

# Risk evaluation of duodenoscope-associated infections in the Netherlands calls for a heightened awareness of device-related infections: a systematic review

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 Appendices 1 s, 2 s

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## ABSTRACT

**Background** The risk of exogenous infections from endoscopic procedures is often cited as almost negligible (1 infection in 1.8 million procedures); however, this risk is based on older literature and does not seem to match the number of infectious outbreaks due to contaminated duodenoscopes reported after endoscopic retrograde cholangiopancreatography (ERCP). Using Dutch data, we aimed to estimate the minimum risk of duodenoscope-associated infection (DAI) and colonization (DAC) in patients undergoing ERCP.

**Methods** A systematic literature search identified all DAI outbreaks in the Netherlands reported between 2008 and 2019. Included cases were confirmed by molecular matching of patient and duodenoscope cultures. Risk ratios were calculated based on the total number of ERCPs performed during the study period.

**Results** Three outbreaks were reported and published between 2008 and 2018, including 21 confirmed DAI cases and 52 confirmed DAC cases. The estimated number of ERCPs performed during the same period was 181 209–227 006. The calculated minimum estimated DAI risk was approximately 0.01% and the minimum estimated DAC risk was 0.023%–0.029%.

**Conclusions** The estimated risk of DAI in Dutch ERCP practice was at least 180 times higher than previously published risk estimates. The actual risk is likely to be (much) higher due to underreporting of infections caused by multidrug-resistant organisms and sensitive bacteria. Greater awareness by healthcare personnel involved in endoscopy and endoscope cleaning is required, as well as innovative technical solutions to contain and ultimately eliminate DAIs.

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## Introduction

Over the years, an increasing number of reports have appeared in the literature describing the risk of patient-to-patient transmission of bacteria by duodenoscopes. These outbreaks were mainly noted and linked to contaminated duodenoscopes through involvement of a multidrug-resistant organism (MDRO), with patients becoming colonized, infected, or dying as a consequence of the infection [1]. Transmission of MDROs through a contaminated medical instrument is considered a preventable event. With duodenoscopy, however, it has become apparent that predictable and adequate decontamination of reusable duodenoscopes is difficult to achieve [2, 3]. In order to determine the extent to which patient-to-patient transmission of bacteria through duodenoscopes contributes to this problem, it is important to understand and scientifically estimate the risk of endoscopy-associated infection (EAI) or, more specifically, of duodenoscope-associated infection (DAI).

For decades, articles and guidelines focusing on transmission of microorganisms through endoscopes cite a report from the American Society for Gastrointestinal Endoscopy (ASGE) published in 1993 by Kimmey et al. [4]. In this study, it was calculated that 1 in every 1.8 million gastrointestinal endoscopies leads to an EAI. However, 20 years later, Ofstead et al. argued that this estimate was partly based on erroneous assumptions [5]. Nevertheless, this risk estimate is still often cited in articles, although intuitively it seems to be an underestimation considering the number of reports that have been published worldwide over the past decade concerning the spread of microorganisms from contaminated duodenoscopes [1, 6].

Attempts to establish a more precise and up-to-date risk estimation are fraught with multiple challenges and difficulties. First, the literature reports, almost exclusively, outbreaks concerning MDROs, which suggests reporting bias. DAIs are exogenous infections as they are caused by microorganisms originating from outside the patient's body, and such infections should be avoided at all times [7]. Endogenous infections are caused by translocation of microorganisms from the patient's own intestinal flora and are an inherent risk of any endoscopic procedure [8]. Moreover, DAIs with sensitive (nonresistant) microorganisms are easily mistaken for endogenous infections and are thus rarely linked to a contaminated endoscope. Finally, not all outbreaks with MDROs are published, and a reliable registry or (mandatory) surveillance system on contaminated endoscopes and transmission to patients is lacking.

The aim of the current study was to calculate a scientifically based minimum risk estimate of DAI and duodenoscope-associated colonization (DAC) by analyzing published outbreaks over an 11-year period in the Netherlands.

