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QUALITY IN FINNISH CLINICAL MICROBIOLOGY LABORATORIES.

EVALUATION OF RESULTS OF EXTERNAL QUALITY CONTROL (EQC) SAMPLES REVEALS THE RELIABILITY OF DIAGNOSTICS FOR INFECTIOUS DISEASES.

Salla Kiiskinen

DOCTORAL DISSERTATION

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ABSTRACT

In Finland, laboratory diagnostics of infectious diseases is done in clinical microbiology laboratories that are approved by the Regional State Administrative Agencies (RSAAs). The Finnish National Institute for Health and Welfare (THL) has given elaborated instructions for laboratories seeking approval. The main purpose of this licensure procedure is to ensure the reliability of diagnostics for infectious diseases regardless of the laboratory performing these investigations. The two main requirements for the approval are a sufficient number of skilled personnel and mandatory participation in external quality assessment (EQA) schemes for each test type that a laboratory offers. The licensure process for clinical microbiology laboratory is mandatory and independent of voluntary accreditation processes.

This thesis focuses on three common clinical microbiological investigations: quantitative urine culture, faecal bacterial culture, and point-of care (POC) testing for infectious mononucleosis (IM) caused by the Epstein-Barr virus (EBV IM POC). External quality control (EQC) results were obtained from corresponding EQA schemes. The results of laboratory investigations will have a direct impact on patient care and in the case of infectious diseases also have epidemiological and public health implications, including a role in recognising disease outbreaks and assessing of epidemiological prevention and control measures effectiveness. For this reason, the high quality of these results is important.

According to the Finnish Communicable Diseases Act laboratories have to give information on EQA schemes to THL by request. However the results from the EQC results sent to EQA provider are confidential. In this study Finnish laboratories were asked for permission to study their EQC results directly from the database provided a Finnish company specialised in producing a wide range of EQA services, Labquality Ltd. Altogether 26,398 EQC results over a nine-year period (2009–2017) from 413 laboratories were collected and evaluated. Of the 413 laboratories, 335 took part in quantitative urine culture rounds, 17 in faecal bacterial pathogens rounds and 273 in EBV IM POC rounds.

This study showed that the commitment to EQA was good in Finnish clinical microbiology laboratories. The laboratories typically attended all four rounds per year. The rate by which the laboratories replied to the EQA by submitting their results for the EQC samples varied from 95% to 99.5% according to the investigation studied in this thesis. This is referred as the response rate.

The success rate for quantitative urine culture testing was 83%. The most common reasons for the 17% false results were due to interpreting the growth of expected pathogens as non-significant, or due to mixed growth, or no growth at all. There were differences in detecting and quantifying of the growth of Gram-negative and Gram-positive bacteria. In those EQC samples where Gram-negative rods were present, the quantitative result was correct in 91% of the results. The most common bacterial pathogen causing urinary tract infections (UTI), Escherichia coli was correctly reported in 93% of the EQC results. In those

EQC samples where Gram-positive bacteria were present; the quantitative result was correct in 68% of the results. The most common Gram-positive bacterial pathogens found in urine culture samples, *Enterococcus* sp. and *Staphylococcus saprophyticus* were correctly reported in 85% of the EQC results. More untypical findings, *Streptococcus agalactiae* and *Aerococcus urinae* were reported correctly only in 23% and 31% of the EQC results, respectively. If the same sample contains several isolates, it is considered contaminated. In this study, two EQC samples containing mixed growth were correctly reported only in 66% of the results.

The success rate for faecal bacterial culture testing was 92%. The common reasons for false results were improper identification of *Shigella* sp. and according to the collected data, the success rate was 89% for *Shigella flexneri* and 71% for *Shigella sonnei*. The success rate for the detection of *Salmonella* sp. was 95%. All false results with *Salmonella* were caused by two samples, one with low number of *Salmonella* Typhimurium cells, and other with *Salmonella* Infantis strain. The success in finding *Yersinia* sp. was 96% and for *Campylobacter jejuni* it was 98%.

The overall success in the EBV IM POC rounds was 99.3%. The success varied between 94.3% for the immunofiltration method to 99.4% for the immunochromatographic method and 99.6% for latex agglutination method. The most significant factor regarding the results' correctness was the clinical classification of the sample. The samples that represented old EBV immunity were the most difficult to interpreted with a 98.9% success rate.

In order to evaluate the effect of the laboratory size on the EQC results, laboratories conducting quantitative urine culture and EBV IM POC investigations were divided according to the size, categorised by the number of named investigations they conducted per year. The laboratory type or size did not influence the success of the EQC results in this setting where all participants were licenced clinical microbiology laboratories.

Key words: external quality assessment (EQA), external quality control (EQC), clinical microbiology, quantitative urine culture, faecal bacterial culture, point-of-care (POC), infectious mononucleosis (IM)

TIIVISTELMÄ

Suomessa tartuntatautien laboratoriodiagnostiikkaa tehdään aluehallintovirastojen hyväksymissä kliinisen mikrobiologian laboratorioissa. Terveyden ja hyvinvoinnin laitos (THL) on ohjeistanut hyväksyntää hakevia laboratorioita toimintaedellytyksien täyttämisessä. Toimilupamenettelyn päätavoite on taata diagnostiikan luotettavuus riippumatta siitä missä laboratoriossa tutkimukset suoritetaan. Toimintaedellytyksistä kaksi tärkeintä ovat riittävä ja ammattitaitoinen henkilöstö, sekä jokaisen tutkimusnimikkeen kohdalla osallistuminen ulkoisen laadunarvioinnin (EQA) kierroksille, jos niitä on saatavilla. Kliinisen mikrobiologian laboratorioiden toimilupamenettely on pakollinen ja akkreditoinnista riippumaton prosessi.

Tässä tutkimuksessa käsiteltiin kolmea yleistä mikrobiologista tutkimusta, kvantitatiivista virtsaviljelyä, ulosteen bakteeriviljelyä, sekä mononukleoosipikatestiä (EBV IM POC) näiden ulkoisen laadunarvioinnin tulosten pohjalta. Laboratoriotulokset vaikuttavat suoraan potilaan hoitoon liittyviin päätöksiin ja infektiotautien ollessa kyseessä niillä on myös rooli taudinpurkausten tunnistamisessa sekä epidemiologisten torjuntatoimien vaikuttavuuden arvioinnissa. Tästä syystä näiden tutkimusten korkea laatu on tärkeä.

Tartuntatautilain mukaan laboratorioiden on pyynnöstä toimitettava EQA kierrosten tulokset THL:lle. Koska EQA palvelun tuottajalle toimitetut tulokset ovat luottamuksellisia, Suomalaisilta kliinisen mikrobiologian laboratorioilta pyydettiin lupaa saada ulkoisen laaduntarkkailun (EQC) tulokset suoraan Labquality Oy:n tietokannasta. Koko yhdeksän vuoden (2009 — 2017) tutkimusjakson aikana kerättiin ja analysoitiin yhteensä 26 398 EQC tulosta 413 laboratoriosta. Näistä laboratorioista 335 osallistui kvantitatiivisiin virtsan viljelykierroksiin, 17 ulosteen bakteeriviljelykierroksiin ja 273 EBV IM POC -kierroksiin.

Tämän tutkimuksen pohjalta voidaan todeta että sitoutuminen ulkoiseen laaduntarkkailuun oli hyvä suomalaisissa kliinisen mikrobiologian laboratorioissa. Laboratoriot osallistuivat tyypillisesti kaikkiin neljään kierrokseen vuodessa. Laboratoriot palauttivat kierroksen järjestäjälle vastauksen 95% — 99,5% tutkittavaksi lähetetyistä näytteistä. Tähän viitataan vastausprosenttina.

