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Review

Presumed aseptic orthopaedic implant revisions: unmasking hidden infections and shaping future directions

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SUMMARY

Unexpected positive cultures (UPCs) during revision of orthopaedic implants in presumed aseptic revision surgeries represent a significant clinical challenge; indeed, it is very difficult to state whether a positive culture indicates a true infection or merely sample contamination. In hip, knee, shoulder, elbow and spinal procedures, the incidence of UPCs remains clinically relevant, ranging from approximately 7% in elbow revisions to approximately 28% in spinal revisions. The organisms most commonly isolated — coagulase-negative staphylococci (23–52%) and *Cutibacterium acnes* (24–65%) — are classic low-virulence pathogens with high contamination potential, reinforcing the uncertainty that accompanies their detection. Although published outcomes vary, most studies suggest that a single UPC rarely compromises implant survivorship, supporting the interpretation that many isolated findings represent contamination rather than infection. In contrast, multiple cultures positive for the same organism indicate occult infection more strongly, as highlighted by the International Consensus Meeting 2023 guidelines, which associate concordant multi-culture positivity with a higher risk of re-revision or failure. Consequently, the emerging clinical consensus is that single low-virulence UPCs can often be observed, whereas multiple concordant UPCs warrant management as true infection, guiding decisions regarding antimicrobial therapy and postoperative surveillance. Given the persistent variability in published management strategies, further study is needed to standardize responses to UPCs. Finally, rapid, cost-effective intra-operative diagnostics may ultimately improve real-time detection of infection, and reduce uncertainty in revision of orthopaedic implants.

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Introduction

The revision of orthopaedic implants, including total joint arthroplasties [1] and internal fixation devices, represents a complex and demanding surgical challenge. These procedures are typically undertaken due to infection, mechanical failure [2], aseptic loosening [3], instability [4], periprosthetic fractures [5], etc., and the possible implant failure can have heavy consequences for patient quality of life [6]. For these reasons, accurate pre-operative diagnosis is essential to optimize treatment strategies and improve long-term prognosis, and, in the case of implant failure, the presence of infection must be excluded. While mechanical instability and poor vascularization are well-recognized causes, undetected or occult infections (i.e. clinically silent infections that are not apparent at the time of evaluation) may also contribute significantly to delayed or failed bone healing. To improve diagnostic accuracy in implant-related infections, international consensus groups such as the 2023 International Consensus Meeting and the European Bone and Joint Infection Society have established standardized diagnostic criteria to differentiate between septic and aseptic failure, combining clinical, laboratory, microbiological and histological findings. Diagnosing infection remains challenging, particularly with low-virulence organisms and mature biofilms that may cause few or no symptoms. As a result, some prosthetic joint failures considered to be non-infectious [presumed aseptic revisions (PAR)] subsequently reveal infection when intra-operative cultures turn positive. These unexpected positive cultures (UPCs) create a major clinical dilemma, as there are currently no standardized guidelines for their management [7]. It is important to distinguish between true occult infections and UPCs: the former are clinically silent infections that are present in the patient, and the latter are laboratory findings on cultured samples that may indicate an occult infection or contamination without clear clinical correlation. Given this background, this review addresses the clinical and prognostic implications of UPCs in PAR. By synthesizing information from nearly 80 articles on hip, knee, shoulder and elbow revision arthroplasties, as well as spinal surgery, it aims to examine the current understanding of this issue comprehensively. Key areas of focus include the incidence of UPCs in PAR (Fig. S2 in online supplementary material), the diagnostic limitations that contribute to missed infections, and the analysis of the main isolated microorganisms. Furthermore, it will explore the currently adopted strategies to manage these complex cases, and analyse the clinical outcomes observed in affected patients. Finally, besides the current methods aimed at detecting infections, such as culture, sonication, polymerase chain reaction (PCR), nuclear medicine techniques, etc. (see online supplementary material), emerging diagnostic technologies and future directions will be discussed, with the goal of revolutionizing the low-grade infection detection tools and improving the overall success rates of revision procedures in orthopaedic surgery.

Methods

Study design, search strategy and article selection

This narrative review aims to summarize the current evidence and outcomes related to PAR of orthopaedic implants involving the knee, hip, shoulder, elbow and spine. The primary objective is to highlight the challenges and limitations associated with detecting occult low-grade infections during revision surgery. Furthermore, the review explores emerging technologies aimed at enabling faster and more reliable detection of UPCs, offering insights into future perspectives in this evolving field. Relevant articles were identified through a comprehensive search of PubMed and Scopus literature databases using keywords such as 'presumed aseptic revision', 'unexpected positive culture' and 'undiagnosed/hidden periprosthetic infection'. Both original research studies and reviews published in the period from 2019 to 2025 were included in this review (in addition, Kim *et al.* [28] was included because it covers a very broad time window from 1950 to 2013, and Wee *et al.* [31] was included due to the scarcity of articles related to the elbow region). They were selected on the basis of relevance and consistency with the topic treated within this review (Table I), being careful not to include original articles that had been covered in the systematic reviews considered. Grey literature, conference abstracts and non-international documents were excluded to ensure the inclusion of studies with consistent methodological rigor and reliable peer-review standards. The studies were selected so that they would report the incidence of the unexpected positive cultures, related diagnostic challenges, intra-operative findings, microbiological assessments, and clinical outcomes of orthopaedic revisions initially considered to be aseptic. Data were extracted and synthesized qualitatively and quantitatively to provide a general overview of the problem, possible controversies, and gaps in the literature. Moreover, given the narrative nature of this review, its aim was to highlight, discuss and compare the findings reported in the literature, rather than to present original results.