## Methods

### Literature search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist were followed for this systematic review (see **Appendix 1 s** in the online-only Supplementary material) [9]. A systematic literature search was

conducted in Embase, Medline, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and Google Scholar. Key words used were “duodenoscope,” “ERCP,” “outbreak,” and “infection” (**Appendix 2 s**). The last search was performed on 15 July 2020. Titles and abstracts were screened to filter outbreak reports based on contaminated duodenoscopes in the Netherlands. Next, the remaining full-text publications were reviewed for original medical content on outbreaks in the Netherlands. The details of these outbreaks were reviewed and noted. References of the selected papers were screened for suitable publications that could be added to the review.

### Outcomes

The primary outcome of this systematic review was the risk of DAI and DAC in the Netherlands calculated per ERCP procedure. Therefore, we counted the DAI and DAC cases described in the outbreak reports. For this study we defined DAI cases as patients reported to have developed a clinical infection caused by the same microorganism (confirmed to be indistinguishable through molecular typing) as that found on the duodenoscope used in the patient during a previous ERCP procedure. Patients were regarded to be infected when they had a fever (temperature  $\geq 38.1\text{C}^\circ$ ) and other signs such as leukocytosis, sepsis, or septic shock [10]. DAC cases were defined as patients who were previously treated with a contaminated duodenoscope and were found to carry the same microorganism at any body site, as confirmed through molecular typing, with or without clinical signs of infection. Thus, DAC cases also included all DAI cases. This approach was chosen because infected patients were, by definition, colonized prior to the infection and could therefore not be separated from colonized patients. Patients who were not treated with one of the contaminated duodenoscopes but were found to be colonized or infected with the corresponding microorganisms through other transmission routes, were not included as cases in this study.

### Estimating ERCP numbers

The total number of ERCPs performed annually in the Netherlands was obtained by consulting the Dutch Hospital Data (DHD) database (Utrecht, the Netherlands), which collects data from all Dutch hospitals. In 2014, the DHD started to collect and store ERCP data using a new method, which no longer supported data searches for previous years, and therefore the database only provides national numbers of ERCP procedures performed since 2014. The total number of ERCPs performed in 2012 was retrieved from an article by Ekkelenkamp et al. on ERCP performance in the Netherlands (**► Table 2**) [13], using ERCP numbers from the DHD; however, the original search of Ekkelenkamp et al. could not be repeated and confirmed. The annual ERCP numbers in 2008–2011 and 2013 were estimated using the available data.

### Statistical analyses

To take account of the uncertainty about the numbers of ERCPs in the years before 2014, the analysis was performed by fitting two linear regression models to the data based on two different scenarios: in scenario 1, the number of ERCPs performed per

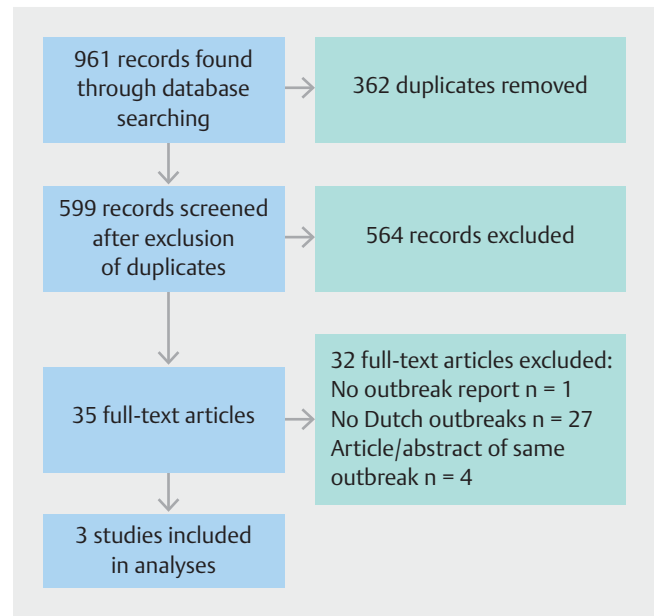
year was assumed to be constant over time; in scenario 2, the number of ERCPs was assumed to have a linear trend over time. The estimated number of ERCPs and corresponding 95% prediction intervals (PIs) obtained from these models, taking account of parameter uncertainty as well as the random variation of the observed values, were used to determine a rough estimate of the missing number of ERCPs.