Laboratorioiden menestys kvantitatiivisen virtsaviljelyn kierroksilla oli 83%. Virheellisistä vastauksista 17% johtui löydöksen tulkitsemisesta merkityksettömäksi, sekakasvuksi tai täysin negatiiviseksi. Grampositiivisten ja gramnegatiivisten bakteerien tunnistamisessa ja kasvun runsauden arvioinnissa oli eroja. Niissä EQC näytteissä joissa löydöksenä oli gramnegatiivinen bakteeri, oikea kvantitatiivinen tulos raportoitiin 91% vastauksista. Kaikkein yleisin virtsatiepatogeeni *Escherichia coli* oli raportoitu oikein 93% EQC vastauksissa. Niissä EQC näytteissä joissa löydöksenä oli grampositiivinen bakteeri, oikea kvantitatiivinen tulos raportoitiin 68% vastauksissa. Kaikkein yleisimmät grampositiiviset virtsatiepatogeenit, *Enterococcus* sp. ja *Staphylococcus saprophyticus* oli raportoitu oikein 85% EQC vastauksissa. Harvinaisempien löydösten, *Streptococcus agalactiae* ja *Aerococcus urinae* tulokset olivat oikein 23% ja 31% analysoiduissa

kierrosvastauksissa. Virtsanäytteiden, joissa kasvaa kaksi tai useampia bakteereita katsotaan olevan kontaminoituneita. Tämän tutkimuksen aineistossa tällaisia laaduntarkkailunäytteitä oli kaksi. Näiden näytteiden osalta osallistuneiden laboratorioiden tulkinta oli oikein vain 66% palautetuista vastauksista.

Ulosteen bakteeriviljelykierroksilla onnistumisprosentti oli 92%. Tässä tutkimuksessa analysoitujen EQC vastausten perusteella vaikeimpia näytteitä olivat ne, joissa odotettuna löydöksenä oli *Shigella* sp., *Shigella flexneri* oli oikein 89% vastauksista ja *Shigella sonnei*. 71% vastauksista. Näytteissä joissa löydöksenä oli *Salmonella* sp. onnistumisprosentti oli 95%. Kaikki väärät vastaukset salmonellaa sisältävien näytteiden kohdalla johtuivat kahdesta EQC näytteestä, joista toisessa oli vain vähän *Salmonella* Typhimurium soluja, ja toisessa rikkivetynegatiivinen *Salmonella* Infantis kanta. Analysoitujen EQC vastausten perusteella *Yersinia* sp. oli oikein 96% vastauksista. Aiemmista tutkimuksista poiketen *Campylobacter jejuni* oli tässä tutkimuksessa raportoitu oikein 98% EQC vastauksessa ja ainoa väärä vastaus johtui mahdollisesta näytesekaannuksesta.

Tässä tutkimuksessa analysoitujen EQC tulosten pohjalta onnistumisprosentti EBV IM POC kierroksilla oli 99,3%. Onnistumisprosentti vaihteli menetelmien välillä ollen 94,3% immunofiltraatiomenetelmillä, 99,4% immunokromatograafisilla menetelmillä ja 99,6% latex-agglutinaation menetelmillä. Tämän tutkimuksen perusteella kaikkein suurin vaikutus tulosten oikeellisuudelle oli analysoidun EQC näytteen edustama kliininen tulkinta. Vanhaa EBV- immuniteettia edustavien negatiivisten näytteiden tulkinta oli näiden EQC raporttien perusteella kaikkein vaikeinta ja niiden kohdalla onnistumisprosentti oli 98,9%.

Vastoin ennakko-odotuksia, laboratorion tyypillä tai koolla ei näyttänyt olevan vaikutusta menestykseen EQA kierroksilla tutkimusasetelmassa jossa kaikki osallistujat olivat toimiluvallisia kliinisen mikrobiologian laboratorioita.

Avainsanat: ulkoinen laaduntarkkailu, ulkoinen laaduntarkkailunäyte, kliininen mikrobiologia, kvantitatiivinen virtsaviljely, ulosteviljely, vieritesti, mononukleoosi

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-III).

I. Ojanen T, Kiiskinen S, Björkman Y, Laitinen H, Virtanen MJ, Siitonen A. Use of External Quality Assessment to Evaluate the Reliability of Quantitative Urine Culture. Archives of Clinical Microbiology 2016;7:2 1-7

II. Kiiskinen S J, Ojanen T, Björkman Y, Laitinen H, Siitonen A. External Quality Assessment in the Evaluation of Laboratory Performance of Faecal Culture. Microbiology Insights. 2017;10:1-8 (https://doi.org/10.1177/1178636117691253)

III. Kiiskinen S J, Luomala O, Häkkinen T, Lukinmaa-Åberg S, Siitonen A. Evaluation of the Serological Point-of-Care Testing of Infectious Mononucleosis by Data of External Quality Control Samples. Submitted

In addition, some unpublished information and results are included.

ABBREVIATIONS

CAP	College of American pathologists
CFU	Colony forming unit
CLIA	Clinical laboratory improvement act/amendments
EBV	Epstein-Barr virus
EFLM	European Federation of Clinical Chemistry and Laboratory Medicine
EHEC	Enterohaemorrhagic *Escherichia coli*
EIEC	Enteroinvasive *Escherichia coli*
EQA	External quality assessment
EQC	External quality control
IM	Infectious mononucleosis
ISO	International organisation for standardizations
MALDI-TOF MS	Matrix-assisted laser desorption/ionization time of flight mass spectrometry
NIDR	National infectious diseases register
PCR	Polymerase chain reaction
POC	Point-of-care
PPM	Provider-performed microscopy
PT	Proficiency testing
QMS	Quality management system
Rili-Bäk	Guidelines of the German Federal Medical Council
RSAA	Regional state administrative agency
SOP	Standard operating procedure
TAT	Turn-around-time
THL	Terveyden ja hyvinvoinnin laitos Finnish Institute for Health and Welfare
USA	United States of America
UTI	Urinary tract infection

INTRODUCTION

Reliable and reproducible laboratory diagnostics is the basis of good patient care and safety. Clinical microbiology uses a variety of test methods ranging from direct microscopy to bacterial culture, identification and interpretation of the growth, antimicrobial susceptibility testing to modern nucleic acid detection based methods. The aim of these methods is to obtain information on the pathogen that is causing symptoms in clinically ill patients. This information is then used to decide the best way to treat the illness. Because test results have a direct impact on patient care, they have to be precise and consistent every time. When diagnostics concern infectious diseases, it has also major epidemiological and public health implications, including a role in recognising disease outbreaks and assessing prevention and control effectiveness.

One tool used to monitor the quality of the routine performance of a laboratory is to follow the laboratories' success in external quality assessments (EQAs). Therefore, in this study, the focus was on three common microbiological laboratory investigations: quantitative urine culture, faecal bacterial culture, and point-of care (POC) testing for infectious mononucleosis (IM) caused by the Epstein-Barr virus (EBV), and the EQA for these. About 26,400 external quality control (EQC) results were collected from Labquality Ltd.'s databank after obtaining permission from 413 Finnish clinical microbiology laboratories. These participating laboratories included large, specialised, clinical microbiology laboratories as well as small health care centre laboratories.

REVIEW OF THE LITERATURE

2.1 QUALITY IN GENERAL

The WHO definition of quality of care is "the extent to which health care services provided to individuals and patient populations improve desired health outcomes". In order to achieve this, the given health care must be safe, effective, timely, efficient, equitable, and people-centred (1). In modern medicine where laboratory results play a part in many decisions, this means that laboratory services are also organised to serve the same goals as the rest of the health care (2).

Quality in clinical laboratories' investigations are dependent on three phases, which are the analytical, the pre-analytical, and post-analytical phases (3–6). In order to be qualitatively good, laboratory results must be accurate, precise, and on time (7–9). For producing reliable test results a laboratory needs professionally qualified personnel, good quality test reagents and equipment (10), and well organised test procedures. The specimens sent to the laboratory to be analysed must be correctly collected, handled, and identified. The request itself must be correct (11,12) and the requested investigations must be appropriate to the medical problem (13) and to this end good communication between the laboratory and clinician is needed (14). The reported results must be comprehensible and lead to correct action and patient care (15).

The most critical pre-analytical steps identified by the European Federation of Clinical Chemistry and Laboratory Medicine working group for the pre-analytical phase (EFLM WG- PRE) are test ordering, patient preparation, transport, storage, sampling, management of unsuitable specimens, quality indicators, patient identification, and paediatric and neonatal sampling (16). Many of these are also applicable to clinical microbiology laboratories. The objective of the working group was to reduce the amount of pre-analytical errors, through assessment, guidance, and harmonisation.

Clinical laboratory investigations are one of the key components in modern medicine (17,18). It has been stated that laboratory results influence as many as 70% of clinical decisions (19,20). To this end the quality and consistency of the results is an important issue for patient care and safety. According to Smit et al. (2009), the variation in the cost of laboratory investigations, and the distribution of expenditure by discipline was very similar in European countries, with average figures of 15% for infectious diseases and 6% for clinical microbiology (21).

The legislation covering laboratory investigations in Europe is diverse. Some countries have specific licensing systems while others prefer obligatory accreditation (22). Despite of the diversity, regular external quality assessment (EQA) plays an important role in assuring the good quality of clinical laboratory investigations in all of the systems in use (23).

