





## Original Article

# Evidence of transmission of New Delhi metallo- $\beta$ -lactamase-producing *Klebsiella pneumoniae* through a gastrointestinal endoscope without an elevator channel

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## Abstract

**Objective:** To investigate the source and transmission dynamics of an endoscope-associated New Delhi metallo- $\beta$ -lactamase-producing *Klebsiella pneumoniae* (NDM-KP) outbreak.

**Design:** Epidemiological and genomic investigation.

**Setting:** Academic acute care hospital in New Jersey.

**Patients:** Five patients with active NDM-KP infection identified on clinical isolates, and four NDM-KP colonized patients identified via rectal swab screening.

**Results:** Over a twelve-month period, nine patients were identified with NDM-KP infection or colonization. Whole-genome sequencing (WGS) revealed that all of the identified cases were related by 25 mutational events or less. Seven of the cases were linked to gastrointestinal endoscopic procedures (four clinical cases and three positive screens among patients exposed to endoscopes suspected of transmission). Two cases demonstrated delayed transmission that occurred five months after the initial outbreak, likely through shared usage of a non-therapeutic gastroscope without an elevator channel.

**Conclusions:** Although all endoscope cultures in our investigation were negative, the epidemiological link to gastrointestinal endoscopes, the high degree of relatedness via WGS, and the identification of asymptomatic NDM-KP colonization among patients exposed to shared endoscopes make the endoscopic mode of transmission most likely. This investigation highlights the probable transmission of NDM-KP via a gastroscope without an elevator channel, observed several months after an initial outbreak. We hypothesize that persistent mechanical defects may have contributed to the delayed device-related transmission of NDM-KP.

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## Introduction

Transmission of carbapenem-resistant Enterobacterales (CRE) through contamination of duodenoscopes and echoendoscopes has been well-described.<sup>1–3</sup> Residual contamination after endoscope reprocessing has been linked to complexities in the design of elevator channels, prompting the U.S. Federal Drug Administration (FDA) to work with manufacturers to redesign devices to allow for more

effective cleaning and disinfection.<sup>4</sup> Few cases of gastroscope-associated infections have been reported,<sup>5</sup> despite a recent meta-analysis demonstrating higher surveillance contamination rate of gastroscopes compared to duodenoscopes.<sup>6</sup> It is evident that the risk for contamination extends beyond the elevator mechanism,<sup>6,7</sup> however, the discrepancy between the increased estimated device contamination rate and decreased reported infection rate of gastroscopes compared to duodenoscopes is unclear.<sup>8</sup>

We describe a multi-patient outbreak of New Delhi metallo- $\beta$ -lactamase-producing *Klebsiella pneumoniae* (NDM-KP), including an episode of delayed transmission most likely via an upper gastroscope without an elevator channel, several months after the initial outbreak. We hypothesize that physical damage and

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mechanical defects of the endoscope played a contributing role to the presumed persistent contamination and transmission of NDM-KP.

## Methods

The work described was performed as a quality improvement project and qualified for Institutional Review Board exemption as per HRP-309 criteria.

### Case definition

Any patient receiving care at a New Jersey health system from January 1, 2022 to August 1, 2023 with a clinical isolate of NDM-KP within 40 mutational events (MEs)<sup>9</sup> of the index case identified in March 2022.

### Outbreak investigation

Clinical and epidemiologic review of all patients with NDM-KP clinical or surveillance isolates between January 1 and Dec 2022 was performed by the hospital's Infection Prevention department in collaboration with the New Jersey Department of Health (NJ DOH). Case review of medical records was performed, including bed tracing, source of admission, and admission to other NJ facilities in the prior six months. A review of procedures and surgeries performed in the prior three months was also performed, including dates and serial numbers of medical devices used.

