



SELF-INSPECTIONS IN STERILE PHARMACEUTICAL MANUFACTURING: A CRITICAL REVIEW OF THE LITERATURE AND OF RECURRENT INSPECTION DEFICIENCIES

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ABSTRACT

Self-inspections, also termed internal audits, are a mandatory element of the pharmaceutical quality system under Chapter 9 of the EU Guidelines to Good Manufacturing Practice, under ICH Q10 and under equivalent international frameworks. In sterile manufacturing the instrument carries particular weight, because the revised Annex 1 requires a formalised contamination control strategy whose effectiveness has to be periodically reviewed, and because published inspection data place sterile operations among the areas generating the highest share of critical findings. Our aim here is twofold: to review what has been published on self-inspection practice in sterile manufacturing, and to ask, against the deficiency data that inspectorates and analysts have put into the public domain, which non-compliances keep recurring at sterile sites and why internal audits so seldom catch them first. PubMed, Embase and Google Scholar were searched purposively for the period 2015 to 2025, together with regulatory and industry sources. Deficiency data were taken from the published MHRA inspection deficiency datasets, from non-compliance reports in the EudraGMDP database and from published analyses of warning letters and inspection observations of the United States Food and Drug Administration. Six recurrent clusters were identified: environmental monitoring design and excursion investigation; contamination control strategy and aseptic practice; cleaning, disinfection and cleaning validation; premises, equipment and utilities; investigations, root-cause analysis and corrective and preventive action; and the integrity of monitoring records. Almost all of these clusters fall within the documented scope of a routine self-inspection, yet they continue to be reported by inspectorates in stable proportions. We argue that what limits these programmes is how deeply they look rather than how widely.

Keywords: Self-inspection; Internal audit; Sterile manufacturing; Annex 1; Contamination control strategy; Environmental monitoring

1 INTRODUCTION

Product quality is a public health matter, and in sterile manufacturing it is an unusually unforgiving one. Contamination cannot be tested out of a finished batch with any confidence, and it is the patient who carries the consequence. Regulatory agencies, among them the European Medicines Agency (EMA), the United States Food and Drug Administration (FDA), the World Health Organization (WHO) and the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), maintain extensive inspection systems to confirm compliance with Good Manufacturing Practice (GMP). Those systems are, however, periodic and external. Between them, the manufacturer is expected to organize and perform self-inspections (known also as internal audits). Chapter 9 of the EU GMP Guidelines requires companies to conduct regular internal audits in order to monitor the implementation of and compliance with GMP principles and to propose the necessary corrective measures [1]. ICH Q10 positions the instrument as an element of continual improvement rather than as a compliance formality [2], and comparable requirements appear in the WHO Technical Report Series, in PIC/S PE 009 and in 21 CFR Part 211 [7, 8].

For sterile products the expectation is more demanding. The revised Annex 1 to the EU GMP Guidelines, applicable since August 2023, requires a documented contamination control strategy (CCS) that covers premises, equipment, utilities, personnel, raw and starting materials, environmental monitoring and the investigation of deviations, and it requires that the effectiveness of that strategy be reviewed periodically [3]. The internal audit is the principal mechanism by which a site tests whether its own contamination controls work as described.

Despite this mandate, self-inspections remain markedly less studied by academia than regulatory inspections. A recent scoping review identified only 14 peer-reviewed publications on the management of GMP inspections over the period 2015 to 2025, out of more than 377 sources screened, a ratio of 3.7% [5]. The disproportion between the practical weight of the instrument and the attention it receives in the literature is the starting point of the present review.

1.1 Regulatory framework

The documents governing self-inspection form a harmonised, though not fully unified, international framework. EU GMP Chapter 9 is the foundational reference for European manufacturers, requiring documented self-inspections that cover all GMP areas, auditors who are independent of the area audited, and effective corrective actions [1]. ICH Q10 links self-inspection to CAPA management and to management review [2]. ICH Q9(R1) supplies the methodological apparatus for risk-based determination of audit scope and frequency [10], and PIC/S PI 037-1 offers an equivalent model on the inspectorate side [11]. WHO TRS No. 1044, Annex 2, sets out GMP for sterile products for regulatory systems outside the EU framework [7], while ISO 19011:2018 remains the reference standard for auditor competence and is widely cited in the pharmaceutical literature [9].

