

## Original article

## Blood culture diagnostics: a Nordic multicentre survey comparison of practices in clinical microbiology laboratories

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## ABSTRACT

**Objectives:** Accurate and rapid microbiological diagnostics are crucial to tailor treatment and improve outcomes in patients with severe infections. This study aimed to assess blood culture diagnostics in the Nordic countries and to compare them with those of a previous survey conducted in Sweden in 2013.

**Methods:** An online questionnaire was designed and distributed to the Nordic clinical microbiology laboratories (CMLs) ( $n = 76$ ) in January 2018.

**Results:** The response rate was 64% (49/76). Around-the-clock incubation of blood cultures (BCs) was supported in 82% of the CMLs (40/49), although in six of these access to the incubators around the clock was not given to all of the cabinets in the catchment area, and 41% of the sites (20/49) did not assist with satellite incubators. Almost half (49%, 24/49) of the CMLs offered opening hours for  $\geq 10$  h during weekdays, more commonly in CMLs with an annual output  $\geq 30$  000 BCs. Still, positive BCs were left unprocessed for 60–70% of the day due to restrictive opening hours. Treatment advice was given by 23% of CMLs (11/48) in  $\geq 75\%$  of the phone contacts. Rapid analyses (species identification and susceptibility testing with short incubation), performed on aliquots from positive cultures, were implemented in 18% of CMLs (9/49). Compared to 2013, species identification from subcultured colonies ( $<6$  h) had become more common.

**Conclusions:** CMLs have taken action to improve aspects of BC diagnostics, implementing satellite incubators, rapid species identification and susceptibility testing. However, the limited opening hours and availability of clinical microbiologists are confining the advantages of these changes. **Anna Åkerlund, Clin Microbiol Infect 2022;28:731.e1–731.e7**

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## Introduction

Modern healthcare systems depend on rapid and accurate diagnostics to optimize in-hospital care and reduce costs [1]. Early diagnosis and appropriate treatment of severe infections such as

bloodstream infections (BSIs) are crucial for survival [2–4]. Due to the global emergence of multidrug-resistant bacteria, it is important to provide susceptibility reports quickly to guide antibiotic treatment decisions [5,6]. Precision medicine, where decisions on appropriate antibiotic therapy are informed by microbiological reports, ensures that septic patients are offered equal and high standards of care [7–9].

Blood culture (BC) remains the cornerstone of BSI diagnostics. Routine methods applied by clinical microbiology laboratories (CMLs) have changed during the past decades following the introduction of continuous-monitoring automated blood culture

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instruments (BCIs), matrix-assisted laser desorption/ionization—time of flight (MALDI-TOF) mass spectrometry, and total or partial laboratory automated systems [10,11]. Still, there is a need for improvements in the diagnostic chain and increased involvement of clinical microbiologists in treatment decisions [8].

In 2013 the Swedish Reference Group for Antibiotics (SRGA) conducted a nationwide web survey on BC diagnostics [12], resulting in several suggested improvements. The survey addressed several aspects of the diagnostic chain: transportation, business hours, BCI systems, and IT solutions for reporting [12]. The aims of the present study were to survey the current BC diagnostics in the Nordic countries, to compare these with the situation in Sweden 5 years earlier, and to identify diagnostic areas with potential for improvement.

## Materials and methods

The study was conducted in collaboration with the SRGA. The questionnaire was designed using the SurveyMonkey platform (San Mateo, CA, USA). From each country, a national coordinator with long experience in microbiological diagnostics was appointed to aid distribution of the questionnaire to the CMLs and to evaluate the respondents' representativeness. In January 2018, the 76 CMLs in the Nordics (Sweden  $n = 27$ , Finland  $n = 20$ , Norway  $n = 18$ , Denmark  $n = 10$ , Iceland  $n = 1$ ) were invited to participate. The national coordinators provided each laboratory with a unique code (laboratory ID) which the respondents stated in the questionnaire. The authors were provided with a laboratory list and laboratory IDs. The study was closed in February 2018, after one reminder had been sent. No incentives were offered. Ethical approval was not required.