UPC detection methodologies

Management of UPCs in PAR (as depicted in Figure 1) consists of two main approaches: preventive and diagnostic. The preventive approach aims to analyse the intra-operative samples in advance in order to minimize the probability of future UPCs, while the diagnostic approach aims to detect the possible presence of postoperative UPCs. PCR is commonly used as a preventive test, which identifies DNA and RNA from pathogens for which sensitivity and specificity depend mainly upon the sample type and bacterial strain (Table II). The review by Qu *et al.* [8] reported pooled sensitivity and specificity of 86% and 91%, respectively, based on prosthetic fluid, biopsy samples and synovial fluid. Li *et al.* [9] reported sensitivity and specificity of 70% and 92% (same specificity as Qu *et al.* [8]) using synovial fluid alone (see Fig. S1, online supplementary material). Given the high sensitivity and the large number of process steps, possible contamination and resultant false-positive findings are common concerns. This is not the only limitation: PCR must be performed in a specialized laboratory by highly trained personnel, and the overall procedure requires a considerable amount of time before results can be obtained. Moreover, three-phase bone scintigraphy with ^{99m}Tc-labelled tracers (nuclear medicine imaging) is a further preventive method for UPCs (see online supplementary material), which reliably assesses the presence of pathogens through a scan result. Nevertheless, despite its high sensitivity, this technique

Table I
Reviews and articles involved, sorted by area of body

	Article	Article type	No. of articles included[a]	Year of publication	Treatment time window[b]	No. of patients included[c]
Hip and knee	Schwarze *et al.* [16]	Systematic review	7	2023	1988–2022	5821
	Simon *et al.* [21]	Systematic review	\	2024	2011–2020	1430
	Kloos *et al.* [19]	Systematic review	9	2021	2000–2021	3325
	Kayani *et al.* [26]	Original article	\	2024	2011–2018	297
	Ludwig *et al.* [23]	Original article	\	2025	2021–2022	60
	Vargas-Revéron *et al.* [22]	Original article	\	2025	2003–2017	554
	Lin *et al.* [17]	Original article	\	2025	2012–2017	450
	Loppini *et al.* [24]	Original article	\	2021	2016–2020	295
Shoulder and elbow	Hodakowski *et al.* [27]	Systematic review	22	2022	2000–2021	2373
	Kim *et al.* [28]	Systematic review	6	2014	1974–2011	1402
	Akgun *et al.* [29]	Original article	\	2020	2013–2018	62
	De Crescenzo *et al.* [14]	Original article	\	2024	//	80
	Eyre-Brook *et al.* [30]	Original article	\	2021	2008–2018	123
	Wee *et al.* [31]	Original article	\	2013	2000–2007	230
Spine	Aldahamsheh *et al.* [32]	Systematic review	12	2023	2015–2022	1108
	Mirghaderi *et al.* [33]	Systematic review	15	2024	2016–2022	1057
	Steinhaus *et al.* [39]	Original article	\	2019	2008–2013	578

[a] Defined for systematic reviews alone.
[b] For reviews, these ranges give the publishing window of the papers included, while for original articles, it indicates the time window of the surgical treatments included.
[c] Number of patients included in each study.

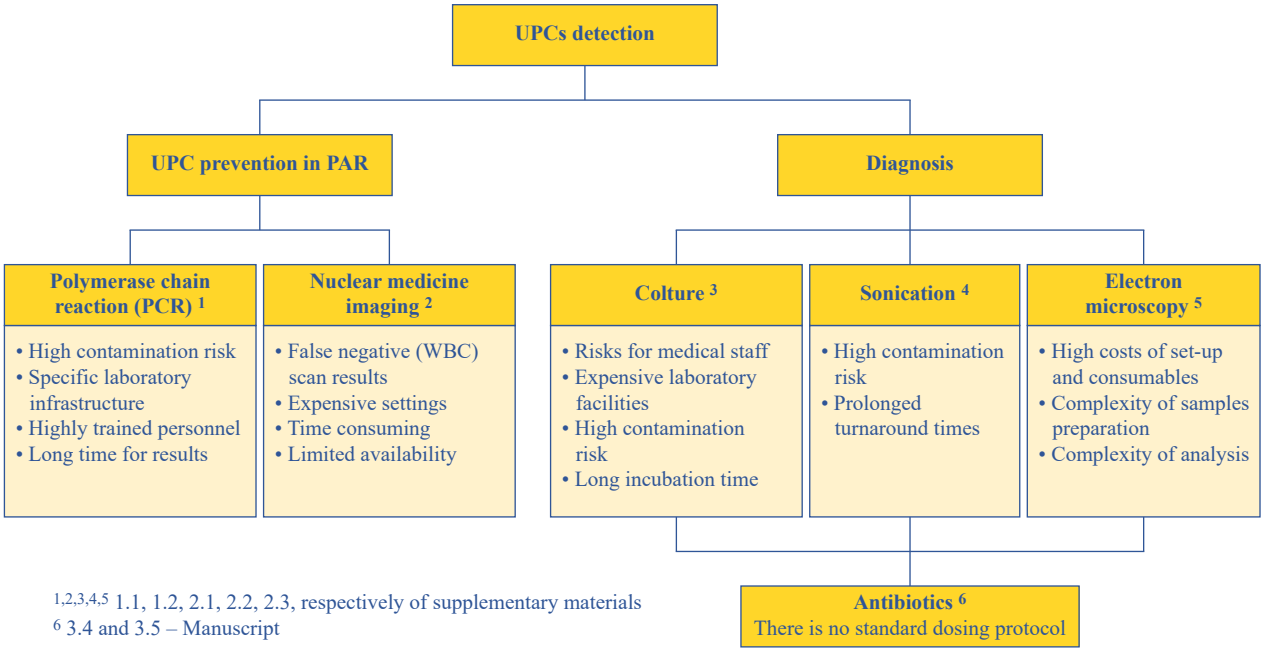


Figure 1. Flowchart summarizing preventive and diagnostic pathways for unexpected positive cultures (UPCs). PAR, presumed aseptic revision; WBC, white blood cell.