Risk estimates were calculated by dividing the number of DAIs by the total number of ERCPs performed during the corresponding time frame. This total number of ERCPs was calculated as the sum of the known and estimated numbers of ERCPs. To take full account of the uncertainty over the unobserved numbers of ERCPs, we additionally calculated intervals for the risk estimates based on the boundaries of the PIs of the estimated numbers of ERCPs. The same procedure was followed for the number of DACs due to contaminated duodenoscopes. All models were produced using R version 3.6.1 (R: R Core Team, Vienna, Austria, 2019–07–05).

## Results

Through our literature search we found 599 unique articles and abstracts (► Fig. 1). After screening, 35 full-text articles were assessed further for eligibility and 3 articles reported unique DAI outbreaks in the Netherlands [10–12]. Most of the remaining 32 articles were excluded because they did not report an outbreak in a Dutch hospital (n = 27).

The three outbreaks reported from the Netherlands involved a total of 21 DAI cases and 52 DAC cases (► Table 1). All three outbreaks involved the spread of MDROs, two outbreaks with *Pseudomonas aeruginosa* and one with *Klebsiella pneumoniae*. Active screening of colonized patients was performed in the outbreaks at the University Medical Center (UMC) Utrecht and Erasmus MC in Rotterdam. The outbreak at the UMC Groningen was reviewed for records of patients treated with the contami-



► Fig. 1 Flow diagram of study selection.

nated duodenoscope; however, no active screening was performed. In the UMC Utrecht outbreak, two contaminated duodenoscopes caused transmission of the MDRO; in the other two outbreaks, transmissions were related to a single contaminated duodenoscope at each center. The reported outbreaks occurred between 2008 and 2015; therefore, we searched for the total number of ERCPs performed in the years 2008–2018. As outbreaks in 2019 might not yet be reported in literature, the year 2019 was not included in the calculations.

► Table 1 Colonization and clinical infection in the three outbreaks.

	UMC, Groningen	Erasmus MC, Rotterdam	UMC, Utrecht	Total
Year of outbreak	2008	2012	2015	
Duodenoscope model	Olympus (model unknown)	Olympus TJF-Q180V	Olympus TJF-Q180V	
Microorganism	MDR <i>Pseudomonas aeruginosa</i>	MDR <i>Pseudomonas aeruginosa</i>	MDR <i>Klebsiella pneumoniae</i>	
DAC cases, n	3	22	27	52
DAC cases without infection, n	Unknown	14	17	31
DAI cases, n	3	8	10	21
Type of DAIs	3 BSIs	4 BSIs, 3 abdominal infections, 1 respiratory infection	9 sepsis, 1 cholangitis	
Patients exposed to contaminated duodenoscope, n	36	81	73	190
Attack rate per duodenoscope, %	≥8.3	27	29 and 35*	

UMC, University Medical Center; MC, Medical Center; MDR, multidrug resistant; DAC, duodenoscope-associated colonization; DAI, duodenoscope-associated infection; BSI, bloodstream infection.

\* Two contaminated duodenoscopes were responsible for DAIs and DACs in the UMC Utrecht outbreak.

► **Table 2** Estimated number and corresponding 95% prediction interval bounds of endoscopic retrograde cholangiopancreatography (ERCP) procedures for each year using linear and constant models. The total number of ERCPs in 2008–2018 is the sum of the estimated values and the known values for the years 2012 and 2014–2018.