Annex 1 (2022) does not treat self-inspection as a separate chapter; it embeds the expectation throughout, most explicitly in the requirement for periodic review of the CCS and in the requirement that environmental and personnel monitoring programmes, aseptic process simulations and cleaning and disinfection regimes be assessed for continued suitability [3]. In practice, these reviews are performed, or are supposed to be performed, through the site's internal audit programme.

One asymmetry deserves note. 21 CFR Part 211 does not require manufacturers to retain records of internal audits, and FDA investigators do not routinely review them, whereas EU inspectors may request self-inspection reports and the associated CAPA records. The literature has identified this asymmetry as a potential friction point in mutual recognition and in global inspection partnerships [6].

1.2 Objectives

We set ourselves four tasks: to map the thematic areas of the published literature on self-inspections in sterile manufacturing; to establish from the published deficiency datasets which non-compliances recur most often at sterile sites; to ask how many of those recurrent findings a properly conducted self-inspection could have caught; and to examine why internal audits miss them, and what this leaves open for research.

2 MATERIALS AND METHODS

2.1 Design of the review

This is a critical review rather than a systematic one. We read the available literature and the published deficiency data alongside each other, group them thematically and say where the evidence runs out. It makes no claim to exhaustive coverage, does not follow a systematic review protocol and was not registered in PROSPERO; the appraisal is

interpretative rather than meta-analytical, which is the appropriate design where the evidence base is heterogeneous and dominated by regulatory and industry sources [5].

2.2 Sources and search strategy

Three groups of sources were used. Academic databases (PubMed/MEDLINE, Embase, Google Scholar) were searched for the period 2015 to 2025 using combinations of the terms ‘self-inspection’, ‘internal audit’, ‘pharmaceutical GMP’, ‘sterile manufacturing’, ‘aseptic processing’, ‘contamination control strategy’, ‘environmental monitoring’, ‘CAPA’, ‘ICH Q10’, ‘auditor competence’, ‘quality culture’ and ‘risk-based audit’. Regulatory and industry portals (EMA, FDA, MHRA, WHO, PIC/S, ICH) and the publications of ISPE, PDA and the ECA Academy were searched for corresponding guidance and practice reports. Finally, published deficiency data were drawn from the MHRA GMP inspection deficiency datasets and the secondary analyses of those datasets [13-17], from the analysis of non-compliance reports in the EudraGMDP database published by Lebanova and co-workers [12], and from published analyses of FDA warning letters and FD-483 observations [19-23]. The search was finalised in March 2026. Inclusion and exclusion criteria are given in Table 1.

Table 1. Scope of the review: inclusion and exclusion criteria

Criterion	Included	Excluded
Publication type	Peer-reviewed articles and reviews; guidance of regulatory agencies (EMA, MHRA, FDA, WHO, PIC/S, ICH); technical reports and practice analyses of ISPE, PDA and ECA; published inspection-deficiency datasets	Blogs, vendor marketing material and teaching material without an identifiable author
Time frame	2015–2025 for the literature; regulatory documents of any date where they form the normative framework	Publications before 2010, unless a fundamental methodological standard
Language	English and Bulgarian	Other languages
Subject scope	Self-inspections and internal GMP audits; contamination control, environmental monitoring and aseptic practice; CAPA systems; auditor competence; quality culture	Clinical research (GCP); pharmacological research unrelated to quality assurance
Manufacturing scope	Sterile and aseptically processed medicinal products, including ATMPs, with non-sterile data retained for comparison	Studies confined to distribution or retail pharmacy with no manufacturing dimension

2.3 Use of artificial intelligence

In accordance with good publication practice, the authors disclose that an AI assistant (Claude, Anthropic) was used to assist in editing the text. A limitation of the deficiency data should be stated at the outset. European inspectorates publish aggregate findings only, and the MHRA, which has published the most granular dataset of any European authority, last released GMP deficiency data for inspections conducted in 2019 [18]. FDA publishes individual warning letters but not a consolidated deficiency taxonomy. Comparisons across jurisdictions are therefore indicative rather than statistical, and the analysis below is presented on that basis.