is costly, time-consuming and is not always available. Sample culture (Figure S2, online supplementary material) is the most typical technique to detect pathogens; it consists of the incubation of a sample previously placed in a suitable growth medium, allowing the growth and identification of bacterial colonies. This technique is characterized by sensitivity of 61–70% (increased to 80% if performed alongside sonication) and specificity >90% (up to 94% in some studies) [10–12] as reported in Table II. However, the risk of contamination is significant and omnipresent from sampling to incubation, and the bacterial samples must be managed inside authorized laboratories. Therefore, these procedures are liable to high equipment and raw material costs, and the possible long incubation time (up to some weeks) results in extended delays

Table II
Key features of techniques for detecting infections in orthopaedic implants

Sample analysis technique	Typical sensitivity	Typical specificity	Type of sample	Mechanism	Contamination risk	Antibiotic effect on outcomes
Polymerase chain reaction	~70—86%	~91%	Tissue, sonication fluid, synovial fluid	DNA and RNA identification	High if not controlled	Not affected significantly
Conventional culture	~61—70%	~90—94%	Tissue, sonication fluid, synovial fluid, swabs	Sample culture	Moderate if carefully collected and processed	Reduced sensitivity
Sonication	~77%	~96%	Removed implant	Disruption biofilm (sound energy)	High if not performed under strict sterile conditions	Not affected significantly
Micro-DTTech	~80%	~90—95%	Sonication fluid, tissue	Disruption biofilm (chemical reaction), sample culture	Minimal, being a closed system	Minimal, especially if combined with sonication

before diagnostic outcomes are obtained, thus postponing therapeutic decisions. Similarly, long turnaround times and a high risk of contamination are the major drawbacks for the sonication technique (Figure S3, online supplementary material), which uses sound energy or ultrasonic waves to dislodge biofilm-associated bacteria from medical devices in a cultured sample for subsequent pathogen identification, with pooled sensitivity and specificity for joint infections of approximately 77% and 96%, respectively (Table II) [13]. Several studies have reported that applying sonication to biological samples prior to culture improves the reliability of bacterial diagnosis. In the case of failure of these techniques, high-resolution electron microscopy (Figure S4, online supplementary material) can be employed to visualize pathogen concentration within a sample and investigate their morphology and structural characteristics. Nevertheless, this method has only been reported in two studies due to the complexity of sample preparation and analysis, as well as the substantial costs of the instrumentation involved. Despite the potential diagnostic outcomes provided by these methodologies, each has pros and cons as reported in Figure 1. It is important to emphasize that therapeutic approaches, often involving antibiotic administration, still lack a standardized universal protocol, and instead rely on the clinician's subjective judgement (as discussed below). Overall, the primary techniques used in the studies included in this review were conventional bacterial culture, sonication and PCR, sometimes combined within the same study to compare results and improve diagnostic specificity. These techniques were performed according to the methodological requirements of each procedure, although certain details, such as the type of sample (synovial fluid, tissues, explants, etc.) or, in the case of cultures, the incubation period (from 5 to 28 days), varied between studies. In particular, short bacterial culture times (2—5 days) enable rapid diagnostics and therefore prompt postoperative intervention; however, when bacterial growth is slow, such time frames may be insufficient for an accurate diagnosis. Longer culture periods (20—28 days) allow the accumulation of a sufficient bacterial load to ensure diagnostic accuracy, even in the case of slow-growing organisms, but this extends the timeline for postoperative intervention and increases the risk of contamination. In order to minimize the risk of contamination and to improve culture sensitivity, De Crescenzo *et al.* [14], employed the MicroDTTech tool (Table II) to culture samples (using dithiothreitol, a biofilm-disrupting agent, to enhance the sensitivity of culture-based detection [15]; see online supplementary material). Among the aforementioned techniques, conventional culture, sonication fluid culture and PCR are used as confirmatory techniques, as they allow identification of the specific bacterial pathogen; the remaining methods are considered primary techniques.

Results and discussion

Incidence

Hip and knee arthroplasties

The overall incidence of UPCs in total hip arthroplasty (THA) and total knee arthroplasty (TKA) in the included studies was approximately 15% (Figure 2, Table III), showing wide variability ranging from 8% to 30%. Studies such as Schwarze *et al.* [16] and Lin *et al.* [17] reported a rate of 14%, with most UPCs consisting of single positive cultures. Both articles identified conventional culture as the method used to detect UPCs; however, one article included in the Schwarze et al. review also employed implant sonication [18]. In contrast, Kloos *et al.* [19] found a lower incidence (8.32%) in exclusively TKA revisions, although with substantial interstudy variability (5—60%), likely caused by non-standardized microbiological and diagnostic criteria. Intra-operative culture was the most commonly used technique to assess the presence of UPCs by all the studies included, and the analysis of implant sonication fluid was investigated by several studies. Fernandez-Sampedro *et al.* [20] concluded that sonication fluid outperforms periprosthetic tissue culture with higher sensitivity. Simon *et al.* [21], Vargas-Reverón *et al.* [22] and Ludwig *et al.* [23] reported values >20% (Table III) using tissue culture alone; Simon *et al.* [21] and Ludwig *et al.* [23] consistently observed higher UPC rates in THA than in TKA (31.5% vs 27% and 26.1% vs 16.6%, respectively). This trend was also observed by Loppini *et al.* [24], with a total incidence of UPCs of 20.3% employing both tissue culture and implant sonication. In particular, UPC rates of 22.4% for THA and 11.1% for TKA suggest a potential joint-specific predisposition related to procedural or anatomical factors. Indeed, the higher incidence of UPC observed in THA