Year	Known value	Estimated value	95%PI estimated value
Scenario 1: constant model			
▪ 2008		19954.20	19 148.21 – 20 760.19
▪ 2009		19954.20	19 148.21 – 20 760.19
▪ 2010		19954.20	19 148.21 – 20 760.19
▪ 2011		19954.20	19 148.21 – 20 760.19
▪ 2012	16 910		
▪ 2013		19954.20	19 148.21 – 20 760.19
▪ 2014	20 284		
▪ 2015	19 939		
▪ 2016	19 855		
▪ 2017	20 110		
▪ 2018	19 583		
Total ERCPs 2008–2018, n		216 452	212 422 – 220 482
Scenario 2: linear model			
▪ 2008		16 644.56	11 099.33 – 22 189.79
▪ 2009		17 026.69	11 970.86 – 22 082.51
▪ 2010		17 408.81	12 811.81 – 22 005.82
▪ 2011		17 790.94	13 612.10 – 21 969.78
▪ 2012	16 910		
▪ 2013		18 555.20	15 033.69 – 22 076.71
▪ 2014	20 284		
▪ 2015	19 939		
▪ 2016	19 855		
▪ 2017	20 110		
▪ 2018	19 583		
Total ERCPs 2008–2018, n		204 107	181 209 – 227 006

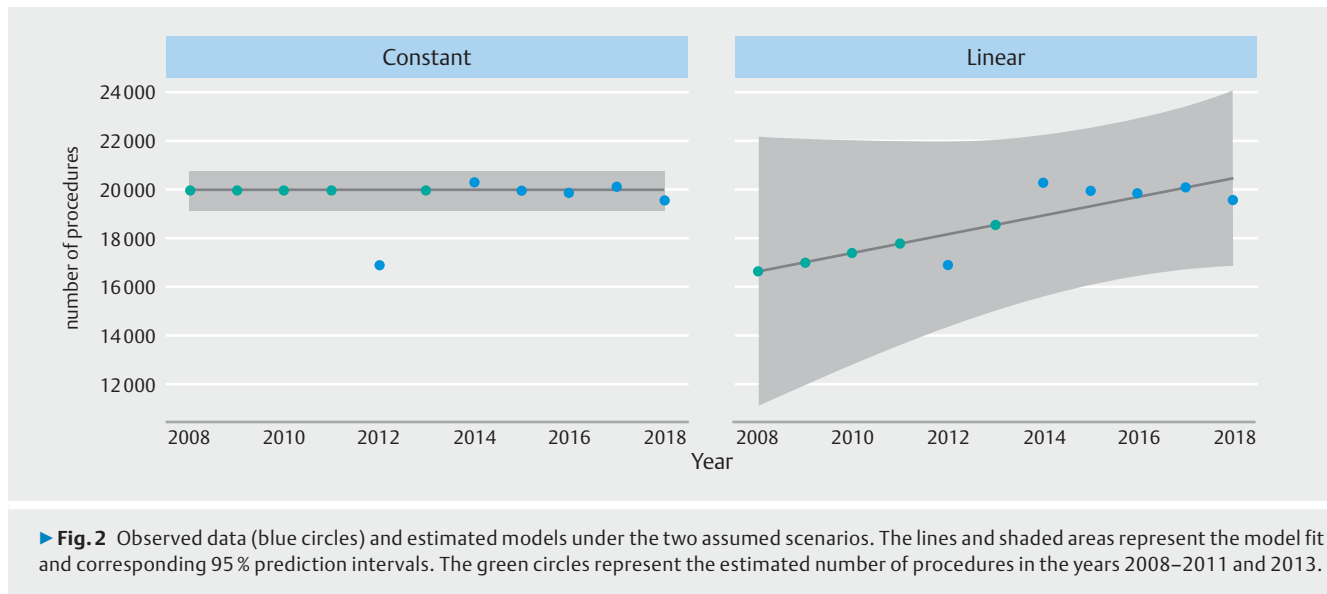
PI, prediction interval.

## Total number of ERCPs

The number of ERCPs in the years 2008–2011 and 2013 was estimated under both scenarios (see Methods; ► **Table 2**, ► **Fig. 2**). As the range of procedures estimated in the constant model lay completely within the range estimated by the linear model, we used the numbers from the linear model for the risk calculations. The resulting estimate for the total number of ERCP procedures in the whole period 2008–2018 was 204 170 (95%PI 181 209–227 006).