The questionnaire consisted of 50 multiple-choice questions, free to comment, divided into nine sections: background, staffing and working hours, pre-analytical routines, equipment and routines in the catchment area, quality indicators, reporting routines, bacterial species determination and susceptibility testing (Supplementary Material Text S1). Quality indicators, particularly investigated, were different turnaround times (TATs) in the diagnostic process as well as proportion of contaminated BCs and BC signalling after closing hours (Question 20–26, Supplementary Material Text S1). One blood culture was defined as a pair of vials (aerobe and anaerobe) or one paediatric bottle.

Descriptive statistics were performed using Excel (Microsoft Corporation, Redmond, WA, USA). Fisher's exact test was performed in R (version R 3.6.2);  $p < 0.05$  was considered significant.

## Results

### Background

The response rate was 64% (49/76), with the highest participation in Sweden (Table 1). The proportion of responding CMLs classified as university laboratories was 67% (18/27) compared to non-academic laboratories at 63% (31/49). The fraction of responding university CMLs per country was Sweden 7/8, Norway 2/7, Finland 4/5, Denmark 4/6, and Iceland 1/1. For non-academic laboratories the response rates were Sweden 15/19, Norway 8/11, Finland 7/15, Denmark 1/4, and Iceland 0/0. The national coordinators assessed that there was no systematic bias regarding size of hospital, geographical location or population coverage. The most frequent incubation time for BC was 5–6 days, prolonged to 9–14 days on suspicion of fungaemia or endocarditis (Supplementary Material Table S1).

**Table 1**  
Number of participating clinical microbiology laboratories (CMLs), blood culture systems and blood cultures (BCs) analysed annually

Country	Number of responding CMLs/total number of CMLs (%)	Blood culture system			Annual number of blood culture count	Number of CML (%)						Number of CMLs with $\geq 30\,000$ BCs analysed annually (% of responding CMLs)	
		BACTEC (Becton Dickinson)	BacT/Alert (BioMérieux)	VersaTREK (Thermo Fisher Scientific)		0–10 000	10 001–20 000	20 001–30 000	30 001–40 000	40 001–50 000	50 001–60 000		>60 000
Denmark	5/10 (50)	1 (20)	5 (100)		1 (20)						1 (20)	3 (60)	4/5 (80)
Finland	11/20 (55)	5 (45)	6 (55)	1 (9)	1 (9)					1 (9)		1 (9)	3/11 (27)
Iceland	1/1 (100)		1 (100)										0/1 (0)
Norway	10/18 (56)	7 (70)	3 (30)		4 (40)		1 (100)						0/10 (0)
Sweden	22/27 (81)	8 (36)	16 (73)		2 (9)	5 (50)	3 (14)		1 (5)	3 (14)	1 (5)		5/22 (23)
Total	49/76 (64)	21 (43)	31 (63)	1 (2)	8 (16)	23 (47)	6 (12)	2 (4)	2 (4)	4 (8)	2 (4)	4 (8)	12/49 (24)

<sup>a</sup> Some laboratories (one in Denmark, one in Finland and two in Sweden) used two different BC systems.

### Equipment and pre-analytical routines

In 59% of the CMLs (29/49), satellite incubators located outside the laboratory had been introduced at other units in the main hospital and/or other hospitals in the region. Satellite incubators were more common in Norway (90%, 9/10,  $p = 0.07$ ) and Finland (82%, 9/11,  $p = 0.16$ ) (Fig. 1). The majority, 86% (42/49), had arranged for staff from other laboratory specialties or the emergency department to load cabinets, and the possibility of starting incubation around the clock was supported by 82% of the CMLs (40/49) (Supplementary Material Fig. S1). For loading timeframes in laboratories with time-restricted possibilities for starting incubation see Table 2.

### Staffing and working hours

The opening hours of the CMLs' BC departments differed markedly (Supplementary Material Fig. S2). One CML offered a daily 24-h service, while two were closed on Sundays. See Table 2 for mean time service in CMLs with restricted opening hours. Extended opening hours (defined as  $\geq 10$  h/day on weekdays and  $\geq 8$  h/day on weekends) were offered by 49% of CMLs (24/49) Monday–Saturday and 35% (17/49) on Sunday/holidays (Table 3).

