol	-	-	1	1	-	-	-	-	2/0
Liquid Soap [a]	-	-	-	-	2	7	2	-	11/0
Cross-sectional surveys (n = 33)	**2**	**5**	**7**	**6**	**2**	**2**	**8**	**1**	**33**
CHG	**-**	**1**	**-**	**2**	**-**	**-**	**-**	**-**	**3**
QUAT	**1**	**1**	**2**	**1**	**2**	**-**	**3**	**1**	**11**
Phenol [b]	**-**	**2**	**3**	**1**	**-**	**-**	**-**	**-**	**6**
Liquid Soap [c]	**1**	**-**	**1**	**2**	**-**	**2**	**4**	**-**	**5/1/4** [c]
Bar Soap	**-**	**1**	**1**	**1**	**-**	**-**	**-**	**-**	**3**

[a] Including antiseptic soap (n = 6), plain soap (n = 3) and no information (n = 2). [b] Including phenol disinfectants (n = 5) and PCMX (n = 1). [c] Antiseptic soap/plain soap/no information. Antiseptic soaps comprised triclosan (n = 3), CHG, cetrimide and hexachlorophene (1 each).

4.2. Products Involved

Both (pseudo-)outbreak reports and cross-sectional surveys had no sound product denominators and reported results may have been influenced by the overall frequency of in-use products used and selection according to the survey's objective. Further, use of bar soap in hospitals was phased out since the 80s and triclosan (a phenol component mainly used in antiseptic soap) was banned more recently [99–101]. Hence, the present data cannot be used to express incidences or compare vulnerability to contamination among products. Nevertheless, some tendencies are apparent.

Products involved in (pseudo-)outbreaks were CHG (n = 31 articles), QUAT (n = 24) and CHG–QUAT (n = 4) (Table 3); together accounting for 72.8% (59/81) of the articles consistently reported over all decades, with 3 outbreaks associated with contaminated CHG published very recently [38,71,102]. Liquid soap products were associated with 10 outbreaks peaking in the 2000s (7/10 articles reporting contaminated soap). Iodophor, alcohol and phenol products accounted for 5, 4 and 2 reports respectively; those associated with iodophors mainly occurring in the 1980s and no report published later than 1992 [68]. Four outbreaks were associated with alcohol-based products: 2 described bloodstream infections after use of isopropyl alcohol pads (in 1 report combined with 2% CHG) during insertion of central vascular lines [103,104], the other 2 reported pseudo-bacteremia related to ethanol used for skin asepsis and disinfection of the blood culture bottle stoppers at blood culture sampling [105,106].

Among cross-sectional surveys (n = 33), 102 contaminated products were detected, including bar soap and QUAT (in 75.8% (25/33) surveys each), liquid soap (72.2% (24/33 surveys), and phenol-based products (45.5% (15/33 surveys) (Table 3). QUAT were reported along all decades till recently; contaminated liquid soaps were mainly reported since 2000 (6/10 surveys).

Most contaminated products (95.1%, 77/81) associated with (pseudo-)outbreaks were water-based. Most (60.9%, 14/23 products for which information was available) outbreak-associated CHG products had concentrations $\leq$0.5% (which is the lowest marketed concentration) or were highly ($\geq$1/1000) diluted. However, 7 products had concentrations $\geq$2% including also 4% (i.e., the highest marketed concentration). In 58.3% (14/24 outbreaks providing information), benzalkonium chloride was the involved QUAT product, 10/14 of these products had low ($\leq$0.15%) concentrations or were highly ($\geq$1/750) diluted. Likewise, all 4 CHG–QUAT products were water-based and diluted, but the original product concentrations were not mentioned. Low product concentrations (due to in-house dilutions) have been noted in a previous review [8] and have been discussed in detail for CHG elsewhere [107].

Iodophor products were involved in 3 outbreaks and 2 pseudo-outbreaks. In 4/5 products, povidone was the carrier, the remaining product used poloxamer. Pseudo-outbreaks occurred during blood culture sampling, by use of iodophor either for skin asepsis or for disinfection of the blood culture bottle's stopper. Of note, iodophor products are delivered as ready-to-use products with fixed factory-based concentrations and hence do not require (or allow) in-house dilution.

Among the contaminated liquid soap products (n = 11), 3 were plain and 6 were antiseptic soaps, containing triclosan (n = 4) and para-chloro-meta-xylenol (PCMX) (n = 1); no information was available for the remaining products. Reasons for the scarcity of articles about contaminated liquid soaps before 2000 may include lack of awareness; as most of the aforementioned reviews and editorials focused on antiseptics and disinfectants but did not include soap products [8,10,12–15]. Soap dispensers have only recently been noted in a review of fomites of healthcare-associated infections [4].

Bar soap was not represented among the products involved in (pseudo-)outbreaks but contamination was detected in early (before 1990) cross-sectional surveys. In a study comparing liquid and bar soap products in the same setting, antiseptic bar soap samples were more frequently contaminated than liquid soap [50].

4.3. Epidemic and Microbiological Methods Used

Three-quarters (74.1% (60/81)) of reported (pseudo-)outbreak investigations involved a clinical–epidemic investigation comprising case definition, time-place curve, retrospective chart review and cross-sectional or case-control studies for associated factors; 1 study added look-back actions and prospective monitoring [94]. Nearly two-thirds (64.2%, 52/81) performed an extensive environmental investigation addressing different fomites. The remaining 35.8% (29/81) uniquely assessed the suspected AS, DI and HH products, partly because they were alerted about potentially contaminated products (e.g., by national health authorities [71]) or because the nature of the outbreak organisms had oriented them to fluids as potential reservoirs [85,108]. In search of the root cause of contamination, 58.0% (47/81) of the investigations did an upstream investigation along the distribution and supply chain (transport containers and sealed, unopened products) and 16.0% (13/81) conducted procedure and practice review through interviews and observations.

Only 40.7% (33/81) of the outbreak investigations reported detailed laboratory methods. Neutralizer or similar techniques (dilution and Kelsey–Maurer method (Supplementary Document S3)) were used in 63.6% (21/33) of the investigations. Culture methods included direct plating (n = 19), filtration (n = 4), the Kelsey–Maurer method (n = 3) and enrichment broths (n = 10); and 6 investigations used combined methods. Semi-quantitative cultures (expressing bacterial counts as Colony Forming Units (CFU/mL) were reported by 15 studies. Bacterial species were mostly identified 71.4% (40/56) (data available for 56/81 investigations) by conventional biochemical methods.

Of the cross-sectional surveys, 18.2% (6/33) described sample selection and 72.7% (24/33) reported laboratory methods. Neutralizers were used in 66.7% (22/33) of the investigations, direct plating and filtration were reported in 39.4% (13/33) and 5 articles reported Kelsey–Maurer methods and enrichment techniques (5 surveys each). Semiquantitative culture results were reported by 54.5% (18/33) of surveys. Identification was mostly done by conventional biochemical methods (79.2% (19/24) of surveys that provided information). Two surveys were purposely sampled during busy hours, i.e., noon or late morning in the midweek, and 1 of them selected products that were in use for longer than 1 week [50,109].