## DAI risk calculation

We identified a total of 21 DAI cases (UMC Groningen 3, Erasmus MC 8, and UMC Utrecht 10) over the 11-year study period, none of which resulted in the death of the patient. For our risk calculations, we presumed that in the years no reports were found, no DAIs had occurred (minimum risk calculation). In the same 11-year period, we estimated a total of 204 170 ERCPs across all Dutch ERCP centers. This results in a calculated risk of 0.01% (95%PI 0.0093%–0.0116%) per ERCP procedure for the development of an exogenous infection due to a contaminated duodenoscope, or, put another way, approximately 1 in every 10 000 ERCP procedures.



► **Fig. 2** Observed data (blue circles) and estimated models under the two assumed scenarios. The lines and shaded areas represent the model fit and corresponding 95 % prediction intervals. The green circles represent the estimated number of procedures in the years 2008–2011 and 2013.

As national ERCP data were not available for the period 2008–2012, an additional calculation was performed excluding these years; in addition, the UMC Groningen outbreak was omitted, and the number of nationally performed ERCPs in 2013 was estimated using the linear model. This resulted in 18 DAI cases divided by 135 237 ERCP procedures (95 %PI 131 715–138 758), producing a minimum risk of 0.0133 % (95 %PI 0.0130%–0.0137%), or approximately 1 DAI per 7500 procedures.

### DAC risk calculation

The report on the UMC Groningen outbreak did not include active screening to identify patients who were colonized without having any symptoms. The risk estimate of DAC after ERCP is therefore limited, and in this case underestimated, by the absence of this information. Based on the available data, a total of at least 52 patients were colonized directly through a contaminated duodenoscope (UMC Groningen 3, Erasmus MC 22, UMC Utrecht 27). This results in a minimum risk of becoming colonized with an MDRO due to a contaminated duodenoscope of 0.025 % per ERCP procedure (95 %PI 0.023%–0.029%), or 1 DAC per 4000 ERCP procedures.

### Discussion

With a minimum calculated risk of 0.01 %, the risk of a DAI in this Dutch national study was at least 180 times higher than previously published risk estimates of infection after endoscopy. The risk of becoming colonized with an MDRO when undergoing an ERCP was at least 0.023%–0.029%. The actual risk is likely to be (much) higher due to underreporting of both MDRO infections and those caused by sensitive bacteria. First, DAIs are not always recognized, thus causing detection bias, and second, even when DAIs are recognized, they are not always published, leading to reporting bias. Moreover, cultures from a contaminated scope may produce false-negative results and hamper the establishment of such association; however, the false-negative rate is unknown.

It is important to note that our approximation is a model-based estimate of the minimum DAI and DAC risk. Because of the likely presence of reporting and detection biases and of not being able to identify the risk of non-MDRO DAI (i. e. infection with an exogenous sensitive bacterium), our approximations must be regarded as bare minimum estimates and most certainly represent an underestimation of the actual risk. It does show, however, that the risk of developing a DAI is grossly underestimated by previous published risk estimates of EAls. Our minimum risk of developing a DAI was approximately 180 times higher than that reported in a publication on EAls published in 1993 by the ASGE [4]. The large difference can be explained by erroneous assumptions and calculations. For example, the authors used only 28 of the 145 documented transmissions in their calculation, and overestimated the annual number of endoscopy procedures by at least 12 million [5]; in addition, the ASGE based its calculation on all types of gastrointestinal endoscopes and not specifically on duodenoscopes alone. Since this report was published, no risk calculation explicitly for DAIs has been published.