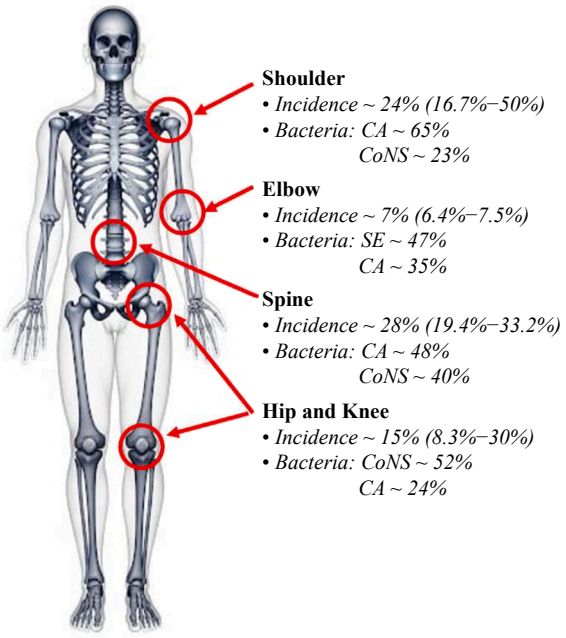


Figure 2. Summary of average incidence (range) of unexpected positive cultures and the two main bacteria detected in each area of the body. CA, *Cutibacterium acnes*; CoNS, coagulase-negative staphylococci; SE, *Staphylococcus epidermidis*.

(compared with TKA) may be explained by several joint-specific and anatomical factors. The hip is a deep-seated, highly constrained ball-and-socket joint surrounded by thick layers of muscle and soft tissue, which can limit early clinical detection of infective complications and promote the development of deep-seated contamination. In addition, the proximity of the surgical field to the groin region, characterized by higher bacterial colonization and moisture, may increase the risk of postoperative contamination. Conversely, the knee joint is more superficial, allowing earlier identification and management of wound-related issues, and is anatomically distant from areas of high bacterial load [25]. Furthermore, Simon *et al.* [21] identified nickel allergy as a significant risk factor for UPCs, and was one of the few studies to make this association. Sex–UPC correlation remains inconsistent between studies: Schwarze *et al.* [16] and Kayani *et al.* [26] reported a predominance of male patients among UPC cases, whereas Lin *et al.* [17] observed a slight predominance of females but without statistical confirmation. Unfortunately, most studies did not analyse sex differences formally, limiting the overall statistical interpretation.

Shoulder and elbow arthroplasties

Regarding shoulder arthroplasty, the incidence of unexpected positive cultures in revision shoulder arthroplasty (RSA) was high, with a pooled average of 24% based on 3840 procedures, and with reported rates ranging from 16% to 50% (Table IV, Figure 2). Furthermore, many of the included studies also analysed data for a sex–UPC correlation, although their conclusions and interpretations should be approached with caution due to the limited available evidence, especially regarding the elbow.

Hodakowski *et al.* [27] reported a pooled incidence of 27.5% by detecting UPCs through conventional culture. Furthermore, the incidence of UPCs in males (30.7%) was almost three times higher than the incidence in females (11.5%), suggesting a clear correlation between male sex and UPC presence as inferred for THA and TKA. Kim *et al.* [28] reported an incidence of 16.7% in six studies employing conventional culture as the UPC detection technique, while Akgun *et al.* [29] observed the highest incidence (50%) by combining sonication of the explant and conventional culture; both studies found a nearly equal sex distribution for the incidence of UPCs. De Crescenzo *et al.* [14] reported an incidence of 19%, identifying a four-fold higher UPC rate in patients with prior procedures or injections and a strong male predominance (87%), in accordance with Hodakowski *et al.* [27]. They employed conventional culture to diagnose UPCs, but using the MicroDTTech tool [15]. In comparison, the incidence of UPCs in revision elbow arthroplasty was substantially lower with respect to RSA, but the interpretation of elbow data is limited by the small number of

Table III
Incidence of unexpected positive cultures (UPCs) in total hip and total knee arthroplasties: relevant data for each study

Article	Sample size	Area of body	UPC incidence/rate	Techniques	Key findings
Schwarze *et al.* [16]	5821	Hip and knee	14% (794/5821)	CC S + CC (one study)	Mostly single positive cultures. UPC (M) > UPC (F)
Kloos *et al.* [19]	1178	Knee	8.32% (98/1178)	CC S + CC	Highest variability of incidence among studies: from 5% to 60%
Lin *et al.* [17]	300	Knee	14% (42/300)	CC	UPC (F) > UPC (M) but without statistical confirmation
Simon *et al.* [21]	1430	Hip and knee	21.5% (309/1430)	CC	UPC (THA) > UPC (TKA). Nickel allergy as risk factor
Vargas-Reverón *et al.* [22]	554	Hip and knee	24.2% (134/554)	CC	UPC (F) > UPC (M)
Ludwig *et al.* [23]	60	Hip and knee	30% (18/60)	CC	UPC (THA) > UPC (TKA)
Loppini *et al.* [24]	295	Hip and knee	20.3% (60/295)	CC S	UPC (THA) > UPC (TKA)
Kayani *et al.* [26]	297	Hip and knee	12.5% (37/297)	CC	UPC (M) > UPC (F)

CC, conventional culture; S, sonication of the explant; UPC (A), incidence of UPCs for the feature A; F, female; M, male.