The overall poor descriptions of the study methodologies is in line with observations made for healthcare-associated outbreak investigation in general [88,110]. In part, it can be explained by the fact that most 72.8% (59/81) of the (pseudo-)outbreak investigations were published before the introduction of the Outbreak Reports and Intervention studies Of Nosocomial infection (ORION) guidelines in 2007 [111,112]. Furthermore, some articles focused on the molecular typing of organisms [113,114] or were published as concise communications, abstract or letters with inherently limited word count [49,66,92,93,93,103,115,116].

The use of neutralizers (such as 2% Polysorbate 80 and lecithin) is essential when assessing antiseptics and disinfectants for contamination [117]. If neutralizers are not available, dilution (as done in the Kelsey–Maurer method) is a second-choice alternative. Some environmental bacteria (e.g., members of the *Burkholderia cepacia* complex) grow poorly when inoculated from water systems to high-nutrient media, which can be countered by an enrichment step (in broth tubes) prior to plating on selective media [118].

Filtration is suitable for investigation of specific pathogens (such as in the monitoring of the manufacturing process), hospital water monitoring and testing for growth of expected sterile products. In the context of outbreak research, use of filtration and enrichment broths without complementary semiquantitative cultures may, however, overestimate the contamination: AS, DI and HH products are mostly not marketed as sterile products and may contain low numbers of nonpathogenic micro-organisms [103,119].

By contrast, semiquantitative cultures generate bacterial counts, which are valuable for interpretation. The Kelsey–Maurer method detects growth at a threshold of 250 CFU/mL onwards and reliably provides colony counting up to 10^3 CFU/mL (Supplementary Document S3) [120]. Contaminated products at counts of 10^3 CFU/mL were reported to have a regular visual appearance (color, viscosity) [121]; and soap with contaminated with *Klebsiella pneumoniae* at counts of 10^6 CFU/mL had visual signs of bulging, blown open seals and color change [49].

Methods for testing of relatedness between contaminating and clinical isolates were reported for 59.2% (48/81) of the (pseudo-)outbreak investigations. They evolved over time and comprised antibiotic susceptibility patterns (43.7% (21/48 investigations), serotyping (8.3%, 4/48) and molecular testing (75.0%, 36/48), and some investigations combined different methods. Molecular methods included Pulsed Field Gel Electrophoresis (n = 30), Random Amplified Polymorphic DNA (n = 5), and Amplified Fragment Length Polymorphism (n = 1). Whole genome sequencing was reported in 1 outbreak [38]. Although molecular analysis is of great value for assessing the relatedness between isolates in outbreak settings, multiple clones of single species may cocirculate. *Bacillus* spp. and *Burkholderia cepacia* complex are notably polyclonal [38,104] but also *Serratia marcescens* and *Enterobacter cloacae* in healthcare-associated outbreaks may be polyclonal [122,123]. Phenotypic characteristics (rare organism, particular characteristic) are helpful for early outbreak detection [94] but antibiotic susceptibility patterns should be interpreted with caution, as healthcare-associated bacteria (*Serratia* spp., *Enterobacter* spp. and *Pseudomonas aeruginosa*) quickly develop resistance during antibiotic treatment [124].

4.4. Microorganisms Involved

A total of 105 different bacterial species were retrieved in 81 (pseudo-)outbreak investigations (Table 4). Nonfermentative Gram-negative bacteria accounted for 69.5% (73/105) of the isolates reported in 87.6% (71/81) of the investigations; most frequently *Burkholderia cepacia* complex (in 39.5% (32/81) of the investigations), followed by *Pseudomonas aeruginosa* and *Achromobacter* spp. (12 investigations each). Enterobacterales accounted for 22.8% (24/105) of the isolates reported in 29.6% (24/81) of the investigations, with *Serratia* spp. the most frequent genus (83.3%, 20/24 investigations). Overall, outbreaks and pseudo-outbreaks yielded similar species but most (87.5%, 21/24) Enterobacterales occurred in outbreaks: 8 of these 21 outbreaks were associated with liquid soaps, of which 5 occurred in neonatology wards. Contaminated alcohol-based products were uniquely associated with *Bacillus* spp. and vice versa.

Isolates (n = 97) from cross-sectional surveys comprised 46.4% (45/97) and 22.7% (22/97) nonfermentative Gram-negative bacteria and Enterobacterales, respectively (Table 5). Most notable was the presence of *Klebsiella* spp. in 8 surveys, of which 5 were liquid soap products and 3 were intrinsically contaminated [49,125,126]. Further, the surveys included a substantial (29.9%, 29/97 isolates) proportion of Gram-positive bacteria (including 3 *Staphylococcus aureus*) isolates, mainly found in bar (n = 14) and liquid soap products (n = 9). This proportion however was probably inflated, as 14 *Staphylococcus* nonaureus isolates were obtained only and in low concentrations by either filtration or enrichment broth cultures [50,127].

The high proportion of nonfermentative Gram-negative bacteria is in line with previous observations [8,14,44]. Hospital niches where these bacteria thrive are humid environments such as sinks and their outlets, sewage and plumbing systems. From there they can reach household items or medical equipment and come in contact with patients [18,119,128,129]. *Burkholderia cepacia* complex is a notable agent of healthcare-associated outbreaks and also the most frequent cause of intrinsic contamination of liquid products, including medicines [130,131]. *Achromobacter* spp. are opportunistic bacteria causing healthcare-associated outbreaks mostly in vulnerable patients, such as hematology–oncology, intensive care unit and neonatology [73,132–134]. Nonfermentative Gram-negative bacteria (e.g., *Burkholderia cepacia*, *Pseudomonas aeruginosa*) and some Enterobacterales (*Proteus* spp. and *Providencia* spp.) have natural resistance to antiseptics and disinfectants, among which QUAT, triclosan and CHG are most affected [131,135,136]. In addition, acquired nonsusceptibility (e.g., by upregulation of efflux pumps or adaptation of outer membrane proteins) against these products has been demonstrated [30,135].

Among the Enterobacterales, *Serratia* and *Klebsiella* species were the most frequent and particularly associated with soap products; this may be partly due to their ability to colonize healthcare providers' hands [109,114,137] which in turn can contaminate dispensers and

containers. Over several decades, *Serratia marcescens* has evolved from an innocent commensal to a multidrug-resistant pathogen responsible for healthcare-associated outbreaks, particularly in neonatal wards [138,139]. The rare contamination rate of alcohol-based antiseptics is ascribed to their immediate and broad-spectrum activity and is in line with results of experimental studies [140,141]. *Bacillus* spp. produce spores which can be resistant to alcohol for weeks [103,105,106]. Although *Bacillus* spp. are mostly regarded as contaminants, *Bacillus cereus* is more virulent and can cause invasive skin and soft tissue infections, as was the case in 1 outbreak [103].

Excluding results obtained uniquely by filtration [50,127], 20 cross-sectional surveys listed results of bacterial counts expressed as CFU/mL. Maximal concentrations of bacteria in samples of liquid products (44 products) ranged between 10^2 and 10^8 CFU/mL; in nearly half and a quarter of products (19 and 10 products), counts were $\geq 10^3$ and $\geq 10^5$ CFU/mL, respectively. The highest counts ($\geq 10^6$ CFU/mL) were noted for QUAT products [133,142–144] and liquid soaps [49,145,146]. Bacterial counts in bar soaps reached 38 and 10^6 CFU/mL in 2 studies [50,147].