### Microbiology

Clinical isolates of carbapenem-resistant *K. pneumoniae* (CRKP) were identified by BD Phoenix automated identification and susceptibility testing system (BD, Franklin Lakes, NJ). CRKP was defined as any *K. pneumoniae* isolate resistant to ertapenem, meropenem, and/or imipenem per Clinical Laboratory and Standards Institute (CLSI) M100 guidelines. CRKP isolates were tested for *bla*<sub>NDM</sub> at the NJ DOH utilizing the ARM-D kit,  $\beta$ -lactamase (Streck, Omaha, NE).

Rectal samples obtained for NDM-KP surveillance were collected using Copan Cepheid Sample Collection Device (Liquid Stuart Swabs 900-0370). The swabs were tested using Cepheid® Xpert® Carba-R PCR to detect *bla*<sub>NDM</sub> and other carbapenemase genes. PCR-positive swabs were inoculated to CHROMagar™, mSuperCARBA™, Direct MacConkey Agar, and MacConkey broth. Suspect colonies were isolated to Thermo Scientific™ Remel™ Blood agar (TSA w/Sheep Blood) and tested by multiplex real-time PCR assays to confirm the *bla*<sub>NDM</sub> gene as described in Prussing et al<sup>10</sup> followed by organism identification by MALDI-TOF MS.

Sampling and culturing of gastrointestinal endoscopes was performed following the 2018 FDA/CDC protocol.<sup>11</sup> Endoscopic accessories, including the connecting tubing of the endoscope channels, were also cultured. Surveillance cultures of the disinfected duodenoscopes had been performed according to the standardized FDA protocol, by brushing the distal end of the scopes and rinsing the operating, suction, and air/water channels with a total volume of 80 mL sterile saline solution. Brushes were vortexed for 20s in saline. Liquid samples (including the saline in which the brush heads were sonicated) were centrifuged at 5000×g for 15 min. Pellets were resuspended in 0.1 mL of Dey-Engly broth. Two drops of each suspension was then added to 5 mL of thioglycolate broth and the remainder was spread on blood agar plates. Plates and broths were incubated at 37C in 5% CO<sub>2</sub> for

72 hr. Sampling of gastrointestinal endoscopes used on October 2022 cases was also performed via a modified technique with the PULL THRU brush as described in Cattoir et al<sup>12</sup> and cultured per the above described protocol.

Environmental sampling of water sources were performed in November 2022 using OMEGA E.Z.N.A. Water DNA kit (OMEGA, USA). Environmental sources sampled included Automated Endoscope Reprocesser (AER) drains and filters (six samples each) and two waste disposal drains in the soiled utility section of the Reprocessing Unit. Samples were collected following Joint Commission Guidelines standards over 25 cm<sup>2</sup> using sterile culturettes. Samples were plated on *Klebsiella* selective media and tryptic soy agar (TSA) culture media.