In clinical microbiology, the pre-analytical phase is critical. Pre-analytic events such as collection, storage, and transport are an important factor in clinical microbiology. These processing times affect the total turn-around-times (TAT)

and the quality of the results (24). If the specimen is contaminated at the time of sampling, or the pathogen is lost during the transport, it is impossible to resolve this error in the laboratory (25). Because nowadays most of the errors occur in the pre- and post- analytical phase (26,27) appropriate quality control and assessment measures spanning all of these three phases are needed (28,29).

2.1.1 QUALITY MANAGEMENT SYSTEM

A quality management system (QMS) is a tool that can be used to ensure that the consistency of a product or service is consistent. Quality management includes quality planning, quality assessment, quality control and quality improvement (30). In clinical laboratories QMS activities effectively increase patient safety (31). Quality policy is formally set in the comprehensive intentions and objectives of a clinical laboratory regarding quality by the laboratory management.

2.1.2 QUALITY ASSESSMENT

These factors can be related to the sample itself, the reagents, or equipment, or test procedures used in the laboratory. If issues that can have effect on the quality of the investigation are encountered, documented corrective actions should be taken. When planning quality assessment programmes, including participation in various quality programmes, laboratory should take into account requirements set by authorities, clients, and stakeholders (32–35).

2.1.3 INTERNAL QUALITY ASSESSMENT

The purpose of internal quality assessment (IQA) is to monitor the day-to-day consistency of test results in the laboratory. IQAs can consist of known positive and negative samples, control strains that are especially important in clinical microbiology, or sometimes even re-testing to detect the level of discrepancies between IQA and patient samples (36). It is important to keep records of the results, reagent batch information (test-kit lot-data), and other observations in order to monitor the situation, and pin-point the problem when needed.

2.1.4 EXTERNAL QUALITY ASSESSMENT

Differences in laboratory measurement values in basic clinical chemistry were observed and described by Belk and Sunderman in 1947 (37), and since then similar observations on variations in testing results have been made in various other countries (38,39). This knowledge led to the conclusion that something had to be done in order to achieve more accurate and concordant test results. In answer to this conclusion it was felt that external inter-laboratory quality control systems should be established. The first inter-laboratory quality control procedure, a predecessor of external quality assessment (EQA), was organised in 1949 (40). The concept of EQA was first used in clinical chemistry laboratories

in the mid-1960s. Clinical microbiology soon followed clinical chemistry. EQA schemes for clinical microbiology were originally developed in the USA, and in Europe a comprehensive microbiological quality assessment scheme for clinical microbiological laboratories was established in the United Kingdom in 1974 (41).

The term EQA is often used as a synonym for the term proficiency testing. EQA is the most objective part of laboratory quality assessment. EQA schemes are comprised of a set of external quality control (EQC) specimens, which are samples that have a known composition and are pretested before sending to the participants. After conducting appropriate clinical tests on these samples, the participants send their results to the EQA provider, who then sends back EQA reports to the participating laboratories. Success in the EQA rounds is said to reflect the laboratory's everyday performance. This requires that the EQC samples are processed in the same way as routine patient specimens. EQA testing is recommended quarterly (32,33) and EQA schemes usually comprise of several rounds per year, though there are variation between suppliers (Table 1.).

In addition to proving its competence, a laboratory can use EQC samples for many different purposes (42–44). EQC samples are used to monitor and improve a laboratory's processes, and failures should always lead to corrective actions. Samples can be used for the development of test methods and method performance evaluation (45–49), as well as risk management, and training of laboratory personnel (50,51). EQC results can be used for post-market vigilance of the performance of diagnostic tests (52) and participant performance evaluation (53–55). EQA is even used to determine the degree of compliance to regulations on transporting infectious substances (56).

2.1.5 EQA ORGANISERS

Today there are several credible providers of EQA schemes for various fields of clinical laboratory science, also in clinical microbiology (Table 1.). In Finland, EQA schemes are most commonly purchased from Labquality Ltd., though the UK Neqas, QCMD and Instand e.V. are also used.

The Finnish company, Labquality Ltd has been specialised in producing a wide range of EQA services since 1971. It has clients ranging from large hospitals to small laboratories and point-of-care (POC) testing sites. Labquality Ltd has a broad clientele of both Finnish and international customers. It currently runs 67 clinical microbiology EQA schemes (Table 1.). For example, EQA schemes for urine culture were started in 1977, quantitative urine culture in 1995, EBV IM in 1987, *Salmonella* culture in 1994, and faecal bacterial pathogens in 2000 (57–59).

Since 1989, European clinical laboratory EQA organisers have been arranged under an umbrella-organisation called the European EQA Organizers in Laboratory Medicine (EQUALM). This provides a forum for co-operation and exchange of knowledge on quality-related matters especially with regard to EQA programmes in Europe. Currently it has 41 European and eight non-European members (60).

Table I Common EQA organisers.

Name of the provider	Established	Country
College of American Pathologists (CAP)	1949	USA
Instand e.V.	1968	Germany
United Kingdom National External Quality Assessment (UK Neqas)	1969	United Kingdom
Labquality Ltd	1971	Finland
Institute for Quality Management in Healthcare (IQMC)	1974	Canada
Clinical Microbiology Proficiency Testing (CMPT)	1982	Canada
Quality Assurance Programmes pty Limited (RCPA)	1988	Australia
External Quality Assurance in Laboratory Medicine in Sweden (EQUALIS)	1992	Sweden
Quality Control for Molecular Diagnostics (QCMD)	2001	Scotland

Participants (total)	No of microbiology schemes	No of distributions per year	Reference
22,000	77	2 - 3	(61,62)
12,500	73	1 - 4	(63,64)
2,310	52	1 - 12	(65)
4,404	67	2 - 4	(59,66)
not known	12	2 - 3	(67)
not known	9	2 - 4	(68)
not known	74	2 - 8	(69)
1,800	27	1 - 4	(66,70)
2,000	82	1 - 4	(71)

2.2 ISO STANDARDS, ACCREDITATION, AND CE MARKING

Accreditation is a demonstration of a competence and compliance to a specific ISO standard (International Organization for Standardizations (Table 2.). The area in which the competence has been assessed is indicated in the accreditation decision (23). Accreditation is sought from a national accreditation body (NAB). In Finland this is Finnish Accreditation Service (FINAS), which is a unit of the Finnish Safety and Chemicals Agency (Tukes). In global markets, the International Authority on Laboratory and Inspection Body Accreditation (ILAC) has a mutual recognition arrangement (MRA). This arrangement means that accreditation achieved in one country is automatically valid in all countries where the MRA is in force (72).

Table 2 *List of different ISO Standards related to clinical laboratories and EQA*

Standard	Name
ISO 17025:2017	Testing and calibration laboratories
ISO 15189:2013	Medical laboratories
ISO 9001:2015	Quality management systems – Requirements
ISO 15190:2003	Medical laboratories – Requirements for safety
ISO 17043:2010	General requirements for proficiency testing
ISO 20658:2017	Medical laboratories — Requirements for collection, transport, receipt, and handling of samples
ISO 22870:2006	Point-of-care testing (POCT) –Requirements for quality and competence

EQA is an important part of accreditation, though specific requirements for schemes have not been implicated in the most commonly used ISO standard 15189, which is used in Finnish clinical laboratories. It is stated in the ISO 15189 standard that the laboratory must participate in an interlaboratory comparison programme appropriate to the investigation and interpretation of the investigation results, and that the results must be monitored by the laboratory and the laboratory should participate in the implementation of corrective actions if predetermined performance criteria are not fulfilled (73).

According to standards, good laboratory practices at the minimum include having trained and competent testing personnel, following test manufacturers' and the laboratory's own standard operating procedures (SOPs), routinely performing and evaluating daily quality control, responding to poor results and correcting problems, applying total quality management and continuous quality improvement principles and practices, participating in EQA, and documenting all activities.

2.2.1 ISO 17025:2017 TESTING AND CALIBRATION LABORATORIES

According to the standard "A laboratory's fulfilment of the requirements of ISO 17025 means the laboratory meets both the technical competence requirements and management system requirements that are necessary for it to consistently deliver technically valid test results and calibrations" (74). The ISO 17025 is a more technically orientated standard than the ISO 15189, which is addressed more to the clinical laboratories.