A total of 24/114 articles provided information about antibiotic susceptibility of 24 isolates. Methods used were disk diffusion (n = 21) and broth dilution (n = 5) but only 2 articles provided enough detail about methods and interpretative criteria [132,148]. Among the bug–drug combinations which provided enough information for comparison with the EUCAST guideline, 9 showed acquired resistance, present among *Serratia* spp. (4 out of 6 isolates), *Achromobacter* spp. (4/4 isolates, 3 of which displayed acquired resistance to 3 categories of antibiotics) and *Pseudomonas aeruginosa* (1/1 isolate). Healthcare-associated Enterobacterales have the potential for quickly acquiring resistance: 1 paper described a soap-associated outbreak of *Serratia marcescens* which evolved from wild-type to multidrug resistance in a 2-month period [122]. *Burkholderia cepacia* complex (n = 4) and *Elizabethkingia meningoseptica* (n = 1) displayed wild-type (intrinsic) resistance patterns which, by themselves, entailed resistance to multiple antibiotic classes [41] and tailored antibiotic treatments [129]. Antibiotic-resistant bacteria are generally equally susceptible to antiseptics or disinfectants compared to their antibiotic-susceptible counterparts [30,57], but reduced susceptibility to CHG has been demonstrated in multidrug resistant *Klebsiella pneumoniae* and *Serratia marcescens* [18,107,149].

Table 4. Bacteria contaminating antiseptics, disinfectants and hand hygiene products as listed in 68 outbreaks and 13 pseudo-outbreaks in healthcare facilities in high-income countries. Numbers in the cells represent bacterial isolates; these numbers outnumber the actual number of articles, since 2 pseudo-outbreaks [82,134] were caused by more than 1 species and in 4 outbreaks [78,94,96,133] the associated product revealed isolates additional to that involved in the outbreak. Abbreviations: CHG = chlorhexidine gluconate, QUAT = quaternary ammonium compounds.

Contaminating Bacteria	Alcohol	CHG	QUAT	CHG–QUAT	Iodophor	Phenol	Liquid Soap [a]	TotalOutbreak/Pseudo-Outbreak
Enterobacterales	**-**	**9**	**7**	**-**	**-**	**-**	**8**	**21/3**
Serratia spp. [b]	-	9	4	-	-	-	8	20/1
Enterobacter cloacae	-	-	2	-	-	-	-	1/1
Pantoea agglomerans	-	-	1	-	-	-	-	0/1
Nonfermentative Gram-negative rods	**1**	**28**	**28**	**4**	**5**	**2**	**5**	**56/17**
Burkholderia cepacia complex [c]	-	14	10	3	3	1	1	24/8
Achromobacter spp. [d]	-	6	6	-	-	-	-	10/2
Pseudomonas aeruginosa	-	1	5	-	2	1	3	11/1
Ralstonia pickettii	-	4	-	-	-	-	-	2/2
Pseudomonas spp.	-	2	1	-	-	-	-	3/0
Pseudomonas fluorescens	1	-	2	-	-	-	-	2/1
Stenotrophomonas maltophilia	-	-	1	1	-	-	-	1/1
Comamonas testosteroni	-	-	1	-	-	-	-	0/1
Elizabethkingia meningoseptica	-	1	-	-	-	-	-	1/0
Pseudomonas putida	-	-	1	-	-	-	-	1/0
Pseudomonas stutzeri	-	-	-	-	-	-	1	1/0
Sphingomonas paucimobilis	-	-	1	-	-	-	-	0/1
Gram-positive rods	**6**	-	-	-	-	-	-	**4/2**
Bacillus cereus	3	-	-	-	-	-	-	2/1
Bacillus spp.	3	-	-	-	-	-	-	2/1
Mycobacterium	-	-	2	-	-	-	-	2/0
Mycobacterium abscessus	-	-	2	-	-	-	-	2/0
Total	**7**	**37**	**37**	**4**	**5**	**2**	**13**	**83/22**

[a] Including one report that did not specify liquid or bar soap. [b] Including *Serratia marcescens* (n = 20) and *Serratia liquefaciens* (n = 1). [c] *Burkholderia cepacia* complex comprises ≥17 related species that require advanced molecular tests for identification [131]. Species names listed in the articles include *Burkholderia cepacia* (n = 26), *Burkholderia cenocepacia* (n = 2), *Burkholderia stabilis* (n = 1), *Pseudomonas kingii* (Pseudomonas EO-1) (n = 2), and *Burkholderia (Pseudomonas) multivorans* (n = 1). [d] Given the difficult phenotypic identification and the changes in classification (*Achromobacter xylosoxidans* has been temporarily classified to the *Alcaligenes* genus) [37], both *Achromobacter* and *Alcaligenes* species were lumped as *Achromobacter* spp. Species' names as listed in the articles include *Achromobacter xylosoxidans* (n = 7), *Alcaligenes faecalis* (n = 2), *Achromobacter denitrificans* (n = 1), *Alcaligenes* spp. (n = 1) and *Pseudomonas-Achromobacteriaceae* (n = 1).

Table 5. Bacteria-contaminating antiseptics, disinfectants, and hand hygiene products in healthcare facilities in high-income countries, for a total of 33 cross-sectional surveys that provided detail about both products and bacteria. Numbers represent the bacterial isolates, which outnumber the actual number of surveys since some surveys detected more than one contaminant. CHG = chlorhexidine gluconate, CNS = coagulase negative staphylococci, QUAT = quaternary ammonium compounds, PCMX = chloroxylenol.

Contaminating Bacteria	CHG Aqueous/Alcohol	QUAT/CHG–QUAT	Iodophor/ Iodine Tincture	Phenol [a]	Liquid Soap Antiseptic/Plain/ No Information	Bar Soap Antiseptic/ Plain	Total
Enterobacterales	**1/0**	**3/0**		**5**	**6/1/1**	**2/3**	**22**
Enterobacter spp.	-	-	-	-	1	-	1
Escherichia coli	-	-	-	2	1	2	5
Klebsiella spp. [b]	-	-	-	1	5	2	8
Serratia spp. [c]	1	2	-	2	1	1	7
Non-lactose-fermenting coliforms	-	1	-	-	-	-	1
Nonfermentative Gram-negative rods	**4/0**	**20/1**	**-**	**9**	**2/1/2**	**5/1**	**45**
Achromobacter spp. [d]	-	5	-	1	-	-	6
Acinetobacter calcoaceticus	-	-	-	-	-	1	1
Aeromonas spp.	-	1	-	-	-	-	1
Burkholderia cepacia complex	1	3	-	-	2	-	6
Flavobacterium spp.	1	-	-	-	-	1	2
Myroides odoratus	-	-	-	-	-	1	1
Pseudomonas aeruginosa	-	4	-	4	3	1	12
Pseudomonas spp. [e]	2	5	-	3	-	2	12
Stenotrophomonas maltophilia	-	1	-	-	-	-	1
Others	-	2	-	1	-	-	3
Gram-positive bacteria [f]	**0/1**	**0/1**	**2/2**	**-**	**9/0/0**	**7/7**	**29**
CNS/Micrococcus spp. [g]	1	1	4	-	4	5	15
Staphylococcus aureus	-	-	-	-	2	2	4
Gram-positive rods [h]	-	-	-	-	3	7	10
Yeast	**-**	**-**	**-**	**-**	**1/0/0**	**-**	**1**
Candida parapsilosis	-	-	-	-	1/0/0	-	1
Total	**5/1**	**23/2**	**2/2**	**14**	**18/2/3**	**14/11**	**97**