### Whole-genome sequencing

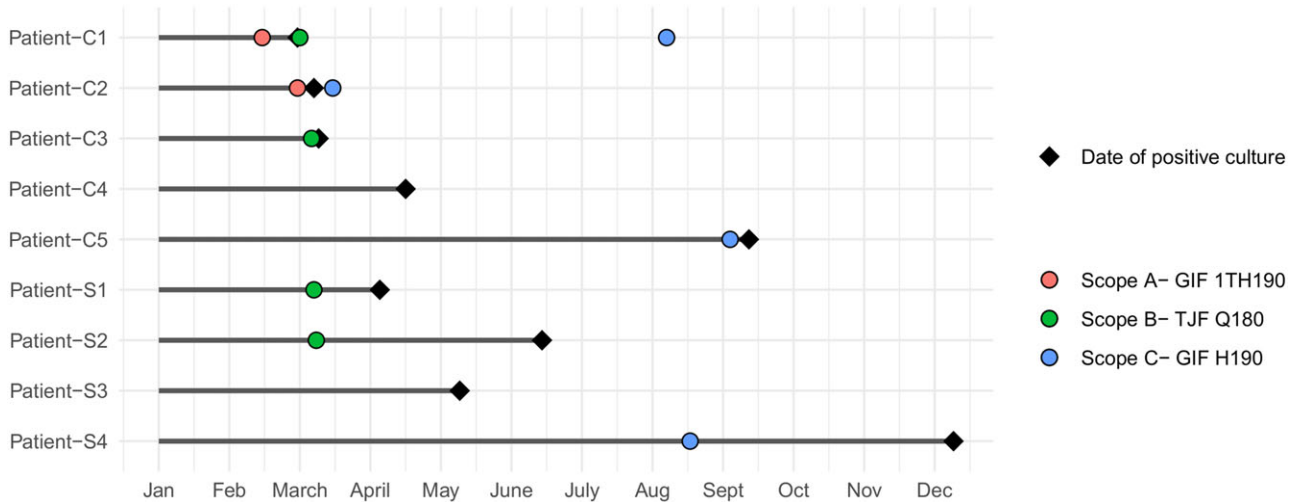
WGS of NDM-KP isolates was performed at the Wadsworth Center, New York State Department of Health sequencing core. WGS was done with Illumina NextSeq 500 and 550. The bioinformatic pipeline used to generate the data is described in Haas et al<sup>13</sup> The bioinformatic pipeline included the use of: Trimmomatic v0.38 for trimming raw Illumina reads,<sup>14</sup> SPAdes v3.12.0 for contig assembly,<sup>15</sup> Minikraken v1.1 for detecting contamination in contigs,<sup>16</sup> Mash v1.1 for reference selection,<sup>17</sup> BWA v0.7.17 and SAMtools v1.9 for mapping against a reference genome,<sup>18</sup> FreeBayes v1.0.2,<sup>19</sup> vcfliib v1.0.0\_rc1 (<https://github.com/vcfliib/vcfliib>), and BCFTools mpileup v1.9<sup>18</sup> for detecting and selecting high quality single nucleotide polymorphisms (SNPs) as well as short insertion/deletion (indel) events encompassing 1–100 nucleotides. Isolates were compared to each other by mutation events (ME). A mutation event includes both SNPs and indels 1–100 nucleotides long. A ME matrix was constructed by pairwise comparison of all reference-aligned sequences and counting MEs.