3 RESULTS AND DISCUSSION

3.1 Recurrent deficiencies in sterile manufacturing inspections

3.1.1 European inspection data

Of the European inspectorates, the MHRA has published by far the most detailed picture of what its inspectors actually find. In the 2015 trending report, the most frequently cited deficiency groups were, in order, quality system, complaints and recall, documentation, quality control, computerised systems, production, premises and equipment, validation, personnel and materials management, with the quality system group alone accounting for 27 critical and 293 major findings [13]. That ranking has barely moved since. Analyses of the 2018 and 2019 datasets show Annex 15 (qualification and validation) and Annex 1 (manufacture of sterile medicinal products) in first and second place among the annexes, with approximately 600 and 450 deficiencies respectively in 2018, against approximately 1,500 citations for Chapter 1 [14].

Raw frequency tells us less than the distribution of severity. Annex 1 ranked first among the annexes for the number of critical deficiencies in both 2018 and 2019 [16]. Of the 137 critical deficiencies recorded in 2019, 34% were associated with Chapter 1 and 23% with Annex 1; among the 1,999 major deficiencies, 31% were associated with Chapter 1, 29% with Annex 1, 10% with Annex 15 and 9% with Chapter 4 [15]. In other words, two areas, the quality system and sterile manufacturing, account for more than half of all serious findings. In the 2018 dataset, which comprised more than 6,000 citations across almost 300 inspections, 38% of critical observations related to Chapter 1; for sterile manufacturers specifically, 12% of all observations cited Annex 1, making it the single most frequent area of concern for that population [17].

The findings within Annex 1 are not spread evenly across the annex. Four paragraphs account for approximately 28% of all deficiencies citing the annex, and the ten most frequently cited paragraphs account for 47% [16]. The two clauses most often associated with critical observations in the 2018 data concerned environmental monitoring techniques and the investigation of environmental monitoring excursions, both of the most serious recurring failures, in other words, were microbiological [17].

At the level of outcome, the EudraGMDP data point the same way. A retrospective analysis of 99 non-compliance reports issued by 21 national competent authorities across 19 countries between 2013 and 2022 identified 1,458 deficiencies, of which 544 (37%) were classified as major and 127 (9%) as critical; in 41 cases the competent authority recommended suspension or voiding of the certificate of suitability and in 36 cases revocation of the GMP certificate [12]. The authors concluded that the observed deficiencies demonstrate the need for continuous monitoring and improvement of manufacturers' processes and quality management systems, which is the job self-inspection is supposed to be doing.

There is little sign that the picture has improved since that last published dataset. Trending of audit and mock-inspection findings collected between January 2024 and 2025 by an independent auditing body reported that the top three deficiency references were unchanged from the 2019 MHRA data, with recurring gaps in management review, training and storage, suggesting that the industry has made limited progress against the same findings [18].

3.1.2 Enforcement data of the United States Food and Drug Administration

Enforcement data from the United States are less neatly aggregated, but they converge on the same themes. A review of warning letters issued during fiscal year 2024 found environmental monitoring to be the most frequently cited subject (16 of 48 letters reviewed), followed by laboratory controls and stability [10] and process validation [6], with the specific regulatory citations concentrated on control of microbial contamination under 21 CFR 211.113(b) and on design and construction features for aseptic processing under 21 CFR 211.42(c)[10] [21]. In fiscal year 2025 the agency issued 303 warning letters concerning drug and biological products, an increase over the preceding year [22].

What the recent letters describe is more telling than how many of them there are. In one 2026 case, an environmental monitoring plate adjacent to an ISO 5 filling area returned a result that was too numerous to count, with confluent bacterial growth and insect larvae, and the batch was nevertheless released on the basis of a passing sterility test; the agency rejected the firm's explanation as an unsubstantiated hypothesis and characterised the finding as a critical failure of the contamination control programme [23]. A second case at a facility that had already received a warning letter in 2023 described corroded equipment, deposits on ceiling-mounted HEPA filters and standing water around the air handling unit serving a filling room [23]. Neither set of conditions arises overnight, and neither requires specialist instrumentation to observe. Both were, in principle, visible to any competent internal auditor walking the area.

None of this is new. An earlier analysis published in this journal, which applied quality risk management tools to microbial contamination events referenced in FDA warning letters and European non-compliance reports between 2008 and 2016, concluded that the affected manufacturers should concentrate on process improvement and microbial control strategies, particularly in microbial analysis and raw material quality control [19]. A recent analysis of contamination control trends in FDA warning letters reaches comparable conclusions for the current period [20].