[a] Including hexachlorophene (n = 1), PCMX (n = 3) and phenol (n = 9). [b] *Klebsiella pneumoniae* (n = 1), *Klebsiella oxytoca* (n = 1), *Klebsiella* spp. (n = 4) and *Raoultella planticola/ornithinolytica* (n = 2). [c] Including *Serratia marcescens* (n = 6) and *Serratia* spp. (n = 1). [d] Given the difficult phenotypic identification and the changes in classification (*Achromobacter xylosoxidans* has been temporarily classified to the *Alcaligenes* genus) [37], both *Achromobacter* and *Alcaligenes* species were lumped as *Achromobacter* spp. [131]. Species names listed in the articles include *Achromobacter xylosoxidans* (n = 3), *Achromobacter* spp. (n = 2), and *Alcaligenes faecalis* (n = 1). [e] Including *Pseudomonas* spp. (n = 8), *Pseudomonas putida* (n = 2), *Pseudomonas fluorescens* (n = 1) and *Pseudomonas chlororaphis* (n = 1). [f] Nine bacterial isolates (5 CNS, 3 *Micrococcus* spp. and 1 *Staphylococcus aureus*) detected by filtration of 100 mL of product, a maximum colony count of 3 colonies in 100 mL. [g] Including CNS (n = 10) and *Micrococcus* spp. (n = 5). [h] Including *Bacillus* spp. (n = 3), *Corynebacterium* spp. (n = 2), *Cutibacterium acnes* (n = 4) and *Nocardia* spp. (n = 1).

4.5. Factors Associated with Contamination

Apart from the natural resistance of contaminating flora and low product concentrations discussed above, a total of 108 articles listed factors conducive to extrinsic contamination of AS, DI and HH products along product, container, processes, and practices (Figure 3). In several articles, combinations of factors were mentioned.

At the product level, 14.9% (17/114) articles evoked the presence of cork, gauze and cotton, 13 of which involved QUAT products. Cork was used as stopper or stopper liners (published in the early decade) [9,150] and cotton balls were typically soaked as ready to use in AS or DI products (11 articles). In one case, nonsterile cotton pads soaked in ethanol caused *Bacillus* spp. pseudobacteremia [105]. Cork and gauze, but also cellulose, and to a lesser extent microfiber, bind QUAT products and decrease their efficacy [26].

Biofilm formation was demonstrated from 1981 onwards [151] and also recently in reusable containers of disinfectant tissue dispensers [142]. Biofilms are communities of bacteria attached to a surface while producing extracellular polymeric substances, which protect them from desiccation but also from antiseptics and disinfectants [152]. Notable biofilm-producing bacteria are *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Achromobacter* spp. and *Serratia marcescens* [18,142,153].

Shortcomings in container design and functioning included dead spaces behind plastic liners in screw caps [154], loose-fitting covers [155], malfunctioning of a spray disinfectant device [156] and contamination of a centralized tubing system supplying a phenol disinfectant to patient rooms [157]. In addition, several papers mentioned that the replacement bottles inserted in refillable soap dispensers were at risk for recontamination by the (re-used) pump system [77,94,122,145,146]. Other factors were large container volumes (resulting in long in-use periods) [9,85], absence of production and expiry dates, and long shelf-life periods [85,121,148]. Prolonged (too long) use of products may cause degradation of preservatives [158,159] and facilitate biofilm production [142].

Errors in reprocessing of containers (18.4%, 21/114 articles) included no or infrequent reprocessing (absent or not detailed procedure, n = 10), inappropriate reprocessing (household-grade washing, no sterilization, omitting the drying step and rinsing with tap water (n = 10)). One paper mentioned bacterial growth in the bottle-washing machine [160].

Another frequent factor (13.1%, 15/114 articles) was the water used for dilution; contamination resulted from tap water [78,96,134,161], deionizing equipment, storage tanks or nonsterile instruments [85,162–164] and reverse osmosis equipment [116]. Ion-exchange resins in deionized water production bind and remove chlorine products from the water and may be a source of contamination for in-house diluted products [79,163–165]; bacterial filters are not always effective for sterilizing hospital tap water [87,132,163]. For preparation of products for hand-hygiene, WHO recommends using distilled or freshly boiled tap water [7].

Healthcare providers' practices fueling contamination included prolonged use of soap products (n = 6 articles) and topping up of the containers (n = 4) [12,146,166,167]. One paper reported leaving personal soap containers (i.e., carried and used by individual healthcare providers) standing inverted on sink areas to drain remnants of soap [168] and another observed failures in maintenance of a disinfectant-diluting apparatus [134]. Deviations from existing procedures comprised the use of water-based instead of alcohol-based CHG [78,165,169], use of nonprescribed products for skin asepsis or disinfection of blood culture bottle septa [67,82,134,170] and the lasck of a timely reprocessing of containers [142]. Human factors—inappropriate practices and deviation from procedures—were linked with ignorance, unclear instructions and labeling of products, inadequate training and unfamiliarity with products [67,89,102,134,170].