2.2.2 ISO 15189:2013 MEDICAL LABORATORIES

According to this standard "A medical laboratory's fulfilment of the requirements of ISO 15189 means the laboratory meets both the technical competence requirements and the management system requirements necessary for it to consistently deliver technically valid test results" (73). This standard has an increased emphasis on the management system and continuous improvement of laboratory processes.

Compared to ISO 17025, ISO 15189 addresses the qualifications of the staff in more detail. As stated in the description of the standard, the profession is practised in different countries at the same level, regardless of the academic background of the professionals. The ISO 15189 standard is crafted so that it allows competent staff members with different academic backgrounds to become directors of clinical laboratories (75,76). In some countries a medical degree is required for the clinical laboratory management.

2.2.3 CE MARKING

Conformité Européenne, CE marking, means a declaration of conformity. It certifies that a CE marked product has met EU health, safety, and environmental standards for the intended purpose of use (77,78). Once granted, CE marking is valid in all European countries. After introduction to the market, manufacturers are obligated to carry out continuous post-market surveillance of the quality of their products (79). From March 2020 onwards, data on CE marked medical devices in the European Union market is collected in an electronical database called Eudamed (80,81). The new regulations on in vitro diagnostic medical devices (IVDR) have tighter rules than CE marking for laboratory tests to enter markets, and it will probably reduce the number of tests that have been developed or modified within a laboratory, so called in-house tests, in clinical laboratories, and will also limit the number of CE marked tests sold by manufacturers (82).

2.2.4 CLINICAL MICROBIOLOGICAL LABORATORIES IN USA, CANADA AND AUSTRALIA

In the United States of America, laboratories must meet standards defined in the Clinical Laboratory Improvement Act. The CLIA'67 was the first act to regulate the practise of clinical laboratory functions. As an improvement, CLIA'88 mandates universal requirements for all clinical laboratory-testing sites (83).

The recent CLIA regulations have outlined three categories of clinical laboratory testing. These categories are waived tests, a limited list of moderate complexity provider-performed microscopy, and moderate and high complexity tests, also known as nonwaived tests.

The waived tests are considered simple tests that present low risks concerning incorrect results and patient safety. PPM procedures are performed during patient visits by physicians or mid-level practitioners. The moderate and high complexity tests are, as stated in the name, tests that represent moderate to high complexity. This is estimated on the basis of the required knowledge, training and experience, reagents and materials preparation, test system troubleshooting and equipment maintenance, interpretation and judgment, characteristics of operational steps, availability and stability of the calibration, quality control, and proficiency testing materials.

CLIA'88 specifically states that the laboratory director must ensure that the testing systems used provide laboratory quality services covering all aspects of test performance, which includes the pre-analytic, analytic, and post-analytic phases of testing. CLIA'88 mandates laboratories to participate in EQA programmes approved by Centres for Medicare and Medicaid Services (CMS). The quantitative performance requirement in CLIA'88 for microbiology laboratories includes the following: the laboratory has to analyse at least five EQC samples per testing event, it has to achieve an 80% correct score on each testing event to achieve satisfactory performance, and it has to perform satisfactorily in two out of three sets of EQA rounds per year (84).

In Canada, accreditation of clinical laboratories is regulated by 10 provincial health authorities. Five of the provinces have provincial accreditation bodies, while in the other five provinces the clinical laboratories are accredited by Canadian Counsel on Health Service Accreditation (CCHSA). ISO 15189 has been accepted in all provinces as the standard for accreditation of clinical laboratories in Canada, though differences in implementation exist.

Australian clinical laboratories require accreditation under the Australian government's Health Insurance Act. Laboratories are assessed according to the National Pathology Accreditation Advisory Council (NPAAC) requirements (85).

2.2.5 EXAMPLES OF ARRANGEMENT OF CLINICAL LABORATORIES IN EUROPEAN COUNTRIES

The European clinical laboratory field has evolved over time to meet the demands of national health care systems. Only a few published studies related to the accreditation level of clinical laboratories have been made and information on the legislation of the European clinical laboratories is mostly scattered in national-level instructions. There are many differences between clinical laboratories in European countries (86), but similarities do exist. The reliability and reproducibility of laboratory investigations are important aspects for clinical laboratories, and

this has led them to demonstrate the quality of their results through accreditation. The number of accredited laboratories varies greatly between European countries. In most European countries, accredited clinical laboratories have adopted the ISO 15189 standard .The highest percentages of accredited laboratories are in Finland, Ireland, the Netherlands, Sweden, Switzerland and the UK (87). Additionally, there are countries such as Slovenia and Albania which have no accreditation process available. Finland, Germany, and France also have national legal requirements for clinical laboratories. According to Datema et al (2011), national quality regulations are recommended if they are available because they are often more detailed and better adapted to the local situation (88).

One of the critical resources for clinical laboratories are adequate and well-trained staff. At the national level, many different names are being used for the professionals of this field and in most European countries the head of the laboratory can be either physician, pharmacist or laboratory specialist with a scientific background (89), and consultant competence criteria vary between countries (75). There is also variation in the numbers and occupational titles of the clinical laboratory personnel in European countries (89). A concern has been raised about the sufficiency of the educated workforce for the clinical laboratory field (90). In order to enhance opportunities for professionals to migrate between EU countries, the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) has crafted a syllabus for postgraduate education and training for clinical laboratory specialists (91).

Below some information is presented on practices in relation to laboratory activities from seven European countries: Estonia, France, Germany, Italy, United Kingdom (UK), Sweden and the Netherlands.

In Estonia, each healthcare providing facility, including hospitals, ambulatory care providers, and private laboratories have a licence from the Health Board of Estonia. Accreditation of the clinical laboratory is not mandatory. If accredited, the standard used is ISO 15189.

France has had mandatory accreditation since 2008 according to ISO 15189 for all of its 800 clinical laboratories (92–94). The development of the quality assessment was started in the 1990s when a guideline for good analysis performance, the Guide de bonne exécution des analyses de biologie médicale (GBEA) was published. In France accreditation is sought from the national accreditation body named the comite Francais d'accreditation (COFRAC).

In Germany, clinical laboratory testing is regulated by the act and guidelines that regulate quality assessment for the field of clinical laboratory medicine. The guideline of the German Medical Association on quality assessment in medical laboratory examinations is called Richtlinien der Bundesärztekammer, Rili-Bäk, and it was issued first time in 1971. Its latest version has been effective since 2014 (95,96). According to the guideline, participation in EQA is mandatory. Accreditation of clinical laboratories is voluntary and 20% of the laboratories are accredited (35).

Italy has about 4,200 clinical laboratories in its 20 regions. The regions have

freedom to set their own accreditation criteria, procedures, and quality requirements (35). A national decree states that regional quality control programmes should be carried out to guarantee acceptable performance of laboratories (97–99). Accreditation is voluntary with the exception of the Autonomous Province of Trento, and only a few clinical laboratories are accredited (100).

In the UK, Public-Health England maintains variety of standards for laboratory investigations (101,102). The providers of EQA programmes relate to and interact with a joint working group on quality assessment and its associated national quality assessment advisory panels (NQAAPs) (103). The NQAAPs are professional groups that have responsibility for maintaining satisfactory standards of analytical and interpretive performance in all clinical laboratories in the UK. The UK was one of the first European countries to introduce accreditation for clinical laboratories (104). Accreditation is not mandatory, but it is widely used in the UK.

In Sweden there are altogether 24 specialised clinical microbiology laboratories (105). There is no licensing system in place and accreditation is not mandatory for clinical laboratories. Based on the quality assessment regulation the health service chooses, laboratories that can meet high standards (106–108). The first two clinical laboratories were accredited by Sweden's National Accreditation Body (SWEDAK) in 1992, and today the majority of the clinical laboratories are accredited (100,109).

The Netherlands had about 400 clinical laboratories, of which about 100 were accredited by the Dutch Accreditation Board for Medical Laboratories, (CCKLtest) at the end of the year 2001 (110). About 80 laboratories are specialised in clinical microbiology and 90% of them are linked to hospitals (111,112).

2.3 QUALITY PROCESSES IN CLINICAL MICROBIOLOGY LABORATORIES IN FINLAND

Accreditation in Finnish clinical laboratories is voluntary but common (113). Most Finnish clinical laboratories are currently accredited against the ISO 15189 standard (114).

The licensing process concerns all clinical microbiology laboratories. However, it differs from accreditation in some requirements (Table 3.). The main difference however is that accreditation is voluntary in contrast to the licensure which is mandatory.