3.1.3 Synthesis: six recurrent clusters

Taken together, the European and United States data point to six recurrent clusters of deficiency at sterile sites. Table II sets these out with their principal regulatory references, the typical finding as recorded by inspectorates, and an assessment of whether the finding lies within the detectable scope of a routine self-inspection.

Table 2: Recurrent deficiency clusters in sterile manufacturing and their detectability by self-inspection

Cluster	Principal references	Typical inspection finding	Detectable by self-inspection?
1. Environmental and personnel monitoring	Annex 1 §9; 21 CFR 211.113(b)	Monitoring locations not justified by risk; sampling frequency reduced without rationale; excursions closed without identification of the organism	Yes — by review of the monitoring rationale and of closed excursion records
2. Contamination control strategy and aseptic practice	Annex 1 §2; ICH Q9(R1)	CCS present as a document but not linked to monitoring data; aseptic interventions not reflected in process simulation; gowning qualification lapsed	Yes — by observation of live operations rather than document review
3. Cleaning, disinfection and cleaning validation	Annex 1 §4; Annex 15	Disinfectant efficacy not validated against site isolates; contact times not achievable as written; cleaning validation limits not justified	Partly — requires microbiological competence in the audit team
4. Premises, equipment and utilities	Chapter 3; Annex 1 §4	Deteriorated surfaces, corrosion, condensate and standing water; HEPA filter integrity and air-handling maintenance overdue	Yes — visible on a walk-through of the facility
5. Investigations, root-cause analysis and CAPA	Chapter 1; ICH Q10	Investigations closed to 'operator error'; retraining as sole corrective action; identical findings recurring in successive cycles	Yes — by trending of previous self-inspection and deviation records
6. Data integrity of monitoring and process records	Annex 11; MHRA data integrity guidance	Audit trails disabled or unreviewed; shared logins on monitoring and building management systems; unexplained deletion of data	Partly — requires computerised-systems competence in the audit team

Our main point sits in the final column. Of the six clusters, four are detectable by an auditor with ordinary GMP competence who observes operations rather than reading documents, and the remaining two are detectable by an audit team that includes microbiological and computerised-systems expertise. None of them depends on information available only to an inspectorate. The recurrence of these findings, in stable proportions, across a decade of published data is therefore not primarily evidence of insufficient regulation or of insufficient audit coverage. It is evidence that self-inspections are being carried out without finding what they exist to find.

3.2 Why self-inspections fail to detect these findings

3.2.1 Risk-based planning that does not change

Risk-based planning is one of the better covered topics in this literature. ICH Q9(R1), revised in 2022, explicitly identifies auditing as an application area of quality risk management, and risk-based auditing requires that the frequency and scope of audits follow process complexity, non-compliance history, previous audit results and regulatory change [10, 11]. Lebedynets and Karamavrova proposed a risk model for internal audit planning tied to PQS processes, emphasising that the annual plan should be a living instrument updated at critical events [25]. Against that expectation, practice analyses identify three recurrent defects: cosmetic planning, in which the plan is unchanged year after year; the desk audit, confined to documentation without verification in the field; and ineffective CAPA, evidenced by identical findings in consecutive audits [26].

At a sterile site this has a particular consequence. An audit plan built around GMP chapters rather than around the CCS will systematically under-sample precisely the areas where critical findings concentrate, because environmental monitoring rationale, aseptic intervention practice and disinfectant efficacy do not correspond neatly to chapter headings.

3.2.2 CAPA systems and the recurrence of findings

How well a site runs CAPA cannot be separated from how well it runs self-inspections. More than 30% of FDA warning letters in the period 2020 to 2022 cited problems connected with internal audit or self-inspection processes [27], and

CAPA-related observations rank consistently among the most frequent FD-483 observations. Raghu and co-workers and Jain and Jain distinguish reactive CAPA, which addresses a specific non-compliance, from proactive CAPA, which addresses the underlying risk, and both emphasise that the recurrence of an identical finding at a subsequent self-inspection is the clearest single signal of CAPA system failure [28, 29].