Table IV
Incidence of unexpected positive cultures (UPCs) in shoulder and elbow arthroplasties: relevant data for each study

Article	Sample size	Area of body	UPC incidence/rate	Techniques	Key findings
Hodakowski *et al.* [27]	2373	Shoulder	27.5% (653/2373)	CC	UPC (M) >> UPC (F)
Kim *et al.* [28]	1405	Shoulder	16.7% (235/1405)	CC	\ \
Akgun *et al.* [29]	62	Shoulder	50% (31/62)	S + CC	UPC (M) = UPC (F)
De Crescenzo *et al.* [14]	80	Shoulder	19% (15/80)	CC (MicroDTTech)[a]	UPC (M) >> UPC (F). Higher UPC rate in patients with prior procedures or injections
Eyre-Brook *et al.* [30]	63	Elbow	6.4% (4/63)	CC	\ \
Wee *et al.* [31]	230	Elbow	7.5% (16/230)	CC S + CC	UPC (F) >> UPC (M)

CC, conventional culture; S, sonication of the explant; UPC (A), incidence of UPCs for the feature A.
[a] MicroDTTech is a tool to culture surgical samples (only used by De Crescenzo *et al.*; see online supplementary material).

available studies and sample sizes: Eyre-Brook *et al.* [30] reported an incidence of UPCs of 6.4% using conventional culture alone, and Wee *et al.* [31] reported an incidence of 7.5% using direct tissue culture and sonicating explants before culture. Furthermore, the latter highlighted a crucial prevalence of female patients in the UPC-positive group, amounting to 75%.

Spinal surgery

A limited number of articles have reported on UPCs in spinal surgery, particularly in comparison with the extensive literature available for knee, hip and shoulder surgeries. This disparity is noteworthy, as the average incidence of UPCs in spinal surgery is 27.8% based on an analysis of 2094 cases (Figure 2, Table V). Aldahamsheh *et al.* [32] reported 1108 cases, including both adult and paediatric subjects, founding a UPC rate of 24.3% in adults and 43.2% in children, highlighting the particular tendency of the latter to have positive cultures. Methodological differences produced notable rate variations, suggesting possible inconsistency in data collection: the highest UPC rate, 28.9%, was observed when conventional cultures were combined with sonication, compared with 23.6% for molecular techniques on sonicated lysate, and 15.5% using conventional culture alone. Aldahamsheh *et al.* [32] also reported higher UPC rates in males compared with females in 10 studies. Mirghaderi *et al.* [33] reported a higher overall UPC rate of 33.2%, ranging from 0% to 53% between studies. Of these studies, four used sonication and culture together, two used sonication alone, and nine used conventional culture; however, in contrast with Aldahamsheh *et al.* [32], there were no significant differences between the incidence rates obtained from the different approaches (39.6%, 31% and 30.5%, respectively). Furthermore, two studies [34,35] used electron and X-ray microscopy (see oneline supplementary material) as complementary diagnostic tools to detect and analyse bacterial biofilm structure on the explants, while Duprè *et al.* [36] used PCR (see online supplementary material) for the same scope. Unlike Aldahamsheh *et al.* [32], this review highlighted a greater tendency for UPCs in females, based on data from Callanan *et al.* and Leitner *et al.* [37,38], while the remaining studies provided no sex-based statistical analysis. Finally, Steinhaus *et al.* [39] used conventional culture samples collected from 112 presumed aseptic cases, and found UPCs in 19.4%. Their multi-variate analysis identified male sex and pseudarthrosis as significant risk factors, aligning with Aldahamsheh *et al.* [32] but contradicting the female-predominant pattern reported by Mirghaderi *et al.* [33].

Involved bacteria

As stated above, determining whether an isolated micro-organism represents a true infection or merely contamination remains a significant challenge. The skin and mucosal surfaces are normally colonized by commensal micro-organisms which

Table V
Incidence of unexpected positive cultures (UPCs) in spinal surgery: relevant data for each study

Article	Sample size	Area of body	UPC incidence/rate	Techniques	Key findings
Aldahamsheh *et al.* [32]	Total: 1108 Adults: 1037 Paediatrics: 81	Spine	Total: 25.7% (287/1108) Adults: 24.3% (252/1037) Paediatrics: 43.2% (35/81)	CC S + CC S	UPC (M) >>UPC (F). Highest UPC rate for C + S. Paediatric patients are prone to UPCs
Mirghaderi *et al.* [33]	1057	Spine	33.2% (317/1057)	CC S + CC S	No UPC rate differences between methods. Two studies used electron microscopy. UPC (F) > UPC (M)
Steinhaus *et al.* [39]	112	Spine	19.4% (36/112)	CC	Male sex and pseudarthrosis as significant risk factors

CC, conventional culture; S, sonication of the explant; UPC (A), incidence of UPCs for the feature A.

reside there naturally without causing any disease, and their isolation in the laboratory is often interpreted as contamination. In contrast, pathogens are organisms whose isolation is more likely to indicate true infection due to their recognized virulence. Examples of skin commensals include *C. acnes* and coagulase-negative staphylococci (CoNS), which can act as opportunistic pathogens when host defences are impaired, tissue barriers are disrupted, or foreign materials such as surgical implants are present. Moreover, mixed cultures or polymicrobial growth patterns should be interpreted with caution, as they may reflect procedural contamination rather than true implant-associated infection.

In all studies evaluating THA and TKA, CoNS and *C. acnes* consistently represented the predominant pathogens associated with UPCs, with incidence rates exceeding 40% (Figure 2). Schwarze *et al.* [16] identified CoNS as the leading organism in five of seven included articles, reporting a wide incidence range of 42—96% and a pooled mean of 58.6%. The remaining two studies cited *C. acnes* as the most frequently detected pathogen, with incidence rates of 38% and 32% (pooled 35%). Similarly, Simon *et al.* [21] observed *Staphylococcus epidermidis* in 31% of cases and *C. acnes* in 21% of cases, with all CoNS species accounting for 47% of the isolated micro-organisms. In line with these findings, Kayani *et al.* [26] and Vargas-Reverón *et al.* [22] reported *S. epidermidis* (49.6%), *Bacillus* spp. (18.9%), *Micrococcus* spp. (16.2%) and *C. acnes* (16.2%) based on analyses incorporating PCR (see Figure S1, online supplementary material). Lin *et al.* [17], Ludwig *et al.* [23] and Loppini *et al.* [24] likewise identified CoNS and *C. acnes* as the principal micro-organisms isolated. Collectively, these studies demonstrate that CoNS (particularly *S. epidermidis*) and *C. acnes* are the bacteria most strongly associated with UPCs in revision THA and TKA (Figure 2).