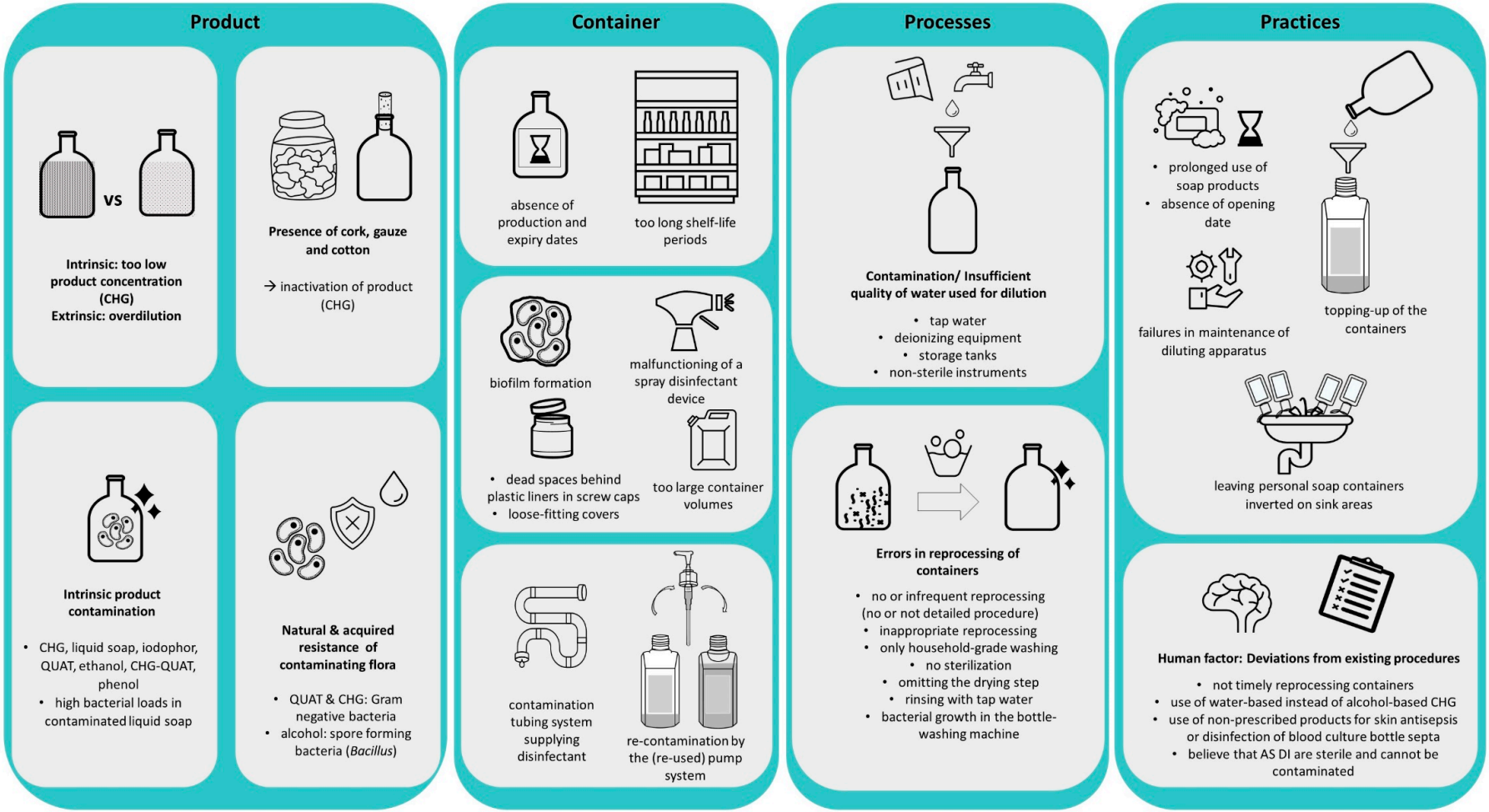

Figure 3. Risk factors associated with bacterial contamination as retrieved by the literature analysis. AS = Antiseptic, CHG = chlorhexidine gluconate, QUAT = quaternary ammonium compound, DI = Disinfectant.

Inappropriate practices identified in the 1950s–1970s, such as reprocessing and storage of (semi)-critical items in low-level disinfectants (see Section 4.6), have been phased out. However, and despite numerous alerts, other inappropriate practices have persisted until the recent past, such as the use of cotton balls and rayon cloths soaked in CHG [108,170], the topping up of soap containers [146], the use of contaminated hospital water [87,116,132] and inappropriate reprocessing of containers with QUAT disinfectant wipes [142,171]. Two articles hypothesized that end-users may minimalize or disregard the risk of contamination as they perceive that AS, DI and HH products eradicate all bacteria [172–174].

Of the 46.5% (53/114) of the investigations that assessed unopened sealed vials, half (47.2%, 25/53) revealed intrinsic product contamination: products involved were CHG (n = 7), liquid soap (n = 6), iodophor (n = 5), QUAT (n = 3), ethanol (n = 2), CHG–QUAT (n = 1) and phenol (n = 1). The panel of bacteria involved (n = 32) was similar to the panel found in (pseudo-)outbreaks: nearly two-thirds (65.6%, 21/32) were nonfermentative Gram-negative bacteria (most frequently *Burkholderia cepacia* complex (n = 13) and *Pseudomonas* spp. (n = 7, including 4 isolates of *Pseudomonas aeruginosa*). Enterobacterales accounted for 25.0% (8/32) of the isolates, including *Serratia marcescens* (n = 4) and *Klebsiella* spp. (n = 3); in the case of alcohol-based products, the associated bacteria were *Bacillus* spp.

Of note are the high bacterial loads associated with intrinsically contaminated liquid soap (i.e., $\geq 10^4$ CFU/mL) of *Klebsiella* spp. and *Pseudomonas aeruginosa* in cross-sectional surveys [49,126,175]. In combination with the fast and large-scale distribution of intrinsically contaminated products, these high counts of virulent pathogens stressed the need for active surveillance and communication [38,72,170]. Root-cause analysis of intrinsically contaminated products revealed similar factors as with extrinsic contaminations such as biofilms in piping systems and contaminated resins, machinery and storage tanks [106,125,176]. Based on data of intrinsic medicine product failures, factors that can cause higher than acceptable levels of microbiological content include (in decreasing frequency): water, pharmaceutical ingredients, processing equipment, personnel and manufacturing environment [177]. The nationwide *Serratia marcescens* CHG contamination in Spain was ascribed to contamination of raw material, although the details were not reported [72].

4.6. Attribution and Transmission

Contaminated fomites may be the factual source of transmission or may be just a "bystander", i.e., one of the several items contaminated without representing a major reservoir or causing transmission [117]. In 13.2% (9/68) of the outbreak reports, no hypothesis of transmission was formulated, and an additional report expressed doubt about the role of the contaminated HH products [178]. Among the remaining outbreaks, 57 described potential transmission routes. Skin and mucosa-asepsis accounted for over half (52.6% (30/57)) of outbreak transmission routes: they included asepsis during catheter (intravascular, urinary and dialysis) insertion, preoperative asepsis, asepsis before intrathecal injection and topical care (wound, tracheostomy, dental care, bladder irrigation).

In 36.8% (21/57) of the outbreaks, contact with semicritical items and noncritical items was demonstrated, mainly by contaminated disinfectants (n = 12) but also by antiseptics used to wipe vials or to store the items [161,179,180]. Semicritical items comprised surgical instruments (n = 3), cystoscopes and bronchoscopes (n = 1) [13] and intravascular, cardiac and urinary catheters (n = 6) [92,93,121,161,180]. Noncritical items included thermometers, bed pans and urine bottles used in high-risk areas [91,148]. Further, contaminated disinfectants in spray bottles reached medical equipment and intravenously or intrathecally administered medication (n = 4) [75,132,156,166] and in four articles, contaminated disinfectants had affected multidose vials [155,167,181,182].

In the six remaining outbreaks (all liquid soap products) [77,94,114,122,168,183], hand-borne transmission (i.e., transmission via hands of healthcare providers) was mentioned as the probable route. Contamination of the soap container or dispenser was assumed to be retrograde, by touching the spout during hand washing or by topping up [77,183,184]. All but one pseudo-outbreak investigation described the probable transmission route, i.e., skin or mucous asepsis (n = 7) and wiping the blood culture bottle stopper before inoculating the blood (n = 7).