The ISPE Advancing Pharmaceutical Quality programme offers a structured framework for assessing CAPA maturity across four levels, and benchmarking data show a positive association between mature CAPA implementation and delivery performance [30, 31]. VanDuyse and co-workers observe that retraining remains too prevalent as the primary corrective measure, and FDA specifically treats the proportion of CAPA closed with retraining alone as an indicator of an immature quality system [32]. This matters more in a sterile environment than elsewhere. ‘Operator error’ is an attractive root cause for a deviation during an aseptic intervention for the simple reason that it asks nothing of facility design, staffing levels or the process itself.

3.2.3 Auditor competence and independence

Few authors dispute that the competence of the auditor largely decides what a self-inspection is worth. Lebedynets and Karamavrova identified eight competence domains: technical GMP knowledge, auditing technique, regulatory knowledge, communication, independence, analytical thinking, documentation skills and continuing education [25]. Edik documented a growing shortage of trained GMP auditors in organisations working to FDA, EMA, MHRA, WHO, TGA and PIC/S requirements [33]. Chen and co-workers provided one of the few quantitative confirmations available, showing that longer tenure of quality assurance personnel is significantly associated with better GMP inspection outcomes [34].

Sterile manufacturing asks for competences that general GMP auditor training does not supply. Three of the six clusters in Table II — monitoring rationale, disinfectant efficacy and the integrity of monitoring data — cannot be assessed meaningfully without microbiological or computerised-systems expertise. Where the audit team lacks that expertise, the audit does not report an absence of competence; it reports an absence of findings. The requirement of Chapter 9 that auditors be independent of the area audited is also harder to satisfy at small sites and at contract manufacturing organisations, where the only staff who understand aseptic operations are the staff who perform them [5].

3.2.4 Quality culture and management engagement

Running through the whole literature is quality culture, the factor on which the other instruments are said to depend. The PDA global quality culture survey identified a significant positive correlation between quality-oriented employee behaviour and quality system maturity, and named five leading indicators of a mature culture: management communication that quality is everyone’s responsibility, formal quality objectives, clear feedback criteria, quality topics in general meetings and error-prevention metrics [35]. The ISPE and PDA guide developed a six-dimensional maturity framework linked to nineteen behavioural indicators and distinguished a quality mindset from a compliance mindset [36]. The FDA Quality Management Maturity programme institutionalises assessment beyond traditional compliance across five dimensions [37], and Bertels and co-workers demonstrated a positive association between quality culture and operational performance [38].

One result of the PDA survey speaks directly to self-inspection. Executive respondents assessed the state of quality culture consistently more optimistically than respondents at large [35]. Where that gradient exists, an internal auditor who reports an uncomfortable finding about an area overseen by senior management is reporting against the organisation’s own self-image, and the mechanisms by which such findings are softened, deferred or reclassified are well documented in audit research outside the pharmaceutical sector. So the audit reports alone cannot tell anyone whether the programme works: on paper, a programme that raises few findings looks exactly like a site with few problems.

3.2.5 Data integrity, remote assessment and digitalisation

The pandemic opened a small literature of its own. Several authorities, among them EMA, PMDA and EDQM, developed remote GMP inspection procedures, and EDQM reported that minor and major non-compliances were successfully identified even in remote format [39]. The experience is directly transferable to self-inspection at multi-site organisations, with the caveat that the four visually detectable clusters in Table II are exactly those that a remote audit cannot address.

Data integrity has since become a subject in its own right, with guidance from MHRA, FDA, WHO and PIC/S behind it [40]. In sterile manufacturing the exposure is concentrated in the systems that record monitoring data: environmental monitoring databases, building management systems and particle counters, where audit trail review, user-access management and the traceability of excursion records are the areas at risk. Electronic quality management systems

support self-inspection through automated CAPA tracking and trend analytics, but they also create the possibility of an audit that examines the system of record while never examining the cleanroom.

3.2.6 Regional differences and resource-constrained settings

Western European and North American publications dominate, but work from elsewhere finds comparable patterns under tighter constraints. Chen and co-workers found that longer QA tenure correlates with better inspection outcomes in China and that bank-dependent companies show weaker results [34]. An analysis of inspections conducted by the Tanzanian regulator between 2018 and 2020 found the most frequent non-compliances to concern laboratory quality control and manufacturing premises, and argued for enhanced regional harmonisation [41]. Varin and co-workers proposed a risk-based desktop inspection model for overseas manufacturers supplying Thailand, demonstrating feasibility in resource-constrained settings [42].