Positive BCs were processed by CML technicians until 0.5–3 h before closing time. In 7/29 satellite hospitals, technicians from other laboratory specialties partially handled positive BCs, in some of them around the clock. In 17/29 satellite sites, however, positive vials had to be transported to the central CML for further processing. The timeframe of processing positive BCs in 47/49 of the CMLs is shown in Table 2 and per country in the Supplementary Material Table S2.

For further extension of the BC handling service, 27% of the CMLs (13/49) were considering adding evening shifts for technicians, whereas in 63% (31/49) personnel from other laboratory specialties were involved/planned to be involved in this process.

Medical microbiologists were available in 57% of the laboratories (28/49) on Saturdays and 49% (24/49) on Sundays/holidays.

### Quality indicators

Twenty-two CMLs provided data regarding 'time from sampling to start of incubation'. In 41% of these (9/22), transport time

exceeded 4 h (Supplementary Material Fig. S3). The proportion of contaminated BCs was monitored regularly by 37% (18/49). Other quality indicators such as 'time from sampling to final report', 'time from positive signal to preliminary or final report' and 'proportion of BC signalling after closing hours' were rarely surveyed.

### Reporting routines

During weekdays, new positive BCs were verbally reported to the treating clinician by all but two CMLs, where the results were called only if the ongoing treatment was suspected to be inappropriate. Forty per cent (20/49) refrained from calling when contamination was suspected. Written information was distributed by all CMLs during weekdays, with preliminary reports sent electronically by 92% (45/49).

BC staff processed positive vials immediately at the beginning of the shift. Preliminary reports were usually conveyed within 1 h (communicated by 62% before 9 a.m. on weekdays and by half of the CMLs during Saturdays (52%) and Sundays/holidays (47%)). A few CMLs did not convey preliminary reports during weekends (Supplementary Material Table S3). The content of written and verbal reports is shown in the Supplementary Material Table S4. Species identification was part of the initial report of five CMLs.

Treatment recommendations varied from antimicrobial resistance alerts to detailed advice on the best option and duration of treatment, presumed focus of infection, catheter removal, and infection control measures. In 40% of the CMLs (19/48) (one response missing) antibiotic therapy was rarely discussed with the physician (estimated at  $<10\%$  of the phone contacts) and, when performed, recommendations were scarce. However, 11 CMLs reported that advice was given regularly ( $\geq 75\%$  of the phone contacts) and was comprehensive. The most detailed recommendations were given by CMLs in Norway and Denmark. Preliminary reports from 22% (11/49) of the CMLs included limited or no treatment advice on weekends.

Laboratory reports were delivered to the infectious diseases department, in addition to the primary ward, by 37% of the CMLs (18/49), either by reporting all positive BC results or just specific findings (*Candida* spp. or *Staphylococcus aureus*). In case of specific resistances or communicable diseases, the infection control unit or county medical officers were contacted.

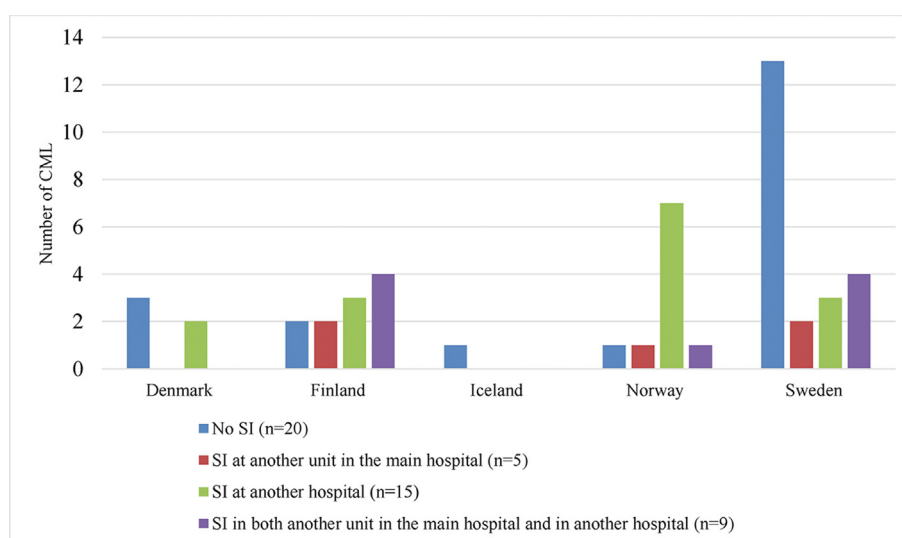


Fig. 1. Location and number of clinical microbiology laboratories (CMLs) with satellite incubators (SIs) per country.