According to the Finnish infectious Diseases Act (115,116), laboratory examinations and tasks required to diagnose infectious diseases may be carried out in the Finnish Institute for Health and Welfare (THL), as well as laboratories that have been issued an operating licence for this purpose, and also in those operating units that are under supervision of the latter laboratories.

These licences are granted by the regional state administrative agencies (RSAAs). Before granting a licence the RSAA requests a statement from THL. The preconditions for granting a favourable statement are that the laboratory must have appropriate premises and equipment, as well as competent staff for performing its tasks, and that its quality controls are organised appropriately (34). For this, laboratories are obligated to participate in EQA rounds at least four times per test item per year. In addition to that, when monitoring its subcontracting laboratories and operating units under its supervision, the laboratory is responsible for assuring that they are organised in an appropriate manner. The licence is of a limited duration, commonly three years, and in the case of shortcomings the RSAA can cancel the granted licence.

At the beginning of the licensure system in the early 1990s, 40% of the clinical microbiology laboratories did not have a valid license from the Board of Health, which was the authority previously responsible for granting the licence. A detailed procedure for the licensing system for clinical microbiology laboratories was created in 1993 (117). Key justifications for the system included patient safety, the quality of clinical microbiology test results supporting communicable disease surveillance for public health purposes, the accelerating competition between laboratories, which at was causing pressure to compromise on the quality of testing, and finally the understanding that accreditation alone was not sufficient to ensure high quality microbiological testing in clinical laboratories. At the early stage of the system, approximately 400 laboratories were involved.

Before 2017 all laboratories, specialised laboratories and smaller operating units under their supervision had their own licences. POC tests such as Streptococcus A Antigen and EBV IM, as well as simple bacterial cultures such as throat- and urine cultures to level where negatives were answered, could be done independently. However, the laboratories carrying out more complex POC tests such as Influenza A and B antigen tests needed a supporting laboratory that is responsible for reliability of the test results. The role of the supporting laboratory was to help the smaller laboratory to choose correct test methods and

EQA, draw up SOPs, educate the personnel, and assist in reporting the findings to THL if necessary (118). After 2017, according to the new communicable diseases act (116), all laboratories are obligated to have expertise in clinical microbiology, either by themselves or from a supervising laboratory.

THL maintains a register of clinical microbiology laboratories and the microbiological specimens investigated in those laboratories. The list of the names of all laboratory investigations (the nomenclature of laboratory investigations) is maintained by the Association of Finnish Local and Regional authorities (119). Currently, more than 700 clinical microbiology laboratories

Table 3 Comparison of the requirements of the ISO 15189 standard, the Finn

System	Accreditation ISO 15189	Finnish licensing sys
Year of publication	2003	1993
Year of latest issue	2012	2017
Validity and other additional restrictions	One accreditation period is four years	Licence is va for three ye
Scope and more detailed Definitions	All clinical laboratory investigations. Named investigations in the accreditation document or flexible scope.	Only clinical microbiolo tions. Three classes of consisting of licensed la either: 1) expert leve 2) limited level of microbiology investig 3) supervised opera performing only P with CE-marked te otherwise generally testing meth
Management and personnel	Led by a professionally qualified person. Personnel with appropriate education, training, experience and demonstrated skills needed to perform the tasks	Led by an expert i microbiolog Clinical microbiolo present in expe laboratory. Personn by the quantity and the operatio

[1] Laboratory-categories were introduced in 1.6.2017 (115)

or operating units are approved for performing diagnostics for infectious diseases. Most of the laboratories are state of the art clinical microbiology laboratories, while the operating units are small medical and healthcare centres, performing only a few microbiological tests, including urine culture, throat swab culture tests and some POC tests with commercial test kits.

Together they conduct over 7,000,000 clinical microbiological investigations per year. Laboratory findings of pathogens listed in Finnish infectious diseases decree (120,121) are reported in the national infectious diseases register (NIDR) maintained by THL. Around 90,000 infectious disease findings per year are entered in the NIDR.

ish licensing system, the German Rili-Bäk and the USA CLIA.

tem	German Rili-Bäk	USA CLIA
	1971	1967
	2014	1988
alid ars	Not stated	Annual competency testing for personnel
ogy investiga- laboratories boratories with el or f clinical gations, and ating units OC tests est kits or y accepted ods.	All clinical laboratory investigations. Requirements of the named investigations are listed in the guidelines.	All clinical laboratory investigations. Three classes of investigations: 1) moderate and high complexity investigations, 2) Provider-Performed Microscopy (PPM) procedures, 3) waived investigations.
in clinical gy. gy expert rt level nel defined d quality of ons.	Led by a professionally qualified person. Personnel who are professionally qualified corresponding to legal regulations. The number of personnel must be sufficient with regard to the amount of work	Led by a professionally qualified person. Personnel who are professionally qualified corresponding to legal regulations. The number of personnel must be sufficient with regard to the amount of work.

Table 3 Comparison of the requirements of the ISO 15189 standard, the Finn

System	Accreditation ISO 15189	Finnish licensing sys
Management and personnel	Led by a professionally qualified person. Personnel with appropriate education, training, expe-rience and demonstrated skills needed to perform the tasks	Led by an expert i microbiolog Clinical microbiolo present in expe laboratory. Personn by the quantity and the operatio
EQA	Mandatory participation in interlaboratory comparison programme(s) (EQA or PT) appropriate for the investigation and interpretations of the results. The laboratory must monitor the results of the programme(s) and participate in the implementation of corrective actions when predetermined performance criteria are not fulfilled.	Mandatory participa EQA on a quarterly it is availab

[1] Laboratory-categories were introduced in 1.6.2017 (115)

ish licensing system, the German Rili-Bäk and the USA CLIA.

tem	German Rili-Bäk	USA CLIA
in clinical gy. gy expert rt level nel defined d quality of ons.	Led by a professionally qualified person. Personnel who are professionally qualified corresponding to legal regulations. The number of personnel must be sufficient with regard to the amount of work	Led by a professionally qualified person. Personnel who are professionally qualified corresponding to legal regulations. The number of personnel must be sufficient with regard to the amount of work.
ation to the basis when le.	Mandatory participation in EQA programmes in accordance with the procedures described in the guideline. The guideline defines the minimum requirements for EQA and IQA for clinical laboratory investigations.	Mandatory participation in approved PT programmes. The testing must be conducted on a quarterly basis, except where the secretary determines for technical and scientific reasons that a particular examination or procedure may be tested less frequently (but not less often than twice per year). Uniform criteria for acceptable performance.

2.4 BASIC PRINCIPLES IN MICROBIOLOGICAL INVESTIGATION

The basics of growing a bacterial culture are same today as they were in the 1880s (123,124). Examined organisms are grown by letting them reproduce in a predetermined culture medium under controlled laboratory conditions. Cultures are grown on agar-plates or dip-slides which are incubated at the optimal temperature for the growth of the suspected bacterial pathogens. In recent years the plating of patient samples has been automated in some laboratories (125,126).

When examining sample materials rich with contaminating bacterial growth, such as in stool specimens, the plates may be given additives to inhibit the growth of undesired bacteria (127–132). Additives can also help to identify the bacteria growing on the plate. By designing a selective base medium and adding chromogenic substrates, media can be designed that allow the differentiation and identification of groups of organisms. There are a variety of chromogenic plates which can be used to cultivate clinical patient specimens to recover pathogens such as *Escherichia coli, Enterococcus* sp. and *Salmonella* sp. (133–135).

Colonies of suspected bacterial pathogens have to be recognised and isolated in order to identify them in detail. Identification is traditionally done using relevant biochemical methods (136–141). Recently matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) is used as the main routine identification method in specialised clinical microbiology laboratories (142,143). In addition, various other modern methods including polymerase chain reaction (144,145), whole genome sequencing (WGS) (146) and microarray methods (147,148) are used in several clinical microbiology laboratories.

In the following three chapters below, a few principles associated with the infections and methods evaluated in this study are briefly described.

2.4.1 URINARY TRACT INFECTIONS AND URINE CULTURE

The clinical diagnosis of urinary tract infection is made on the basis of the symptoms. However, the microbiological diagnosis is based on detecting the growth of known bacterial pathogens in numbers that are considered significant (149,150). UTIs are one the most common infections treated in healthcare (151–154) and the quantitative urine culture is the most common clinical microbiological investigation performed in clinical laboratories. According to THL's register of licenced clinical microbiology laboratories, nearly 200 laboratories annually cultivate over 1.2 million urine specimens in Finland (data from THL's register). While the number of laboratories has declined, the numbers of investigations have remained constant (155). The majority of UTIs are caused by *E. coli, Klebsiella pneumoniae, Enterococcus faecalis*, and *Staphylococcus saprophyticus* (156–158). If the same sample 33 contains several isolates, it is considered contaminated.