## Results

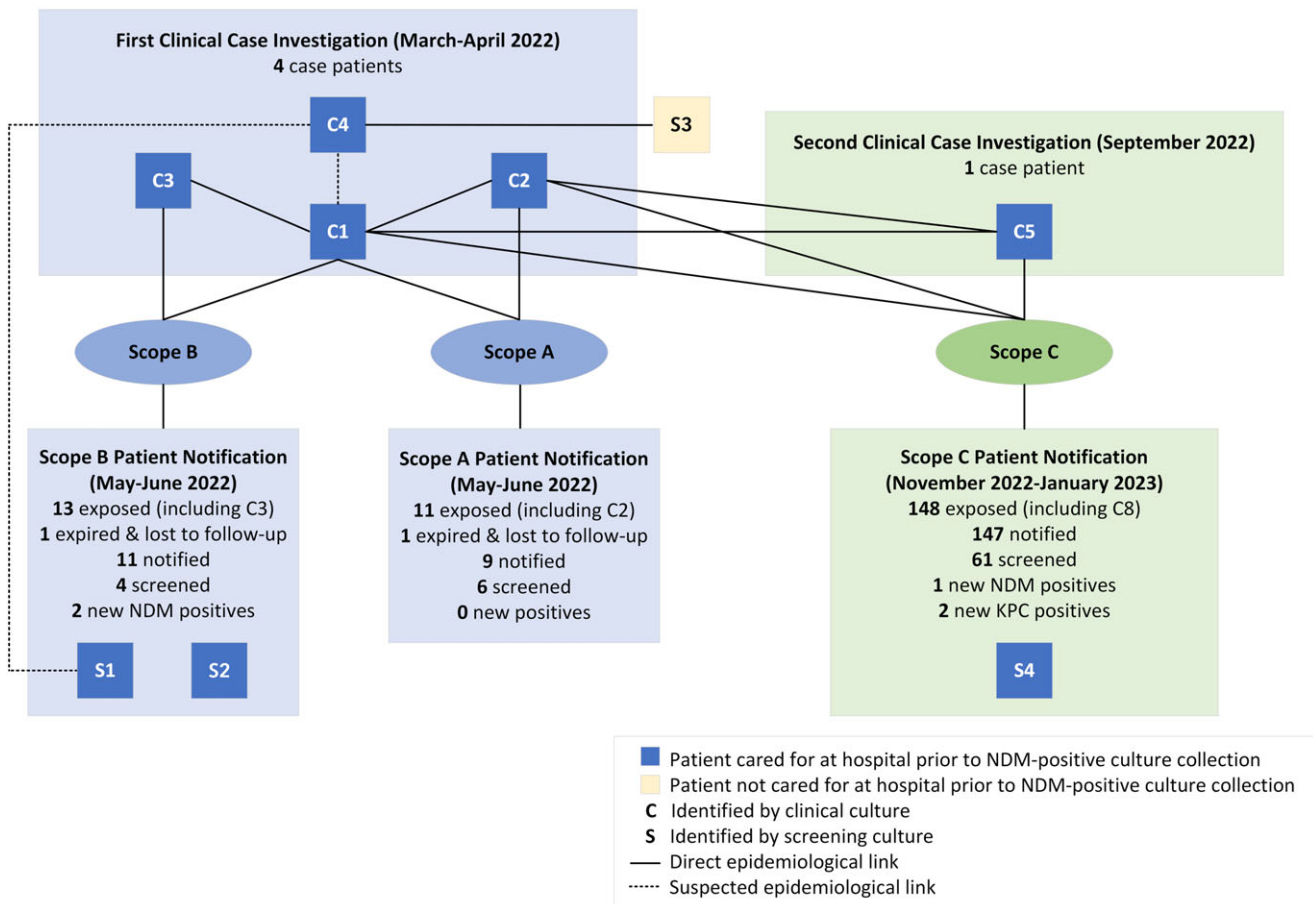
### Outbreak characteristics and investigation summary

In March 2022, a CRKP isolate (Patient-C1) with resistance to ceftazidime-avibactam and meropenem-vaborbactam was identified from an abdominal abscess culture obtained by CT-guided percutaneous aspiration of a patient transferred from an outside hospital six weeks earlier with necrotizing pancreatitis. Carbapenemase testing of the isolate confirmed NDM-KP. The patient had no history of international travel history or prior NDM-KP infection. The patient underwent six upper gastrointestinal endoscopic procedures during admission prior to NDM-KP identification, including three necrosectomies, stenting of previously placed lumen-apposing metal stents (LAMS), placement and subsequent removal of percutaneous endoscopic gastrojejunostomy (PEG-J). Within two weeks of the first case identification, two additional patients (Patient-C2 and Patient-C3) admitted to the same unit as Patient-C1 were found to have NDM-KP isolates from abdominal abscesses (Figure 1). A point prevalence survey (PPS) of patients residing on the same unit as the index patient was performed using rectal swabs. 21 patients had rectal samples collected and cultured; none tested positive for NDM-KP (Figure 2).

None of the patients had international travel history or prior hospitalizations at shared facilities, though all patients demonstrated at least one risk factor for multi-drug resistant organism acquisition, including underlying malignancies, prior and/or prolonged hospitalizations, or recent antibiotic use. Patient-C1, Patient-C2, and Patient-C3 had all undergone gastrointestinal



**Figure 1.** Timeline of identified NDM *Klebsiella pneumoniae* isolates. Isolates identified from clinical infections are identified C1–C5. Isolates identified from rectal swab screening are identified S1–S4.