In the context of RSA, pathogen distributions varied, although *C. acnes* remained predominant. Hodakowski *et al.* [27] reported *C. acnes* in 76.4% of infections, with additional deep-culture isolates including CoNS [most notably *S. epidermidis* (7.8%)] as well as *Staphylococcus aureus* (3.2%) and *Escherichia coli* (2.3%). Polymicrobial cultures were reported in several studies, although inconsistently. Kim *et al.* [28] similarly found *C. acnes* at an incidence of 63.4%, followed by CoNS at 17.5%. Akgun *et al.* [29] reported *C. acnes* in 67.7% of cases and CoNS in 38.7% of cases, with polymicrobial results present in six patients. De Crescenzo *et al.* [14] further confirmed *C. acnes* as the most common organism, followed by *Peptoniphilus asaccharolyticus*. Overall, *C. acnes* emerged as the leading pathogen in RSA, followed by CoNS, although with high variability between studies (Figure 2).

For revision elbow arthroplasty, Eyre-Brook *et al.* [30] documented four distinct pathogens among their UPCs: *Micrococcus luteus*, *S. epidermidis*, anaerobic spore bearer and *C. acnes*. Wee *et al.* [31] identified *S. epidermidis* as the most common pathogen (47%), followed by *C. acnes* (35%). These findings indicate that *C. acnes*, followed by CoNS, predominates in revision elbow arthroplasty, consistent with trends observed in shoulder procedures (Figure 2).

In spinal surgery, all reviews demonstrated a similar pattern, with *C. acnes* as the most frequently isolated organism. Indeed, Aldahamsheh *et al.* [32] reported *C. acnes* in 42.5% of adult cases and 57.7% of paediatric cases, with CoNS identified in 39.9% and 30.5%, respectively. Likewise, Mirghaderi *et al.* [33] found *C. acnes* and CoNS at incidence rates of 43% and 39.5%, respectively. Steinhaus *et al.* [39] also reported *C. acnes* as the leading pathogen, with an incidence of 48.8%. Overall, these findings confirm that *C. acnes* is the predominant micro-organism in UPCs following spinal surgery, followed by CoNS, mirroring the microbial profile observed in other anatomical regions (Figure 2).

Risk of contamination of bacterial culture

The risk of contamination is a critical factor in interpreting microbiological results. It can arise at any stage of sample collection, handling or laboratory processing, and may lead to detecting micro-organisms that do not reflect the patient's true infecting flora. Such events can compromise diagnostic accuracy, resulting in misinterpretation of clinical findings and inappropriate antimicrobial therapy. In general, the isolation of *S. epidermidis* or *C. acnes*, both common commensal skin micro-organisms, from superficial or non-sterile sites is often considered indicative of contamination. However, these species can act as opportunistic pathogens under specific clinical conditions. *S. epidermidis* is a well-known cause of device-associated infections due to its capacity to form biofilms and adhere to artificial surfaces. Likewise, *C. acnes* has been implicated in prosthetic joint and cardiac device infections, as well as other chronic, low-grade infections, although contamination during sampling of these sites remains possible. Therefore, the clinical relevance of these micro-organisms must be assessed carefully, considering the sampling site, the presence of compatible clinical symptoms, and the overall microbiological context to distinguish true infection from contamination. Another source of contamination arises from direct or indirect contact with materials in the environment where the procedures are carried out, such as lapses in operator attention and inadequate cleaning of the workspace (e.g. the incubator where the bacterial cultures are grown). These circumstances may lead again to false-positive UPC findings, as the observed bacterial growth could originate from environmental sources rather than from the patient. The highest risk of contamination occurs during sample collection and treatment in the surgical room, due to direct exposure of the sample to skin, environmental microbes, and surgical instruments/gloves, while it is significantly lower in the laboratory, where aseptic procedures and controlled conditions minimize possible contamination. In order to minimize this risk, at least three to five tissue samples should be collected from different locations around the implant, avoiding areas prone to contamination, such as the skin edges. Each sample should be handled with separate sterile instruments, minimizing contact with gloves or other surfaces, and placed in individual sterile, leak-proof containers with validated transport solutions. Finally, samples should be transported promptly to the laboratory in a refrigerated container (2—8 °C) and analysed within 1—2 h.

Outcomes

In this section, orthopaedic implant outcomes were discussed by body area. Despite the large number of studies included and the consistent patient population, the reported outcome data were extremely heterogeneous. This heterogeneity arose from differences in sample processing methods and highly variable and relatively short follow-up periods, which, on average, ranged from 2 to 5 years. Furthermore,

many original articles were constrained by heterogeneous outcome measures and small patient cohorts, restricting the ability to draw strong conclusions regarding long-term implant survival.