The risk estimate presented here may seem to translate into a relatively small absolute risk, especially compared with the 2%–4% overall risk of severe infections associated with ERCP procedures [14]. However, it is unknown which fraction of these post-ERCP infections is attributable to endogenous infections versus exogenous infections. Most often in clinical practice, the former is assumed and antibiotics are prescribed. In cases of sensitive microorganisms, patients will recover swiftly and few will even consider that the infection might have been caused by exogenous bacteria. Our newly calculated risk estimate, even with the knowledge that it constitutes a bare minimum risk, may not immediately encourage action to be taken. In our opinion, this would be an erroneous conclusion, not only because of the presumptive underestimation of the risk, but also because DAIs are often serious infections.

It is often only due to the interest and alertness of the physician or the hospital infection prevention specialist that an

MDRO infection/outbreak is traced back to a contaminated endoscope. It is even more difficult to estimate the prevalence of infection and colonization with sensitive microorganisms, as these will not become readily apparent as an outbreak, leading to detection bias. Therefore, it is also unclear whether duodenoscopes contaminated with MDROs cause more DAIs than those contaminated with sensitive microorganisms, or whether they are just discovered more quickly.

Importantly, we were able to calculate the “attack rate,” which is the chance of being colonized or infected when undergoing ERCP with an MDRO-contaminated duodenoscope. The two outbreaks mentioning DACs, revealed attack rates of 27%–35% per contaminated duodenoscope. In these outbreaks, 36% (Erasmus MC) and 37% (UMC Utrecht) of the DAC cases developed DAIs. In the Erasmus MC outbreak, patients had a 9.9% risk of developing a DAI after treatment with the contaminated duodenoscope; in the UMC Utrecht outbreak, this risk was 13.7%. Reported attack rates from outbreaks in other countries range from 15% to 41% [15, 16].

In the two duodenoscopes causing DAIs in the UMC Utrecht outbreak, respectively >200 colony-forming units (CFU)/20 mL and 34 CFU/20 mL of the microorganism of interest, in this case gut flora, were detected in the cultures. This suggests that even lower levels of contamination can cause DAIs. Unfortunately, the Utrecht outbreak was the only outbreak in which CFU counts were reported. In international outbreaks, CFUs found in duodenoscopes are rarely mentioned. It is important to consider duodenoscope contamination with >1 CFU of gut microorganisms as a risk to patients and to use sensitive culture methods.

In order to accurately calculate DAI prevalence in daily ERCP practice, a large multicenter study collecting samples from both duodenoscopes and patients before and after ERCP would be necessary; however, this would be a very laborious and expensive undertaking. Deducing prevalence numbers from literature can be complicated by the different definitions of EAls and by the absence of information on endoscope types and evidence of transmission [17]. For instance, the study by Spach et al. reported 180 infections from upper gastrointestinal endoscopy between 1974 and 1991, but did not specify whether transmission was via gastroscopes or duodenoscopes [18]. In addition, it is unclear how the authors defined EAls and what methods were used to prove transmission from endoscopes to patients. Another often cited article dating back to 1991 investigated the prevalence of EAls by sending US endoscopy nurses a questionnaire, and reported that an EAI had occurred in 6% of the endoscopy centers [19]. Interestingly, compared with the reported number of outbreaks caused by duodenoscopes, few outbreaks have been described with other gastrointestinal endoscopes [20, 21]. There are multiple possible explanations for this, including reporting bias, the risk for contamination being dependent on the complexity of the scope design, and the fact that with ERCP, sterile barriers are breached, which is associated with a higher chance of translocation and hence clinical infection. A recent study identified 24 DAI outbreaks worldwide since 2008, including 490 infected patients and 32 deaths; unfortunately it is unclear how many ERCPs were performed during the same period [1]. Curiously, over all these years, out-

breaks have only been reported in the USA, China, and Western European countries (Germany, France, Italy, the Netherlands, Spain, UK). This makes one wonder about the awareness and vigilance regarding DAIs in other areas of the world.