**Figure 2.** Network diagram of NDM *Klebsiella pneumoniae* isolates and screening procedure.

endoscopic procedures within two weeks prior to their infection, including four instances of shared devices with the index case prior to positive NDM-KP culture. The shared devices included one gastroscope (GIF-1TH190-Scope A) and one duodenoscope with fixed end caps (TjF-Q180V-Scope B). The shared devices were sequestered, underwent sampling and culturing, and were

returned to the manufacturer and a third-party agency for examination of physical defects. Although all device cultures were negative for bacterial growth, review of inspection and repair records identified physical damage, including critical failures, scratches, and use of non-manufacturer components (Supplementary 2).

Patient-C1	0	2	8	11	4	15	5	15	14
Patient-C2	2	0	6	11	3	14	5	15	12
Patient-C3	8	6	0	11	8	13	6	15	18
Patient-C4	11	11	11	0	13	19	9	14	21
Patient-C5	4	3	8	13	0	15	7	17	15
Patient-S1	15	14	13	19	15	0	13	23	24
Patient-S2	5	5	6	9	7	13	0	14	16
Patient-S3	15	15	15	14	17	23	14	0	25
Patient-S4	14	12	18	21	15	24	16	25	0
	Patient-C1	Patient-C2	Patient-C3	Patient-C4	Patient-C5	Patient-S1	Patient-S2	Patient-S3	Patient-S4

**Figure 3.** Mutational event matrix of NDM *Klebsiella pneumoniae* isolates. A mutation event includes both single nucleotide polymorphisms (SNPs) and insertion/deletion events (indels) 1–100 nucleotides long.

The decision was made to notify patients who were exposed to shared endoscopes between the index case and discovery of secondary case. Twenty-four patients were identified as exposed and eleven patients elected to undergo rectal swab screening for NDM-KP, 2/11 (18%) resulted positive (Patient-S1, Patient-S2).

Another case of NDM-KP (Patient-C4) was identified from a urine culture of a patient hospitalized with asymptomatic bacteriuria in late April 2022. Patient-C4 had no prior endoscopy and was admitted to a different unit than prior cases, triggering a PPS of this unit; no new cases were identified among 22 patients screened. Of note, Patient-C3, Patient-S1, and Patient-C4 had recent procedures by interventional radiology (Patient-C3 and Patient-S1 abdominal abscess drainage, Patient-C4 carotid stenting). The possibility of IR transmission was investigated; case review revealed that all procedures occurred on different dates and none shared the same procedure rooms, however, this was the only commonality identified between C4 and other genetically-related cases identified at the acute care hospital.

NDM-KP isolates from all seven patients underwent WGS (Figure 3). WGS of an additional NDM-KP isolate outside our health system by the NJDOH also revealed that the Patient-C4 was most closely related to an additional patient that was never admitted to our hospital (Patient-S3), indicating subsequent transmission likely occurred at the commonly shared nursing home following Patient-C4's acute care hospital admission.

An audit of endoscope reprocessing was performed by an outside consultant in April 2022, revealing potential cross-contamination during manual cleaning and episodes of delayed device preprocessing. Best practices for infection prevention and reprocessing were reviewed with staff and closer monitoring for compliance was instituted. All duodenoscopes were transitioned to disposable end cap models (TJF-Q190V) in June 2022.

In September 2022, an 8<sup>th</sup> case of NDM-KP infection (Patient-C5) was identified in a patient admitted for elective pancreaticoduodenectomy who underwent two endoscopic procedures to treat a postoperative biliary leak. The patient had no hospitalizations or prior nursing home stays or history of international travel. WGS of the NDM-KP isolate from this patient revealed a two ME difference from Patient-C2 (in March 2022). Two shared gastroscopes were identified with Patient-C2 (GIF-1TH190-Scope A and GIF-H190-Scope C). GIF-H190 and GIF-1TH190 are gastroscopes

without an elevator channel. Both devices were sampled per FDA protocols and a second time using the modified technique with PULL THRU brush in attempts to increase sample yield; cultures of all samples were negative. A total of 148 patients were exposed to GIF-H190 between April and October 2023. Of 61 patients exposed to GIF-H190 who elected to undergo colonization screening; 1/61 (2%) was positive (Patient-S4), with 14 MEs from Patient-C2.