Hip and knee arthroplasties

Most authors have reported that a single UPC does not worsen outcomes meaningfully, as shown in five of the seven studies summarized by Schwarze *et al.* [16], where revision-free and infection-free survival remained comparable to culture-negative cohorts despite heterogeneous follow-up durations (12—95 months). Barrack *et al.* [40], Vargas-Revéron *et al.* [22] and Neufeld *et al.* [41,42] also found no increased risk of re-revision with a single UPC, supporting the interpretation that isolated positivity is often contamination. In contrast, several authors quantified a concrete risk of re-revision when two or more UPCs were present, particularly from the same micro-organism. Simon *et al.* [21] demonstrated that patients with more than one identical UPC had a five-fold higher rate of septic re-revision (20%) compared with the single UPC group (4.1%). The TKA meta-analysis by Kloos *et al.* [19] further emphasized this distinction, reporting a re-revision rate of 18.45% in unsuspected prosthetic joint infection (PJI) vs 2.94% in aseptic revisions. Lin *et al.* [17] provided a clear correlation between the presence of UPCs and infection-free survival rate, with the inclusion of a control group: re-revision due to PJI occurred in 26.2% of UPC cases compared with 15.1% of culture-negative patients, and there was a significant decrease in 60-month infection-free survival with higher UPC counts (92.1% for negative cultures, 91.1% for one UPC, and 54.3% for more than two UPCs). These significant differences in re-revision rate suggest that a substantial proportion of UPCs are likely to be associated with true implant-related infections rather than accidental contamination, indicating a clinically meaningful impact on outcomes. Outcome variability between studies further highlights methodological differences: indeed, implant survival ranged widely, from 58.2% at 2 years (Berger *et al.* [43]) to 100% (Portillo *et al.* [44]), while Kayani *et al.* [26] observed no recurrence in PJI over 60—144 months. Purudappa *et al.* [45] highlighted survival rates between 85% and 100%, although most included studies documented some development of PJI after UPC detection. Short-term follow-up studies, such as Ludwig *et al.* [23] (12-month follow-up) and Loppini *et al.* [24] (18-month follow-up), reported no PJI following UPC detection, but the limited duration of follow-up severely restricts the interpretation reliability. Finally, the stratified analysis by Vargas-Revéron *et al.* [22] showed no significant differences in failure at 60 months among the three culture-based groups (Group A: aseptic; Group B: one UPC; Group C: more than one UPC), but Group C was much smaller than the other two groups, thus reducing the comparative reliability. Overall, the quantitative evidence in THA and TKA suggests that risk remains minimal with a single UPC, but rises substantially with multiple concordant UPCs.

Shoulder and elbow arthroplasties

On the basis of the reviewed articles, the clinical significance of UPCs in shoulder and elbow arthroplasties remains uncertain. Hodakowski *et al.* [27] found no significant difference in reoperation rate between UPC and culture-negative groups; nonetheless, the pooled reoperation rate for patients with UPCs was 5.4%, compared with 3.4% in culture-negative patients. In Kim *et al.*'s review [28], with a mean follow-up of approximately 48 months, true infection after a UPC occurred in 10.2% of shoulders, with *C. acnes* accounting for 75% of cases. Akgun *et al.* [29] reported that the mean time to revision was significantly shorter in patients with UPCs (12.4 months) than in culture-negative patients (20.5 months), suggesting that UPCs may represent clinically relevant infections that manifest earlier and prompt revision rather than incidental contaminations. They also observed a higher rate of postoperative stiffness in culture-positive cases; notably, 91.7% of patients with two UPCs of the same organism had stiffness compared with 65.7% of patients with only one UPC. Conversely, De Crescenzo *et al.* [14] found no periprosthetic infections among 80 patients with UPCs at 24 months. Evidence for elbow arthroplasty is limited due to the small number of articles retrievable in the literature: Eyre-Brook *et al.* [30] reported 82.4% revision-free survival at 96 months for presumed aseptic elbow revision, but did not include a control group. Wee *et al.* [31] considered 10 of 12 patient cultures to be contaminated; among these, nine patients remained infection-free, and one patient developed an infection 3 months post-revision. Collectively, these data suggest that although many UPCs may be clinically insignificant, a meaningful minority are associated with higher complication rates and earlier need for revision.

Spinal surgery

In the review by Aldahamsheh *et al.* [32], only four studies reported outcomes of spinal surgery in patients with UPCs: Plaass *et al.* [46] found that two of 18 patients with UPCs developed surgical site infections (SSIs), while the other three studies [47—49] reported no SSIs among patients with UPCs. Mirghaderi *et al.* [33] provided limited and poorly detailed postoperative outcome data, although it indicated no significant differences in patient-reported outcomes such as satisfaction, physical functioning and bodily pain between the UPC and control groups. Overall, data on outcomes following revision procedures for spinal fusion remain scarce compared with other anatomical regions. Notably, in spinal surgery, implants may often be retained even in the presence of infection, leading to inconsistent or incomplete reporting on implant survival. Moreover, Wei *et al.* [50] reported that postoperative spinal implant infections can be managed successfully with hardware retention in select cases, particularly when early diagnosis is achieved and when the infection involves specific organisms. Early recognition appears to correlate with higher rates of successful retention; to reduce the risk of late-onset infection, further research into targeted preventative strategies is essential. Finally, Yudistira *et al.* [51] suggested that implant retention is appropriate when SSIs occur within 3 months of surgery; however, if the infection persisted beyond that period, implant removal was generally recommended.

Case management for UPCs

Clinical management following the detection of UPCs is extremely diverse and devoid of specific guidelines as there is no validated treatment algorithm at this stage. By summing all the papers, most authors concur that antibiotic administration is an 'unclear' practice to manage UPCs, as stated, for

example, by Schwarze *et al*. [16]: 'The role of systemic antibiotic treatment remains unclear'.

Many of the included studies reported postoperative antibiotic prophylaxis, but each study followed different criteria, and it is extremely difficult to compare them under definite criteria. Some studies included in the reviews by Aldahamsheh *et al*. [32] and Mirghaderi *et al*. [33], and the article by Burkhard *et al*. [52] concurred that every patient with UPC needs to be followed directly by an infectious disease specialist, while Ohrt-Nissen *et al*. [35] and Shiban *et al*. [53] agreed to treat the presence of UPCs following a more targeted case-by-case approach based upon antibiogram results. Only Callanan *et al*. [37] stated that the presence of UPCs should be managed directly by surgeons.