**Table 2**

The proportion of clinical microbiology laboratories (CMLs) with 24 h, time-restricted or no (0 h) service for important parts of blood culture (BC) diagnostics

Day of the week	Starting of incubation <i>n</i> = 49 (% of CMLs)				Opening hours of BC department <i>n</i> = 49 (% of CMLs)				Processing of positive BCs at the main hospital <i>n</i> = 47 <sup>a</sup> (% of CMLs)			
	24 h	Time-restricted	0 h	Mean time coverage (h), if time-restricted service	24 h	Time-restricted	0 h	Mean time coverage (h), if time-restricted service	24 h	Time-restricted	0 h	Mean time coverage (h), if time-restricted service
Weekday	82 <sup>b</sup>	18	0	12.2	2	98	0	9.9	0	100	0	10.0
Saturday	82 <sup>b</sup>	18	0	11.6	2	98	0	7.5	0	100	0	7.9
Sunday/holiday	82 <sup>b</sup>	18	0	10.7	2	94	4	7.0	0	96	4	7.6

<sup>a</sup> Two CMLs did not report their timeframe of processing positive BCs.<sup>b</sup> In six of the CMLs with 24-h service for starting incubation, access to the incubators around the clock was not given to all of the cabinets in the catchment area.**Table 3**Number of clinical microbiology laboratories (CMLs) per country, with extended ( $\geq 10$  h for weekdays,  $\geq 8$  h for weekends/holidays) and not extended ( $< 10$  h for weekdays,  $< 8$  h for weekends/holidays) opening hours. The distribution of CMLs with  $\geq 30$  000 blood cultures (BCs) analysed annually is given in brackets. Total number of CMLs: *n* = 49. Total number of CMLs with  $\geq 30$  000 BCs analysed annually: *n* = 12

Opening hours [mean; range]						
Country	Total number of CMLs (number of CMLs with $\geq 30$ 000 BC analysed annually)					
	Weekdays		Saturdays		Sundays/holidays	
	$< 10$ h [8.4; 7–9]	$\geq 10$ h [12.0; 10–24]	$< 8$ h [6.4; 4–7]	$\geq 8$ h [9.3; 8–24]	$< 8$ h [5.6; 0–7]	$\geq 8$ h [9.8; 8–24]
Denmark	1 (0)	4 (4)	1 (0)	4 (4)	1 (0)	4 (4)
Finland	6 (1)	5 (2)	8 (3)	3 (0)	9 (3)	2 (0)
Iceland	0 (0)	1 (0)	1 (0)	0 (0)	1 (0)	0 (0)
Norway	8 (0)	2 (0)	5 (0)	5 (0)	7 (0)	3 (0)
Sweden	10 (1)	12 (4)	10 (1)	12 (4)	14 (2)	8 (3)
Total	25 (2)	24 (10)	25 (4)	24 (8)	32 (5)	17 (7)

### Bacterial species determination and susceptibility testing

Forty-seven CMLs (96%) used MALDI-TOF for species identification, some combined with traditional phenotypic methods or semi-automated biochemical identification systems, some combined with nucleic acid amplification techniques (NAATs)/sequencing or microarrays. The species identification strategies are shown in the [Supplementary Material Fig. S4a](#). Rapid identification directly from positive BCs was routinely performed by 39% of the CMLs (19/49): 16 using MALDI-TOF, two using NAAT, and one using both methods. The rapid identification strategy was established mainly in the Norwegian CMLs (90%, 9/10,  $p < 0.001$  compared to the other countries).

Rapid antimicrobial susceptibility testing (AST) conducted on aliquots directly from positive BCs, read after 4–8 h of incubation, was performed by 39% (19/49), most commonly by using a modified disc diffusion method with varying inoculum and breakpoints for SIR (sensitive, intermediate, resistant) categorization

([Supplementary Material Fig. S4b,c](#)). All but two verified the rapid AST results with a standardized method. Nine CMLs (18%) were performing both rapid identification and AST.