The average contamination rate based in a Q-probes study of CAP was about 15% (159). In order to reduce the workload of culturing of all the urine samples sent to the laboratory, flow cytometers are used to screen negative samples in some larger clinical microbiology laboratories (156). The rising trend of antimicrobial resistance is an urgent public health threat (160). From a public health perspective, bacterial strains isolated from urine specimens give valuable information on antibiotic resistance situation in the country.

For example, at present, approximately half of the Extended-spectrum betalactamases (ESBL) producing *E. coli* and *K. pneumoniae* strains (161) and Carbapenemase-producing *Enterobacterales* (CPE) strains (162) in Finland have been found in urine samples.

2.4.2 GASTROINTESTINAL INFECTIONS AND FAECAL BACTERIALCULTURE

Gastrointestinal infections are a major public health issue (163,164). Many of the gastrointestinal infections in Finland are associated with travellers' diarrhoea (161,165). Approximately 70,000 faecal bacterial cultures are conducted each year to clear the ethiology of a suspected diarrheal disease (166). These cultures are done in clinical microbiology laboratories operating in university and central hospitals and in the private sector. The minimum content of a faecal culture panel in Finland specified in the nomenclature of clinical investigations (118) include common diarrhoea-causing bacteria: *Salmonella, Shigella, Campylobacter*, and *Yersinia*. Enterohaemorrhagic *E. coli* is not routinely investigated in all clinical microbiology laboratories.

Annually approximately 4,500 *Campylobacter*, 2,000 *Salmonella*, 100 *Shigella*, 600 *Yersinia*, and over 100 EHEC intestinal infections are reported in Finland (161). There are some new PCR based methods developed to detect bacterial pathogens from stool samples (144,145). However, pure bacterial cultures from samples are still needed for antimicrobial susceptibility testing and epidemiological investigations.

2.4.3 POINT-OF-CARE TESTING AND INFECTIOUS MONONUCLEOSIS

Point-of-care tests have become more common in recent decades in multiple health care settings (167,168). These tests are often used because they are relative easy to use and can be carried out near the patient to shorten the turnaround time and help in patient management (169–171). A variety of POC tests have been developed in order to speed up the diagnosis of certain diseases and streamline the patient flow in healthcare facilities (172–175). At best, POC test results can have an immediate effect on patient care. Because respiratory tract infections are the most common cause of healthcare visits (151,152), the most common POC tests used in Finland are those that are used to diagnose various respiratory tract infections. Thus, streptococcal antigen tests are done in about 670 laboratories

and testing sites with altogether 305,000 tests per year, Influenza A and B antigen tests are carried out in about 210 laboratories and testing sites with 52,000 tests per year, and 22,500 EBV IM tests per year are carried out in 190 test sites (data from THL's register). Laboratory findings on respiratory viruses such as Influenza A and B, Respiratory syncytial virus (RSV) and Adenovirus are mandatorily reported to the NIDR and published annually in the Infectious Diseases in Finland report (161). Numbers of EBV IM findings are not registered.

One of the common viral pathogens causing symptoms of sore throat, fever and fatigue is EBV. It has been estimated that at least 90% of adults worldwide have been infected by it in some point of their lives (176,177). The diagnosis of EBV IM is based on clinical, haematological and serological findings (178–180). Heterophile antibody tests (181) are commonly used for this purpose because they are cheap to perform, robust (182), and available at the POC.

3 AIMS OF THIS STUDY

This study gives insight into the accuracy of the daily diagnostics of patient specimens in Finnish clinical microbiology laboratories and testing sites, and thus patient safety.
Specifically, the study focuses on external quality assessment (EQA) by evaluating the results of external quality control (EQC) samples for three investigations of public health or epidemiological importance. These are:

(I) Quantitative urine cultures

(2) Cultures of faecal bacterial pathogens

(3) Mononucleosis screening tests

4 MATERIALS AND METHODS

4.1 LABORATORIES AND DATA COLLECTION

The data was collected from Finnish clinical microbiology laboratories participating in the EQA process provided by Labquality Ltd. Only the data from those Finnish laboratories who conducted quantitative urine cultures, cultures of faecal bacterial pathogens and/or EBV IM POC tests, were included in the retrospective evaluations. Altogether 413 laboratories met the criteria. The laboratories included large specialised laboratories in university and central hospitals, smaller specialised laboratories focusing on a narrow field of microbiological investigations, as well as POC testing sites operating in small health care centres, private health clinics and occupational health clinics (Table 4.). The number of the laboratories per year changed during the 9 year study period as some laboratories finished and new ones started their microbiological operations.

The laboratories were divided according to their size categorised by the number of named investigations they conducted per year. Quantitative urine culture investigations were done in a total of 335 laboratories, from which 139 were small and 196 large laboratories. Small laboratories analysed less than 1,000 samples per year and large laboratories analysed 1,000 samples or more per year.

All of the 17 laboratories investigating stool samples for faecal bacterial pathogens were large specialised clinical microbiology laboratories, including three private laboratories, four university laboratories and ten central hospital laboratories.

EBV IM investigations were done in a total of 273 laboratories, of which 155 were small and 118 were large laboratories. Small laboratories conducted 50 or less EBV IM investigations per year, while large laboratories conducted 51 or more EBV IM investigations per year. Of the total of 18,885 EQC results, 9,689 came from small, and 9,198 results from large laboratories.

Table 4 *Definition of the large and small laboratories in different EQA rounds. Data on the annual sample number was collected from THL's register of clinical microbiology laboratories.*

Study	EQA Round	Small laboratory	Large laboratory	No of small laboratories	No of large laboratories
I	Quantitative urine culture	<1,000 samples/year	≥1,000 samples/year	139	196
II	Faecal bacterial culture	NA	NA	0	17 [1]
III	EBV IM point-of-care testing	≤50 samples/ year	>50 samples/ year	155	118

[1] All participants were specialised clinical microbiology laboratories.

The EQC results sent by the laboratories to Labquality Ltd are confidential. Access to the Labquality Ltd.'s database was possible only after receiving permission from each laboratory. Letters (Appendix I.) to ask permission was sent to 949 laboratories in Finland and abroad participating in any of Labquality Ltd.'s microbiology EQA schemes during 2009—2012. The same request was sent again the following year. Letters were sent by Labquality Ltd. and the permissions were collected in THL. Laboratories located outside Finland were excluded, in addition to the Finnish laboratories that did not take part in any of the three EQA rounds selected for this evaluation.

Most of the laboratories gave permission for the use of their data from Labquality Ltd. After receiving permission, the data from the laboratories participating in EQA rounds included in this study was collected from this database. The data on the laboratories and from the EQA rounds were merged in THL. The number of laboratories in this study corresponded to the number of participants in the selected EQA rounds and laboratories that conducted these named investigations according to the THL's register. Most of the excluded 536 laboratories did not conduct investigations included in this study, or had discontinued their microbiological operations or were located outside Finland.

Additional information on the laboratories was collected from the register kept by THL of licenced clinical microbiology laboratories and information affecting their operating conditions.

4.2 EQA ROUNDS AND EQC SAMPLES

Of the total of 413 laboratories, 335 took part in quantitative urine culture rounds, 17 in faecal bacterial pathogenic rounds and 273 in EBV IM POC rounds (Table 5.). Quantitative urine culture, faecal bacterial culture and EBV IM POC investigations were selected for the study because the occurrence of UTIs, gastrointestinal and EBV infections are widely investigated in the participating laboratories. The EQC samples in these rounds had been pretested beforehand by an expert clinical microbiology laboratory and the original EQC results were graded by a clinical microbiology expert appointed by the Labquality Ltd. These procedures determined the expected, correct or false, results. In these studies the performance of the laboratories was evaluated based on the number and proportion of correct and false results obtained from Labquality Ltd.'s register. The data accompanying the EQC results contained information on culture and identification methods as well as information on the test kit used.

Altogether data on 26,398 EQC results from 167 EQC samples were evaluated in three different studies regarding EQA rounds during the nine-year study period 2009-2017 (Table 5).