The aforementioned outbreaks have led to the understanding that the complex design of duodenoscopes is responsible for persistent contamination. In particular, the forceps elevator has proven to be a site of bacterial contamination and a source of transmission of microorganisms [22, 23]. In addition, the working channel and the air and water channels are sensitive to biofilm formation, which is notoriously difficult to remove [24, 25]. As a response to the numerous outbreaks based on transmission of microorganisms through duodenoscopes, manufacturers have already implemented several adjustments to duodenoscope design. Detachable and even disposable distal tips (with or without a disposable elevator forceps) have been designed specifically to improve accessibility of the forceps elevator for cleaning and are now recommended by the US Food and Drug Administration. The duodenoscopes used in the three outbreaks were all made by Olympus, and did not contain a disposable cap or elevator, but instead had a concealed distal tip. The TJF-Q180V model, which was associated with two of the three outbreaks, has been used in almost all Dutch ERCP centers, but is often used alongside other models [26]. Therefore, owing to its high market share in Dutch ERCP centers at the time of the studies, it comes as no surprise that this particular model was associated with at least two of the three outbreaks. Importantly, it has been proven that the occurrence of duodenoscope contamination and associated outbreaks can be linked to all available duodenoscope brands [27, 28]. Two fully disposable duodenoscopes have recently been introduced to the market. The design of these devices aims to completely eliminate the risk of exogenous infections [29]. The first studies using disposable duodenoscopes have shown promising results with regard to performance [29, 30], but cost-effectiveness considerations will determine the viability of a (part) conversion to disposable duodenoscopes. Despite the benefits related to avoidance of exogenous endoscope infections, the currently available evidence on technical performance, economics, and the environmental impact of associated waste materials requires further study before widespread use of disposable endoscopes can be advocated.

A limitation of this study is its dependence on published reports of outbreaks or transmissions, making reporting bias likely. It is unclear how many DAIs were not reported during the study period. Another limitation relates to the difficulty in reliably estimating the exact number of ERCPs performed in the Netherlands before 2014. A third limitation is the absence of an active screening protocol to detect colonized patients in the UMC Groningen outbreak, which most likely contributed to the underestimation of the true risk of DAC. Furthermore, we chose to start the study period in the year of the first outbreak report. However, we repeated the calculations for the period 2009–2018, excluding the UMC Groningen outbreak, and using the total estimated ERCP numbers from 2009–2018, and calculated the same DAI risk estimate of 0.01%. Given the limited number of detailed outbreak reports, it is currently not possible

to reliably estimate a maximum risk for the development of exogenous MDRO duodenoscope infections. As the Netherlands has a relatively low MDRO prevalence [31], the risk of MDRO DAIs is likely to be (substantially) higher in countries with a higher overall prevalence of MDROs. Furthermore, reprocessing protocols, the quality of execution and adherence to protocols, sampling and culture methods, and surveillance strategies vary from country to country. Detection and reporting biases are also likely to differ between countries. Therefore, the minimum risk estimate calculated in the current study cannot be generalized to other countries. It would be interesting to assess the minimum risk estimate for the USA using the same method, as most of the reported outbreaks were in this region. However, some of the US reports lack sufficient detail and reliable estimates of annual ERCP volume for the entire USA are not available.

## Conclusion

We estimated a minimum DAI risk of at least 0.01% per ERCP procedure in the Netherlands. Given the likely detection and reporting biases involved, this risk estimation is expected to be an underestimation of the actual risk. More research and vigilance are needed to more reliably assess the incidence and clinical impact of DAIs caused by MDROs and susceptible microorganisms in daily practice. The results of this study call for increased awareness by healthcare personnel involved in endoscopy and endoscope cleaning, and for innovative technical solutions to contain and ultimately eliminate DAIs.

## Competing interests

J.A. Kwakman has received grant funding from Pentax Medical and Boston Scientific. M.C. Vos has received grant funding from 3M, Pentax Medical, and Boston Scientific (development of disposable duodenoscopes). M.J. Bruno is a consultant for Boston Scientific (development of disposable duodenoscopes) and Cook Medical, and has received grant funding from Boston Scientific (development of disposable duodenoscopes), Cook Medical, Pentax Medical, 3M, Mylan, and InterScope. N.S. Erler has no conflicts of interest.

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