Although not designed for this purpose, seven cross-sectional surveys assessed potentially associated transmission. Three articles provided arguments in favor of transmission: relatedness between products' and patients' isolates [171,185] and a decreasing incidence of infections by the product's isolate after corrective actions [9]. Four other articles did not show potential transmission; they failed to demonstrate presence of relatedness between product and clinical isolates [49,160,175] or changes of incidence of infections by the product's isolate [49].

In the case of wound care, insertion of catheters and contact with semicritical items, transmission routes were mostly plausible. In other cases, insights into potential transmission were mainly obtained by epidemic analysis, interviews with staff and observations of nursing and cleaning practices (n = 10 articles). Culture-based evidence of transmission (e.g., from catheter exit sites [38,102,103,186] and multidose vials [167,187]) were rare.

Moreover, culture-based investigations were hampered by the fact that—at the time of intended sampling—"pieces of the puzzle" were lacking, such as soap products of all index patients, enough representative clinical isolates (used for genetic comparison), multidose vials (potentially implicated in transmission) and tools used to prepare antiseptics [38,102,113,155,186]. In one outbreak, the physician's office was relocated and key fomites were thrown away, while in another outbreak, the ward was closed for three weeks because of legal issues [94,155].

Apart from phenotypical and molecular typing (see above), arguments supporting attribution included epidemic evidence such as temporal-spatial association [77,78], case-control studies [168,183], ruling out of any other potential reservoirs [79,94,108] and observing a halt in cases after corrective actions, including removal of the putative reservoir [37,78,113,170,186,188].

4.7. Interventions

Seventy-seven (67.5%) out of 114 articles, including 79.0% (64/81) (pseudo-)outbreaks, reported interventions. As for outbreak reports in general, interventions were difficult to assess for effectiveness, given the inherent retrospective observational design of the investigations [189] and the application of multiple interventions (n = 27 articles). Furthermore, in several papers, interventions were only briefly and not clearly described and even the discontinuation of the contaminated product(s) was not always mentioned. Likewise, the end date of the outbreak after the start of intervention was mostly lacking.

In addition to removing the contaminated product from the ward(s), 11 articles mentioned product recall by the manufacturer. Some articles described a change of product: water-based QUAT or CHG used for skin asepsis was replaced by alcohol-based CHG (n = 6) or iodine (n = 1); in three other cases [94,122,183], liquid soap was replaced by alcohol-based handrub.

Modification in production, preparation or dilution was reported by nearly a third of the articles (33.8%, 24/77); examples were cleaning, sterilization of equipment (n = 6), review and adaptations of procedures (n = 2), reduction of shelf-life or permissible period after opening of products (n = 5), exclusion of organic material (cork, gauze, n = 2), improved water quality (n = 4), adding alcohol-based preservatives (n = 4), and use of commercially available ready-to-use products instead of in-house diluted products (n = 1). Permissible period after opening for in-house-prepared water-based QUAT and CHG products were variable and ranged from 1 day to 1 month [9,190].

Interventions on the containers were mentioned in 15 (19.4%) articles, including reprocessing (n = 8, mostly autoclaving), use of smaller volume containers (n = 4), changes in design (n = 4, including hands-free command, sealed airless system refills and pump replacement, anti-reflux valve), changes in labeling (n = 1, adding expiry date) and discontinuation of a spray bottle (n = 1). In one pseudo-outbreak investigation, a clear distinction (color and labeling) between water- and alcohol-based CHG products was introduced [170]; another article implemented cleaning of the external surface of soap containers [146].

Patient care procedures were adapted in another 16 articles (20.8%); they included reinforcing procedures about use of AS, DI and HH products, intravenous sampling, intravenous infusions, and dialysis care as well as selective use of urinary tract catheters. Other examples were rational use of products and equipment (n = 6) such as discontinuation of a vaginal douching device, implemental policy of disinfectant use, removal of remaining soap after patient discharge, and a risk-based use of soap products. Training and education of staff in the handling and use of products as well as strengthening general IPC measures were explicitly mentioned by six and eight articles, respectively. Among the latter, 2 articles mentioned cohorting of colonized and infected patients.

In addition to interventions, 36 articles expressed recommendations for prevention, most of which were overlapping with the above-described interventions. Of note were calls for awareness and vigilance of patients' isolates that could potentially be of environmental origin (n = 5). Calls were also made to strengthen regulation and improve manufacturing (n = 7) and for the rational use of products ((n = 3), e.g., abolish use of QUAT for reprocessing endoscopes, wiping medication vials and skin asepsis). Twelve articles reported follow-up activities, mostly by passive surveillance (n = 10).

4.8. Outstanding Issues, Research Questions and Recommendations

Table 6 lists the outstanding knowledge gaps and research questions, some of which have been discussed in the sections above; others are presented below.

As for healthcare-associated outbreaks in general [191], the retrieved articles probably presented only the tip of the iceberg [192]. In addition to the challenges of outbreak suspicion and detection, time constraints and fear of medicolegal consequences may cause under-reporting [192]. (Supra)national surveillance networks such as the European Healthcare-associated Infections Surveillance Network (HAI-Net) [193] focus on antimicrobial use and point prevalence surveys of healthcare-associated infections are not designed to detect outbreaks [194]. Dedicated initiatives such as the Worldwide Database of Nosocomial Infections [88], health authorities and professional associations may increase awareness and stimulate reporting and debate. At the healthcare level, laboratory information and surveillance systems (such as the free WHONET software [195] can be programmed for automated detection of healthcare-associated outbreaks. Further, there is a need for application of harmonized terminology in product names and categories as well as for outbreaks versus pseudo-outbreaks.

Although there is no doubt that water-based QUAT, CHG and liquid soap products were most frequently and most severely affected by bacterial contamination, the present review does not provide data about the comparative vulnerability of other AS, DI and HH products. This is the case, for instance, for antiseptic versus plain soap, a question which is listed by WHO as an outstanding issue in the scope of hand hygiene [7]. Experimental studies could be instrumental here. Further, given the difficulty of manufacturing some products such as CHG [49,196], simple tools for verification of product concentrations at the point of use would be welcome.

Apart from adherence to the ORION guidelines, there is also need for guidance and interpretative criteria for environmental investigation [4]. As an example, Craven et al. demonstrated that sampling the surface of the liquid content in a container revealed *Burkholderia cepacia* (which is strictly aerobic) whereas culture results of the lower two-thirds of the bottle were unsuccessful [67]. As to microbiology methods and reporting, the MICRO criteria (Microbiology Investigation Criteria for Reporting Objectively guidelines [197]) provide a valuable guidance for methods and information. To optimize analysis and interpretation, semiquantitative testing should be promoted and permissible standards for colony counts should be established [4]. Furthermore, accurate and accelerated detection and identification methods for the environmental nonfermentative Gram-negative bacteria are welcome and could be provided by dedicated databases for MALDI–TOF MS equipment [198].

Expert opinion has called on microbiological studies to extend towards molecular typing of isolates (e.g., to identify the occurrence of particular clones) and to explore, for instance, the particular associations of *Serratia* and *Klebsiella* with contaminated liquid soaps. As *Burkholderia cepacia* complex is also one of the main causes of contamination in pharmaceutical products, experts have proposed to add *Burkholderia cepacia* complex to the core list of so-called objectionable micro-organisms, i.e., bacteria that must be contained during the manufacturing process and for which absence should be demonstrated before product market release [118,198].