Table 5 *Composition of the studies I, II and III, years, and the numbers of samples, participants and number of results evaluated.*

Study	EQA Round	Years	EQC Samples	Participants	EQC Results
I	Quantitative urine culture	2009-2011	24	335	6,932
II	Faecal bacterial culture	2009-2014	48	17	581
III	EBV IM point-of-care testing	2010-2017	95	273	18,885
All			167	413[1]	26,398

[1] Total number of participating laboratories

In quantitative urine culture rounds Gram-negative bacteria were present in 14, and Gram-positive bacteria were present in 7 of the 24 EQC samples (Table 6.). The most common bacteria present was *E. coli*, which was the sole expected pathogen in 8 samples. The urine culture EQC samples were lyophilised microbial suspensions, which were suspended in a 100ml buffer solution to represent a urine specimen and then cultured according to the laboratory's routine method.

Table 6 *List of the expected findings in 24 quantitative urine culture EQC samples (Study I).*

Expected finding	No of samples
Gram-negative bacteria	
Escherichia coli	8
Klebsiella pneumoniae	2
Klebsiella oxytoca	1
Salmonella Virchow	1
Pseudomonas aeruginosa	1
Acinetobacter baumannii	1
Gram-positive bacteria	
Enterococcus faecalis	2
Enterococcus faecium	2
Streptococcus agalactiae	1
Staphylococcus saprophyticus	1
Aerococcus urinae	1
Negative (Mixed growth)	
Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa	1
Escherichia coli, Proteus mirabilis, Enterococcus faecalis	1
Negative (No growth)	1
All	24

Table 7 List of the expected findings in 48 faecal bacterial culture EQC samples (Study II).

Expected finding	No of samples
Salmonella Abony (serogroup B)	8
Salmonella Agona (serogroup B)	2
Salmonella Enteritidis (serogroup D)	1
Salmonella Give (serogroup E)	4
Salmonella Infantis (serogroup C)	1
Salmonella Poona (serogroup G)	1
Salmonella Typhimurium (serogroup B)	6
Salmonella Virchow (serogroup C)	2
Shigella flexneri	5
Shigella sonnei	2
Yersinia enterocolitica	5
Yersinia pseudotuberculosis	1
Campylobacter jejuni	5
Enterohaemorrhagic *Escherichia coli* O157 (EHEC)	1
Two pathogens	
Salmonella Typhimurium, *Campylobacter coli*	1
Shigella flexneri, Aeromonas hydrophila	1
Shigella boydii, Salmonella Typhimurium	1
Salmonella Enteritidis, *Campylobacter jejuni*	1
Salmonella Enteritidis, *Salmonella* Agona	2
Negative (Normal faecal microbiota)	**5**
All	48

The EBV IM POC EQA rounds were comprised of 95 samples, of which 36 were positive and 59 were negative (Table 8.). From the negative samples 23 represented cases with no EBV antibodies and 36 represented cases with old EBV antibodies.

Table 8 List of the expected findings in 95 EBV IM POC EQC samples (Study III).

Expected finding	No of samples
Positive (recent EBV infection)	36
Negative (no EBV antibodies)	23
Negative (old EBV antibodies)	36
All	95

4.3 STATISTICAL ANALYSIS

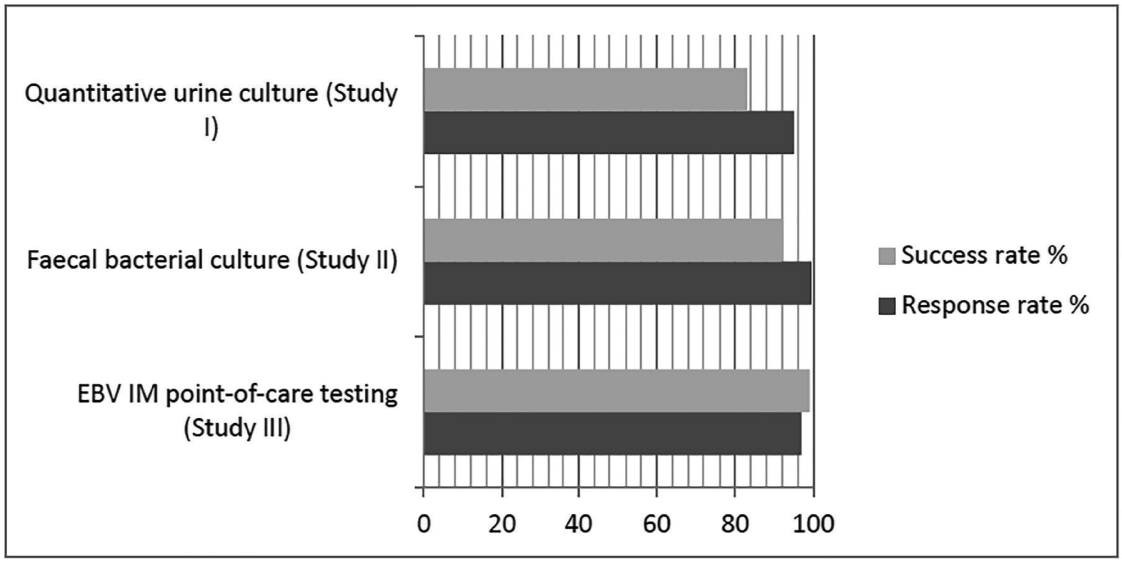
A Fisher exact test and chi-square test were used to compare the results between different sized laboratories, methods used in the investigations, and different sample groups. The effects as changes in percentages were estimated using the delta method. For the more complex associations, a logistic regression analysis was used. (181). A p-value < 0.05 was considered to indicate statistical significance (Table 9.).

Table 9 The statistical methods used and the studies they were used in.

Statistical method	Used in study
The Fisher exact	I, II, III
Chi-square	I, II, III
Delta method	I
Logistic regression	I, III

5 RESULTS

The success rate for quantitative urine cultures was 83%, for faecal bacterial cultures it was 92%, and for EBV IM point-of-care testing it was 99% (Graphic I). The Finnish laboratories that were enrolled on named schemes attended all four rounds per year. The commitment to the EQA was good in all three studies. The laboratories responded by reporting their EQC results to Labquality Ltd in 95% to 99.5% of the cases (Graphic I.).



Graphic I Success and response rates (Studies I, II, III).

5.1 EQA SUCCESS OF QUANTITATIVE URINE CULTURES (STUDY I)

According to the data collected from the EQC samples, the overall success in the quantitative urine culture rounds was 83%. The most common reasons for the 17% false results were interpreting the growth of expected pathogen as non-significant, or that the culture contained mixed growth, or that there was no growth at all. There were differences in detecting and quantifying the growth of Gram-negative and Gram-positive bacteria (Tables 10. and 11.).

Most of the participants were laboratories that only screened samples for significant growth and sent samples classified as positive to a reference laboratory for further investigations. Only 72 (26%) of the 335 laboratories identified growth that was interpreted as significant.

5.1.1 EQC SAMPLES CONTAINING GRAM-POSITIVE BACTERIA

In the data for 7 EQC samples in which Gram-positive bacteria were present, the quantitative result was correct in 68% of 1,994 results (Table 11.). The most common Gram-positive bacterial pathogens found in the urine culture samples, *Enterococcus* sp. and *Staphylococcus saprophyticus* were correctly reported in 85% of the 1,424 EQC results. More untypical findings, *Streptococcus agalactiae* and *Aerococcus urinae* were reported correctly only in 23% and 31% of the 296 and 274 EQC results, respectively

Table 10 EQC results of urine cultures according to the expected findings. CFU/ml in the urine samples ≥10^5.

Expected finding	No. of samples	No. of results	Success rate %
Gram-negative	14	3,964	91
E. coli	8	2,250	93
Klebsiella sp.[1]	3	861	80
other Gram-negative [2]	3	853	99

[1] *Klebsiella pneumoniae* and *Klebsiella oxytoca*

[2] *Salmonella* Virchov, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

5.1.2 EQC SAMPLES CONTAINING GRAM-POSITIVE BACTERIA

In the data for 7 EQC samples in which Gram-positive bacteria were present, the quantitative result was correct in 68% of 1,994 results (Table 11.). The most common Gram-positive bacterial pathogens found in the urine culture samples, *Enterococcus* sp. and *Staphylococcus saprophyticus* were correctly reported in 85% of the 1,424 EQC results. More untypical findings, *Streptococcus agalactiae* and *Aerococcus urinae* were reported correctly only in 23% and 31% of the 296 and 274 EQC results, respectively Table 11 EQC results of urine cultures according to the expected findings. CFU/ml in samples ≥10^5, expected *Aerococcus* ≥10^{4-5}

Table 11 *EQC results of urine cultures according to the expected findings. CFU/ml in samples ≥10^5, expected Aerococcus ≥10^{4-5}*

Expected finding	No. of samples	No. of results	Success rate %
Gram-positive	7	1,994	68
Enterococcus sp.[1]	4	1,130	84
Staphylococcus saprophyticus	1	294	89
treptococcus agalactiae	1	296	23
Aerococcus urinae	1	274	31

[1] *Enterococcus faecalis and Enterococcus faecium*

5.1.3 EQC SAMPLES WITH NO GROWTH OR MIXED GROWTH

According to the collected data, three of the EQC samples during the three–year study period were negative (with no growth or mixed growth). The one EQC sample with no bacterial growth was correctly reported by all (100%) participants and two EQC samples containing mixed growth were correctly reported only in 66% of the results (Table 12.). They were often reported as growing, but the laboratories had commented that in the case of a real patient sample they would be to be sent to the reference laboratory for further investigations. The expected result in these cases was negative, mixed growth.