On the other hand, Leitner *et al*. [38] stated that, in spinal surgery, it should be sufficient to remove the infected implant without any other treatment. They argued that this strategy should lead to a reduction in the use of antibiotics, thus limiting possible bacterial resistance, especially when the patient shows an indolent infection.

To summarize, many of the included reviews [16,27,32,33], based on results derived from their extensive datasets, appear to be more reliable and comprehensive than individual original studies. Given that, they concur with the lack of clarity surrounding antibiotic use in cases with one or multiple UPCs, emphasizing the heterogeneity of the approaches currently employed by different authors, and suggesting the need for future prospective studies on this issue.

Limitations and discussion

At this stage, it is clear that the issue of UPCs in orthopaedic implant revision remains unresolved, and requires further prospective studies to reach reliable conclusions. While the pathogens involved are relatively well defined and consistent in all the studies, the incidence, management and outcomes are highly variable and inconsistent (Table VI). A crucial limitation affecting the reliability and comparability of the data between studies is the significant heterogeneity in diagnostic criteria and techniques. As reported in the literature, this heterogeneity may influence the reported incidence of UPCs, which depends on the detection techniques and criteria (or their combination) used.

As stated above, management of the presence of UPCs remains unclear: some authors recommend infectious disease consultation and antibiotic therapy, whereas others do not consider it necessary. These therapeutic dilemmas may also be influenced by the fact that the main detection method is based on culture, which presents several limitations including the long incubation period (up to 28 days) and the possibility of contamination during sample collection or laboratory processing.

Moreover, outcome data between different anatomical sites are extremely heterogeneous, and when evaluating the reported results, it should be considered that many studies only included a short follow-up period (2—5 years) (Table VI). Consequently, a gap currently exists in the literature regarding long-term survival and outcomes of revision surgeries in which UPCs are detected. On this basis, it would be interesting to investigate whether there is a relationship between the pathogen identified in one or multiple UPCs and the survival of the revision implant through a standardized follow-up. Therefore, further studies with standardized follow-up, preferably reporting results stratified by pathogen, are needed, as well as research into new technologies capable of detecting pathogens rapidly and with high reliability.

Finally, publication bias may be present, as studies reporting moderately high UPC rates could be more likely to be published.

Table VI
Summary of unexpected positive culture characteristics by part of body

	Average incidence	Average incidence	Average bacterial incidence	Average follow-up (months)
Hip and knee	~15%	M: 62 % F: 38 %	~52% CoNS ~24% CA	~50[3]
Shoulder	~24%	M: 72 % F: 28 %	~23% CoNS ~65% CA	6—48 [27][a] ~47 [28][a]
Spine	~28%	M % > F %	~40% CoNS ~48% CA	~43 [33][b]
Elbow	~7.3%	Not provided	~47% SE ~35% CA	~54[c]

M, male; F, female; CoNS, coagulase-negative staphylococci; CA, *Cutibacterium acnes*; SE, *Staphylococcus epidermidis*.

[a] If the values differed significantly between the studies, they are reported separately with the relative reference.

[b] Only five articles included in Mirghaderi *et al*. [33] reported data about follow-up.

[c] Evaluation obtained through weighted mean throughout the values retrieved in the included articles.

Conclusions and future perspectives

This narrative review suggests that the presence of UPCs is a serious problem with high incidence, especially in shoulder and spinal surgery, affecting more than one in four people, with *C. acnes*, CoNS and *S. epidermidis* being isolated most frequently. The clinical implications for UPCs could be crucial, as multiple concordant UPCs suggest potential occult PJI, leading to potential prosthetic failure; for this reason, they should be managed as probable infections. On the other hand, it is reasonable to cautiously consider single UPCs as contamination. In any case, the typical slow response and moderate sensitivity of current detection methods, as well as the lack of specific guidelines for cases with UPCs, make clinical detection and management very complex and often inconsistent. Furthermore, the outcomes reported by the different studies were highly heterogeneous, and this heterogeneity mainly arose from differences in sample collection and processing methods, and highly variable and relatively short follow-up periods. Given these limitations and uncertainties, further studies are required to shed light on this topic. Moreover, based on a comparison with the literature, the most promising primary techniques that should be used to detect low-grade infections are sonication combined with conventional culture, and culture performed using a MicroDTTech device. These techniques, together with standardized follow-up periods, should be employed in future studies to obtain results that are as comparable and reliable as possible. Finally, novel fast-responding

and reliable techniques should be developed with the aim of improving and refining the detection of UPCs and, consequently, the management of these cases [54]. For instance, metal oxide (MOX) sensors or electrochemical biosensors, capable of detecting bacterial gas emissions or liquid-phase molecular releases, respectively, could be suitable for this application. In particular, MOX sensors have been used already in the biomedical field to analyse exhalations from biopsies, blood and cultured cells, and were found to be sensitive to bacteria which represented the main contaminants [55—59].

CRediT authorship contribution statement

M. Astolfi: Writing — review & editing, Writing — original draft, Validation, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **E. Artioli:** Writing — original draft, Formal analysis, Conceptualization. **M. Masin:** Writing — review & editing, Writing — original draft, Investigation. **C. Malagù:** Supervision, Methodology, Conceptualization. **P. Artioli:** Writing — original draft, Validation. **A. Sartorello:** Writing — original draft, Conceptualization. **A. Mazzotti:** Supervision, Conceptualization. **C. Faldini:** Supervision, Methodology. **G. Rispoli:** Writing — review & editing, Writing — original draft, Methodology, Conceptualization.

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Appendix A. Supplementary data

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