### Comparison of Swedish CMLs in 2013 (*n* = 26) and 2018 (*n* = 22)

MALDI-TOF was used in 100% of the responding CMLs in 2018 compared to 62% in 2013. Species identification, within 6 h processing of positive vials, was conducted significantly more often ( $p = 0.02$ ), generally by analysing early colonies with MALDI-TOF. Otherwise, no statistically significant increase in BC service was seen ([Table 4](#)).

### Comparison between CMLs with $\geq 30$ 000 and $< 30$ 000 BCs analysed annually

Twelve CMLs (24%), all university laboratories, had an annual output of  $\geq 30$  000 BC analyses ([Table 1](#)). Compared to CMLs with a

**Table 4**Blood culture diagnostic service in Swedish clinical microbiology laboratories (CMLs). Comparison between 2013 (*n* = 26) and 2018 (*n* = 22)

	2013 Number of CMLs (%)	2018 Number of CMLs (%)	p-value
Satellite incubators	5 (19)	9 (40)	0.12
Loading of incubators around the clock	12 (46)	16 (73)	0.08
Extended opening hours	Weekdays ( $\geq 10$ h/day)	16 (62)	0.77
	Saturdays ( $\geq 8$ h/day)	12 (46)	0.77
	Sundays/holidays ( $\geq 8$ h/day)	8 (31)	0.76
MALDI-TOF in daily routine	16 (62)	22 (100)	0.00 <sup>a</sup>
Species ID within 6 h after handling of positive vials	11 (42)	17 (77)	0.02 <sup>a</sup>
Rapid species-ID with MALDI-TOF directly from positive vials	3 (19 <sup>b</sup> )	3 (14)	0.68 <sup>b</sup>
Rapid AST directly from positive vials	10 (38)	10 (45)	0.77
Treatment advice given in $\geq 75\%$ in phoning occasions	3 (12)	3 (14)	1.0

MALDI-TOF, matrix assisted laser desorption/ionization—time of flight; AST, antimicrobial susceptibility testing.

<sup>a</sup> Statistically significant.<sup>b</sup> *n* = 16 in 2013, since only 16 of the 26 Swedish laboratories had access to an in-house MALDI-TOF.

lower output, longer working hours during weekdays was observed ( $\geq 10$  h,  $p = 0.008$ ) (Supplementary Material Table S5).

## Discussion

This study showed intra- and international differences in how Nordic CMLs organized their BC process. Despite efforts to increase the service level and shorten TATs, there are still shortcomings. As in a Swedish survey in 2013, the major gaps still concerned pre-analytical and analytical service coverage during the day [12]. Many hospitals, especially in Sweden and Denmark, lacked satellite incubators, resulting in delayed incubation. Satellite laboratory processing of BCs, as well as processing of positive vials around the clock, was sparsely implemented, and the service levels were lower at weekends. Major differences were noticed in the presence of medical expertise taking an active part in treatment decisions, with Norwegian and Danish physicians generally being more active.

The Clinical and Laboratory Standards Institute (CLSI) and Public Health England (PHE) recommend a maximum TAT of 2 and 4 h respectively for BC collection to start of incubation [13,14]. Our survey showed that CMLs in Finland and Norway could adhere to those recommendations (data not shown) whereas some CMLs in Sweden and Denmark could not. Granting access to incubators around the clock does not benefit samples from remote hospitals lacking cabinets, especially in areas with long transport times. Outsourced incubators available around the clock can even out differences between weekdays and weekends and could significantly reduce processing time [15], resulting in improved sensitivity [16]. Still, 40% of the Nordic CMLs lack satellite cabinets. In addition, this survey shows that the staff working hours covered only part of the day, leaving cultures unprocessed in the incubators for 60–70% of the daily hours. While Nordic CMLs otherwise follow international trends by introducing rapid diagnostics available 24 h per day, BCs are rarely included [17], and with processing of positive BCs not being outsourced, service around the clock is still far from a reality.