### Microbiology and molecular typing

Genomic comparison of nine NDM-KP isolates (eight isolates from hospital patients and one from an associated nursing home) demonstrated that all nine isolates were closely related. The isolates were all MLST 4843 and harbored the *bla*<sub>NDM-1</sub> gene variant. Using WGS, the nine isolates were found to differ by 25 or fewer MEs from each other. The isolate (Patient-S4) with the greatest number of MEs compared to other isolates was notably identified by surveillance cultures after prolonged asymptomatic colonization.

### Repair history

Investigation revealed that between 1/1/22 and 7/1/22 there were four separate servicing repairs at our hospital for Scope C (GIF-H190), including: insertion tube replacement, bending rubber replacement, and fluid removal (1/7–2/1); biopsy channel replacement, bending rubber replacement, and fluid removal (4/19–4/27); biopsy channel and light guide tube replacement (5/18–6/1); insertion tube replacement and bending rubber replacement (7/12–7/22). No other endoscopes identified in this outbreak had multiple repairs for defects resulting in fluid intrusion.

### Quality improvement

The quality improvement measures implemented because of this outbreak investigation included standardizing the endoscope drying process to CDC guidelines, reducing time delay between endoscope procedure and manual cleaning of instruments, retraining staff on core infection prevention measures, instituting endoscope culturing for surveillance, and transitioning to duodenoscopes with disposable endcaps or fully disposable duodenoscopes. Borescopic evaluation of endoscopes was initiated and the hospital switched endoscope repair work from a third-party company to the device manufacturer. No further cases of postendoscopy NDM-KP infection or colonization have been identified to date.

### Discussion

Although *Klebsiella pneumoniae* carbapenemase (KPC) remains the predominant carbapenemase in the United States, there is a growing concern surrounding non-KPC carbapenemases. Data from the CDC Antibiotic Resistance Laboratory Network 2017 to 2019 showed 6% of *Klebsiella spp.* isolates carried New Delhi metallo- $\beta$ -lactamase (NDM).<sup>20</sup> The study also demonstrated increased prevalence of NDM-producing CRE in the northeast region, where 16% of CRE isolates harbored NDM.<sup>20</sup>

Over a twelve-month period, nine patients were identified with NDM-KP infection or colonization, with all cases closely related by WGS. Seven of the cases were linked to gastrointestinal endoscopic procedures, highly suggestive of device-related transmission. Our conclusions are limited by the fact all endoscopic cultures remained negative. We additionally recognize genomic relatedness



determined by WGS is not sufficient to confirm transmission, but when interpreted in conjunction with epidemiological links of shared procedures and negative workup for environmental sources, is highly suggestive of endoscope device transmission. Of particular interest, two cases (C5, S4) demonstrated delayed transmission events that occurred five months after the initial spring outbreak, likely through shared usage of a non-therapeutic gastroscope without an elevator channel (Scope C). Patient S4 was not exposed to any other endoscopes used on any other NDM-KP cases, and was identified via rectal swab surveillance cultures of patients exposed to Scope C, making Scope C the most likely mode of transmission. Following the implementation of quality improvement measures in endoscope reprocessing, the transition to duodenoscopes with disposable endcaps, and removal of devices with repeated repairs, no further cases of postendoscopy NDM-KP infection have been identified.