Mitigation of extrinsic contamination has included review and improvement of containers and dispensers [162,199], including location and ergonomics [22]. In line with the low-volume containers mentioned in several articles, regulatory authorities and IPC professional associations endorsed the use of unit-dose containers; for multi-dose containers, they recommend defining the period after opening [200,201]. Also listed as an outstanding issue for hand hygiene by the WHO [7] is the grade and quality of water at the point of use. Likewise, feasible techniques to prevent and control biofilm formation are required. Behavioral studies and interventions should clarify and correct healthcare providers' concepts and perceptions (e.g., the assumption that antiseptics are sterile [104,200] as well as understand the factors behind inappropriate practices and deviation of procedures.

As to the mitigation of intrinsic contamination, scientific debate 10 years ago [192,202] concluded that the manufacturing of sterile antiseptics was—in view of problems of product integrity and manufacturing capacity—a bridge too far, except for sterile alcohol pads which were recommended for procedures requiring strict sterility [203]. Instead, focus was put on Good Manufacturing Practices and labeling of AS products as sterile versus nonsterile [204,205]. The U.S. FDA recently published a comprehensive guidance (at the time of writing in draft version) for production of nonsterile medicines, comprising a dedicated chapter for antiseptics [206]. Methods and acceptance criteria for microbiological testing during manufacturing are described in the harmonized chapters of the European, Japanese and U.S. Pharmacopoeia [207]; the U.S. Pharmacopoeia recently (2019) added a compendial test method for *Burkholderia cepacia* complex [208].

Meanwhile, microbiological monitoring of the production and the in-use phase of alcohol-based antiseptics and handrubs has confirmed the absence of pathogens [141,209] and sterile antiseptics are entering the market [210]; an expert call has been made to define a risk-based approach for use of sterile antiseptic products [119]. Given the widespread and intensive use of antiseptics (e.g., CHG bathing of patients), the risk of acquiring resistance at sublethal product concentrations and the potential of combined antiseptic–antibiotic resistance, antiseptic stewardship should be considered to optimize product use [107,119]. Likewise, along the evolutions of sterile products and single-use packages, affordability and cost-efficiency need to be considered [200].

Improved understanding of the cycle of transmission in healthcare outbreaks allows guiding species-specific IPC measures [189]. Outstanding issues are the factors (product, bacteria, technique of handwashing) conducive to the colonization of the healthcare providers' hands [183,211,212], the handborne contamination of dispensers and containers [77,183,184] and the role of the container as a high-touch surface [77,146]. A pending question is the usefulness of monitoring in-use antiseptics for bacterial contamination as recommended by experts [90,173]: although relevant as part of interventions and follow-up, it is so far not recommended as routine practice [117].

At the supranational level, harmonization and simplification of regulatory frameworks is desirable. Worldwide AS, DI and HH products fall under different legal frameworks; depending on their intended use, antiseptics may be classified as biocides, medicinal products or cosmetics in the European Union [99,213,214], whereas in the U.S., disinfectants are regulated either by the Food and Drug Administration (when used for (semi-)critical devices) or by the Environmental Protection Agency (when used on noncritical surfaces) [215]. Among the consequences are that medicinal products and cosmetics, but not biocides, are subject to Good Manufacturing Practice [213]. In addition, some evidence-based applications of antiseptics, such as disinfection of central line ports, are currently off label and should be adopted as intended use [200,216]. Furthermore, vigilance and early alerts should be well coordinated at the (supra)national level [126,170]. In addition to the multicenter outbreaks associated with povidone iodine and CHG mentioned above, other product recalls (alcohol- and povidone iodine-impregnated wipes) illustrated the multistate and multicountry extent of intrinsic contamination [203,217].

Table 6. Outstanding issues, research questions and recommendations about the bacterial contamination of antiseptics, disinfectants, and hand hygiene products in healthcare facilities. AS DI and HH = antiseptics, disinfectants and hand hygiene, CHG = chlorhexidine gluconate, IPC = Infection Prevention and Control, ORION = Outbreak Reports and Intervention studies Of Nosocomial infection [218].

Section	Outstanding Issues, Research Questions and Recommendations
Setting and overview of studies	What is the risk and impact of contamination of AS, DI and HH products? How to monitor frequency and characteristics? ○ Presently, outbreaks are overlooked, underreported, and with bias in reports. ○ Need for an early alert and suspicion of outbreak: laboratory surveillance system (e.g., WHONET) [195] ○ Need for barrier-free reporting (e.g., Worldwide Database of Nosocomial Outbreaks) [59,88,219] Need for consequent use of harmonized definitions and terminology ○ Antiseptics, disinfectants, and products for hand hygiene ○ Pseudo-outbreaks versus outbreaks
Products involved and assessed	Which products are most vulnerable to contamination? What is the actual risk for contamination of AS, DI and HH products during use? ○ Present articles had no sound denominator ○ Experimental studies assessing vulnerability of AS, DI and HH products should complement field reports Need for measurement systems of active product concentrations ○ For in-house dilutions and entrance/reception control ○ Given difficult manufacturing, for instance, of CHG [107,196]
Epidemiological and microbiological methods used	Need to adhere to ORION guidelines [112,218] Need for additional guidance and criteria: environmental investigation ○ Sample selection and representativeness (cross-sectional studies) ○ Best moment of the day or week, record in-use time of sample [50,109] ○ Express product potency as concentration (e.g., 0.5%), not as dilution (e.g., 1/750) Need for additional guidance and harmonization: microbiological investigation [4] ○ MICRO guidelines [197] ○ Sampling details (liquid content, dispenser) [67] ○ Use of neutralizer [117] ○ Perform semiquantitative enumeration, use filtration and enrichment only for sterility control or to detect specific bacteria ○ Harmonization of culture media and incubation ○ Stream-up analysis to assess distribution chain and intrinsic contamination ○ Report results of culture negative items

Table 6. *Cont.*

Section	Outstanding Issues, Research Questions and Recommendations
Microorganisms, antimicrobial resistance and typing	Need for accelerated/feasible phenotypic identification/typing of environmental bacteria [198] ○ Some bacteria can only be identified by molecular methods (*Burkholderia cepacia* complex, *Achromobacter* spp., *Alcaligenes* spp.) ○ Assess and explore molecular and antibiotic resistance typing of isolates [198] ○ Regulation ○ Add Burkholderia *cepacia* complex to the core list of objectionable organisms [118] Why are *Serratia/Klebsiella* associated with contaminated liquid soap? ○ Confirm hypothesis of retrograde contamination of containers during handwashing [183] ○ Transmission and carrier/colonization studies [77] Need to monitor development and spread of antimicrobial resistance ○ Environmental bacteria are mostly not part of cumulative data used for monitoring [220] Consider antiseptic stewardship, e.g., for CHG [107,119] ○ Widespread use can stimulate acquired resistance ○ Appropriate and restrictive use (indication, dose and duration)
Factors associated with contamination	Which type of container provides the best mitigation of contamination? [145,199] ○ Prevent transfer of bacteria from container to user ○ Protect container content from contamination by users' hands [77,183,184] ○ Hand hygiene products: ergonomics and integration in handwash station [22] Why do inappropriate practices with AS, DI and HH products persist? ○ Perception by end users: AS, DI and HH products are sterile [104,200] ○ Perception by end users: AS, DI and HH products eradicate (all) bacteria [173,174,221] ○ Understand reasons behind inappropriate practices and deviation from procedures ○ Need for behavioral studies to identify, understand, and correct these perceptions How can biofilm be prevented and controlled? Which quality/grade is needed for water and how can it be assured? [7] What is the role of single-dose containers? ○ Provided affordability, unit-dose packages are promoted [200,213] Which is the role for sterile products? ○ Technical and manufacturing challenges to make sterile antiseptics [203] ○ Regulation: labeling antiseptics as sterile or nonsterile [201], improve pathogen-free production [204,205] Which is the period after opening (in-use product stability time)? [200,201,213]