Several studies demonstrate that rapid identification and AST are essential for antibiotic stewardship, and that implementation of rapid analyses results in reduced time to targeted therapy as well as improved patient outcome [18–21]. It has been shown that concurrent implementation of an antimicrobial management team, to which microbiology test results are verbally and directly communicated in a timely manner, will reinforce the benefits [20,22–25]. A multidisciplinary team of experts can interpret rapid results correctly, diminish the use of unnecessary broad empirical therapy, and tailor and shorten treatment, thereby reducing the risk of drug toxicity, antimicrobial drug resistance and healthcare-associated infections. This in turn decreases ICU and hospital length of stay (LOS), and mortality in severely ill patients [21,23,25–29]. Rapid analysis (particularly with MALDI-TOF) with direct reporting to expert teams has also been shown to reduce healthcare costs, largely because of decreased LOS [21,26,27,29]. The great cost benefit of MALDI-TOF probably includes the user-friendly interface, short analysis TAT, and ability to detect a broad range of organisms. Nevertheless, species identification and rapid AST directly from positive BCs were performed by only approximately 1/3 and 2/5 of the CMLs, respectively. Additionally, treatment recommendations were seldom given. This might be explained by the absence of medical expertise, especially during weekends. Clinical microbiologists should provide real-time support to clinicians with evidence-based antibiotic recommendations [30]. Despite the need for medical guidance [31], plans on expanding working hours often did not include medical doctors. Even though some CMLs communicated directly with infectious disease physicians, no real-

time operating antibiotic stewardship teams involving a clinical microbiologist were reported.

Recently, a similar survey was distributed to selected CMLs in 25 European countries [32]. A lower percentage of outsourced incubators (15%) and loading of cabinets around the clock (42%) were seen, while processing of positive BCs and validation of laboratory reports around the clock were offered by 13% and 5% of the CMLs, respectively. The participating European countries were further ahead with implementing the combination of both rapid species identification and AST (44%) compared to the Nordics (18%); this can perhaps be explained by differences in antimicrobial resistance challenges in different parts of Europe.

Following our study, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) published a standardized rapid AST (RAST) disk diffusion methodology intended for positive BCs [33–35]. A short questionnaire was therefore sent to the responding CMLs during the summer of 2020 to follow up implementation of the method. All but one CML responded, and one announced that they no longer handled BCs. Of the remaining 47 CMLs, 24 (51%) performed RAST (of which 11 used the EUCAST method), compared to 19 (39%) in 2018.

Since rapid reports of positive BCs are vital for proper management of BSIs, a full around-the-clock diagnostic service should be provided. Different prerequisites and local needs—depending on budget, geographic area, patient population, local pathogens, resistance patterns, antimicrobial prescribing and stewardship policies—require customized solutions [7–9].

Continuously monitoring the quality of pre-analytical and analytical aspects of the diagnostic chain, by using quality indicator measurements, is not just part of the accreditation procedure [16,36] but is of significant importance to identify problems within laboratories [9]. Therefore, local evaluation of algorithms, cost/benefit effects and workflow should take place. European standardization of blood culture practices is desirable, and regular surveys and quality assessments could lead to improvements. Explicit defined interim targets—such as maximum TAT for BC collection to start of incubation and processing cultures after a positive signal, implementation of rapid species identification and AST, as well as participation in treatment strategies—should be developed and could be carried out under the auspices of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID).

## Strengths and limitations of the study

This study addresses important areas in the BC diagnostic chain, and the participation of CMLs across the Nordic countries enabled a comparison of countries with similar settings regarding demographics, geography, financial resources and low levels of antimicrobial resistance. The participating CMLs constitute a representative sample of each Nordic country regarding population coverage, geographic distribution and size of the CMLs. The response rate of 64% was good, although limiting the statistical evaluation of the data. Finally, in self-reported questionnaires it is impossible to control whether respondents state estimated values.

## Author contributions

All authors were involved in the conceptualization of the initial idea. AÅ and AP composed the questionnaire, with all authors' providing intellectual input. KM designed the web questionnaire. AÅ and AP collected the data and performed data management. AP and CG performed the statistical analyses. AÅ and AP drafted the

manuscript, to which all authors provided input. All authors approved the final version of the manuscript.

## Transparency declaration

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2021.09.003>.

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