Despite adherence to FDA/CDC guidelines with modifications to the brush method to improve sensitivity,<sup>12</sup> all endoscope cultures in our investigation remained negative. It is important to note that the lack of positive culture results does not rule out contamination of the scopes. Strong epidemiological and genomic evidence and the absence of further cases following the implementation of quality improvement measures in endoscope reprocessing support the transmission via endoscopic procedures during this outbreak. Multiple guidelines exist for sampling and routine microbiological surveillance of endoscopes and vary by frequency, methodology, and bacterial threshold required for a positive screen.<sup>21</sup> The current FDA/CDC/ASM guideline currently suggest the flush-brush-flush sampling method for channels with available brushes, which has shown higher sensitivity than other methods of surveillance including conventional flush sampling with sterile water or saline without a brush.<sup>11,12,21</sup> Beyond the sampling method, other factors such as culture media, incubation temperature and duration, and sample concentration techniques can influence the sensitivity of endoscopic surveillance.<sup>22</sup> The lack of positive endoscope culture in our outbreak underscores the challenges associated with microbiologic surveillance of medical equipment. The possibility of “false-negative” or “false-positive” results should be considered when considering the utility of implementing endoscope surveillance programs.<sup>23</sup> Endoscope culture surveillance is not required by regulatory bodies and may not be cost effective in settings of low CRE prevalence.<sup>24</sup> Other risk mitigation strategies include adenosine triphosphate testing for residual bio burden after reprocessing or utilization of single use endoscopes on patients with or at risk for CRE colonization.<sup>25–27</sup>

Most endoscopic CRE outbreaks have been linked to duodenoscopes with elevator mechanisms that are prone to persistent bacterial contamination despite appropriate reprocessing per manufacturer instructions. In a 2018 systematic review of endoscope-associated infections, only one out of eighteen outbreaks was associated with gastroscope transmission. As we found in our investigation, gastroscopes can carry risk for persistent bacterial contamination as well. Presently, the standard of care for endoscope reprocessing involves manual cleaning and high-level disinfection (HLD). Despite these measures, bacterial contamination and outbreaks persist due to the intricate design of endoscopes and the formation of biofilms. Adopting sterilization as a method of decontamination could potentially enhance the safety margin and improve decontamination rates. However, there are several barriers to sterilization, including the heat labile devices unsuitable for steam sterilization, high toxicity and endoscope degradation with ethylene oxide, and incomplete penetration of narrow channels with

vaporized hydrogen peroxide.<sup>28,29</sup> Due to the inability to undergo sterilization for duodenoscopes, the FDA has recommended using duodenoscopes with disposable elevator caps to minimize the risk of patient infection.<sup>30</sup> It is important to acknowledge that disposable elevator caps do not address potential contamination in other parts of the duodenoscope or in endoscopes without elevator channels. Therefore, continued innovation is needed to develop reusable endoscopes suitable for either heat or chemical sterilization.

Leak-testing and visual inspection remain important alarm systems for early detection of damage and defects among devices during endoscope reprocessing. Current guidelines from the Association for the Advancement of Medical Instrumentation (AAMI) ST91:2021 propose that visual inspection of the internal components via borescope evaluation may be useful for identifying occult damage and residual intraluminal debris or residue. The Scope C gastroscope in this outbreak associated with delayed transmission was notably sent to a repair company four times over the span of seven months, and we hypothesize that the persistent defects likely predisposed the scope to bacterial biofilm formation and contamination.

In conclusion, strong epidemiologic evidence supported by genomic data demonstrate the putative transmission of NDM-KP via a gastroscope without an elevator channel, observed several months after the initial outbreak. The delayed transmission is potentially due to challenging-to-repair mechanical defects and damage, the limitations of HLD, and the lack of options for disposable components in gastroscopes. Continued efforts are needed to improve reprocessing protocols, enhance surveillance methods, and develop innovative endoscope designs that ensure patient safety during endoscopic procedures.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/ice.2024.55>.

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**Competing interests.** All authors report no conflicts of interest relevant to this article.

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