3.3 Synthesis and implications for practice

The literature and the deficiency data agree with one another. Sterile manufacturing generates a disproportionate share of serious inspection findings; those findings cluster in a small number of areas; the clusters are stable across a decade and across jurisdictions; and almost all of them are detectable by a competent internal audit. The gap, therefore, is not regulatory. EU GMP Chapter 9, Annex 1 and ICH Q10 already require what would be needed to close it.

A recurring contradiction runs through the reviewed sources: ICH Q9(R1) provides a clear methodological basis for risk-based audit planning, while practice analyses identify the unchanged annual plan as one of the most common weaknesses in the field [10, 26]. A second contradiction concerns evidence. The recurrence of identical findings is universally described as the principal indicator of CAPA failure [28, 29], yet few organisations trend their own self-inspection findings across cycles in a way that would make recurrence visible, and no published instrument exists for measuring the maturity of a self-inspection programme in the way that CAPA maturity and quality culture maturity have been operationalised [30, 36].

Several things follow for a sterile site, none of which waits on a change in the rules. Audit plans can be built around the contamination control strategy rather than around GMP chapters, so that scope follows contamination risk. Audit teams can be constituted to include microbiological and computerised-systems competence rather than assembled from available quality assurance staff. Self-inspection findings can be trended across cycles alongside deviations and regulatory observations, so that recurrence becomes a monitored metric rather than an anecdote. And the programme can be measured against an external yardstick: what regulators and customer auditors find at the site that the internal audits had not.

Several limitations should be acknowledged. Grey literature dominates the sources, reflecting the paucity of peer-reviewed empirical research on self-inspection as a distinct practice. The deficiency datasets are not directly comparable: the MHRA data are granular but end with inspections conducted in 2019 [18]; the EudraGMDP analysis covers only sites that reached formal non-compliance [12]; and FDA warning letters represent the escalated tail of enforcement rather than the distribution of findings. Analyses of the MHRA datasets used here are secondary interpretations of the published data [14-17]. The search was limited to English and Bulgarian sources. Finally, the central inference of this review, that recurrent findings indicate detection failure rather than absent audit coverage, is an argument from converging evidence and not a directly measured result; testing it would require paired data on self-inspection findings and subsequent regulatory findings at the same sites, which are not currently available in the public domain.

4 CONCLUSION

Self-inspections remain substantially less studied than regulatory inspections, and the literature that exists is dominated by guidance rather than by empirical research. Published deficiency data show that sterile manufacturing accounts for a disproportionate share of critical and major findings, concentrated in environmental monitoring, contamination control and aseptic practice, cleaning and disinfection, facility condition, investigation and CAPA quality, and the integrity of monitoring records. These clusters have been stable for a decade and lie within the detectable scope of an internal audit, which suggests that the binding constraint on self-inspection effectiveness is the depth of the audit rather than its coverage: risk-based plans that do not change, audit teams without microbiological or computerised-systems competence, corrective actions that terminate in retraining, and a quality culture in which uncomfortable findings are costly to raise.

Four lines of research follow from this. First, empirical cross-sectional studies of self-inspection practice at sterile sites, including the composition and competence of audit teams. Second, the development and validation of an instrument for measuring self-inspection programme maturity, comparable to those that exist for CAPA and quality culture. Third,

paired analysis of internal audit findings and subsequent regulatory findings at the same sites, which would convert the central proposition of this review into a testable hypothesis. Fourth, investigation of how digitalisation, including electronic quality management systems and automated environmental monitoring, changes what internal audits detect and what they cease to observe. Central and Eastern European sites, Bulgaria among them, are under-represented in all four areas, and are an obvious place to begin.

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All authors declare no conflict of interest in relation to this manuscript. She performs GMP, GDP, GCP and GVP audits in a professional capacity; no audited organisation contributed to, reviewed or funded this manuscript.

Author contributions

KIT, ASV-M and AHS contributed equally to the conception and design of the study, the literature search and screening, data extraction and drafting of the manuscript. AHS reviewed and critically revised the final version. All authors read and approved the final manuscript.

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