Table 6. *Cont.*

Section	Outstanding Issues, Research Questions and Recommendations
Attribution and transmission	How to optimize (pseudo-)outbreak investigations ○ Have a system of temporary storage of relevant clinical isolates [220] ○ Timeliness of investigation (authorizations, laboratory consumables ready) ○ Consider general IPC status, recent changes (instruments, products) and practices ○ Consider and test scenarios of transmission Understand better the cycle of transmission ○ Retrograde contamination of containers and dispensers by hand contact (see above) ○ Critical pathways of reservoir and transmission (high touch surface) e.g., reuse of dispensing or spray device, pump, external container surface [146] ○ Location and ergonomics of containers, correct use [22] ○ Transmission efficacy of bacteria from contaminated soap to hands (see above) ○ Experimental transmission studies [77,212]
Interventions	Are active surveillance cultures of AS, DI and HH products useful? ○ Monitor in-use antiseptics for bacterial contamination [90,173] or entrance control of procured products [222] ○ Not recommended by leading guidelines as routine activity [57] Vigilance and early alerts at the healthcare level ○ Most contaminating bacteria are "endemic" [189] and not listed as multidrug-resistant priority pathogens for surveillance Rational use and Regulation: ○ Harmonization of regulation—AS DI and HH products fall under different regulatory frameworks In some frameworks, evidence-based use of antiseptics for some indications, such as intravenous catheter care, is currently off label [201] ○ Antiseptic stewardship (in line with antibiotic stewardship); most appropriate use of antiseptics [107,119] ○ At the healthcare level: integrate AS DI and HH products in the quality management system Vigilance and early alerts at the (supra-)national level in particular for intrinsic contamination ○ Example: European Union Safety Gate [126,170,223]. Human factors: ○ Training of all cadres, including trainees, housekeeping staff, and contracting staff ○ Understanding and anticipating users' perceptions, beliefs, and inappropriate practices (see above)

4.9. Limitations and Strengths, Generalizability

In addition to the above discussed limitations of the articles retrieved, the present review process faced several challenges. The long time span of the search may have caused difficulties, as illustrated by the fact that nearly one-third of the articles were retrieved by hand searching. Likewise, most literature predated molecular taxonomy and it was difficult to trace the taxonomic history of certain species names (e.g., *Pseudomonas kingii*). Organisms identified to the genus level (*Pseudomonas* spp.) 60 years ago [161] could not be (re)named according to current nomenclature; however, based on the typical antimicrobial resistance pattern (resistance to colistin and aminoglycosides [41]), some might have been members of the *Burkholderia cepacia* complex. Furthermore, the broad scope of the articles and objectives did not allow the documentation of systematic bias and the retrospective nature of the (pseudo-)outbreak articles did not allow an assessment of evidence of the recommendations.

As to the strengths, unlike previous reviews [8,14], the present review also addressed products used for hand hygiene, including liquid soaps. Furthermore, in addition to outbreaks, cross-sectional surveys and pseudo-outbreaks were included, allowing a wider spectrum of product-bacteria combinations in contamination to be assessed. Products, bacteria and risk factors were similar along the three groups of articles; pseudo-outbreaks were further overlapping with outbreaks in some articles, thereby confirming that they constitute serious IPC nonconformities [37,146]. The review further explored extrinsic versus intrinsic contamination and its long period (1951–2022) allowed depicting evaluations over time.

The findings of this review are generalizable to AS, DI and HH products in other settings (community, veterinary sector [158,224,225]) and other applications (e.g., mouthwash [23], but also to related products used in healthcare facilities such as hospital water [21,22,226], cleaning agents [2,227,228] and cosmetic products (hand lotion, body milk) [24,229,230]. Moreover, mutual sharing experiences and lessons with these settings and users add to understanding and risk mitigation [4].

Finally, the risk of contamination should also be considered in light of the expected growing market of antiseptics and disinfectants. The COVID-19 pandemic has increased awareness of IPC [231–233] and, despite disturbances in the supply of raw materials, positively impacted the antiseptics and disinfectants market. In 2020, hand sanitizers sales increased 1,800% year-on-year in Italy and global annual market growth rates were expected to rise from 5.06% to 45.71% [234]. The quickly rising demand eased regulations and increased the focus on new product design and the rapid growth of medicinal manufacturing sectors [235].

5. Conclusions

AS, DI and HH products used in healthcare settings are not safeguarded from bacterial contamination. Nonfermentative Gram-negative bacteria as well as Enterobacterales (*Serratia*, *Klebsiella*) may be introduced into the products during use or even during manufacturing. In favorable conditions, they can survive and grow to high counts and be transmitted to patients by direct contact with medical instruments or via the hands of healthcare providers. Outbreaks associated with contaminated AS, DI and HH products were probably underreported but affected vulnerable patients and caused a serious burden, most frequently through bloodstream infections with considerable case fatalities. Contaminated products were also reported from (pseudo-)outbreaks and cross-sectional surveys during the past 70 years, along with product-, procedure- and practice-related risk factors. Most affected were water-based CHG and QUAT products, although no product was exempt from contamination. Outstanding issues include figure mitigation and early alerts of intrinsic contamination, antiseptic stewardship, defining the place of unit doses and sterile products, and the study of healthcare providers' perceptions and practices.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/hygiene3020012/s1. Table S1: Search strategy of PubMed database; Document S1: List of original articles included in the scoping review of bacterial contamination of antiseptics, disinfectants and products used for hand hygiene; Document S2: Data extraction; Document S3: In-use test of Kelsey–Maurer procedure.

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Abbreviations

APIC	Association for Professionals in Infection Control and Epidemiology
AS	Antiseptics
CDC	Center for Diseases Control
CFU/mL	Colony-Forming Unit per milliliter
CHG	Chlorhexidine gluconate
DI	Disinfectants
EML	Model List of Essential Medicines
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
HH	Hand hygiene
HIC	High-income countries
IPC	Infection Prevention and Control
LMIC	Low- and middle-income countries
ORION	Outbreak Reports and Intervention studies Of Nosocomial infection
PCMX	Chloroxylenol
QUAT	Quaternary ammonium compounds

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