Table 12 *EQC results of quantitative urine culture EQC samples according to the expected findings.*

Expected finding	No. of samples	No. of results	Success rate %
Mixed growth	2	560	66
Negative (no growth)	1	286	100

5.2 EQA SUCCESS OF FAECAL BACTERIAL CULTURES (STUDY II)

The overall success rate in the faecal bacterial culture rounds was 92%. Common reasons for false results were improper identification of *Shigella* sp. and one biochemically atypical *Salmonella* strain leading to a false negative culture result for those faecal bacterial pathogens. One sample with a low *Salmonella* cell count was also reported to be falsely negative in several participating laboratories.

5.1.2 *SALMONELLA* SP., *CAMPYLOBACTER* SP, *YERSINIA* SP., EHEC AND *SHIGELLA* SP.

During the 6-year study period *Salmonella* sp. was present in 22 EQC samples, of which in 18 cases it was the sole bacterial pathogen (Table 15.). According to the collected data it was correctly identified by all of the participants in 20 EQC samples. All false results with *Salmonella* were caused by two samples, one with a low number of *Salmonella* Typhimurium cells, and other with the *Salmonella Infantis* strain.

According to the collected data, the success rate was 98% for *Campylobacter jejuni* and 96% for *Yersinia* sp. (Table 15.). One false *Campylobacter jejuni* result and one false *Yersinia enterocolitica* result were due to a possible sample mix up. The only false positive result from the negative sample was caused by a suspicion that a normal *E. coli* strain in that sample could have been EHEC. The laboratory responsible for this result stated that if found in a patient sample, the strain would have been sent to the reference laboratory for further investigations.

Table 13 *EQC results of faecal bacterial cultures according to the expected findings.*

Expected finding	No. of samples	No. of results	Success rate %	No. of samples with false results
Salmonella sp.	18	221	95	2
Yersinia sp.	6	75	96	3
Campylobacter jejuni.	5	59	98	1
Escherichia coli EHEC	1	13	92	1
Negative (normal faecal microbiota)	5	59	98	1

RESULTS

According to the collected data, the success rate was 89% for *Shigella flexneri* and 71% for *Shigella sonnei*. Only one EQC sample containing the *Shigella flexneri* strain was correctly reported by all of the participants in that particular EQA round. The results of the remaining six EQC samples contained at least one false negative report per sample from the participating laboratories. In two other EQC samples where *Shigella* was present with some other bacterial pathogen, it was correctly reported in 63% of the 24´ EQC results (Table 17.).

Table 14 EQC results of faecal bacterial cultures according to the expected findings.

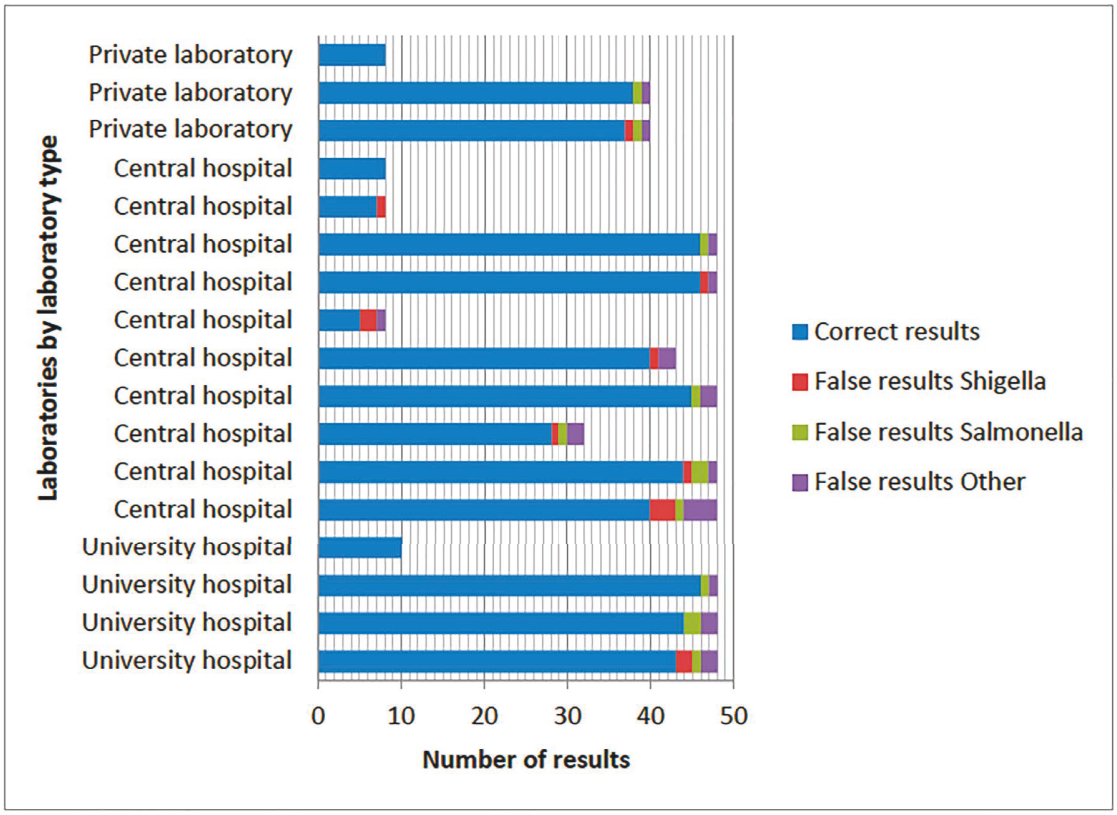
Expected finding	No. of samples	No. of results	Success rate %	No. of samples with false results
Shigella flexneri	5	57	89	4
Shigella sonnei	2	24	71	2

Table 14 EQC results of faecal bacterial cultures according to the expected findings.

Expected findings (two pathogens)	No. of samples	No. of results	Success rate %	No. of samples with false results
Campylobacter sp.[1], *Salmonella* sp.[2]	2	23	100	0
Salmonella Enteritidis, *Salmonella* Agona	2	22	100	0
Shigella boydii, Salmonella Typhimurium	1	12	50	1
Shigella flexneri, Aeromonas hydrophila	1	12	25	1

[1] *Campylobacter coli* and *Campylobacter jejuni*.
[2] *Salmonella* Typhimurium and *Salmonella* Enteritidis.

In this study the participating laboratories were all specialised clinical microbiology laboratories. Investigations of the EQC samples were done in 17 large specialised clinical microbiology laboratories, four of which were university or university hospital laboratories, 10 were central hospital laboratories and three were private laboratories (Graphic 2.).



Graphic 2 The Faecal bacterial culture EQC results from 17 large specialised clinical microbiology laboratories. The laboratories are sorted by the laboratory type (3 private, 10 central hospitals and 4 university hospitals).

False results occurred in 14 of the 17 laboratories, and these laboratories had one to eight false results per laboratory. The three laboratories that reported all the EQC samples correctly participated only in five to four EQA rounds. False results occurred in 14 of the 17 laboratories, and these laboratories had one to eight false results per laboratory. In the laboratories that had reported all the EQC samples correctly the total number of reported EQC results was 10 or less.

5.2.2 SUCCESS OF THE OTHER EUROPEAN LABORATORIES IN FAECAL BACTERIAL CULTURE EQA

In the study the results of tests for faecal bacterial pathogens of other European laboratories were also reviewed. Because the Finnish Communicable Diseases Act only applies to Finnish laboratories, the data was collected only from Labquality's round reports. The number of other European laboratories varied significantly from 17 to 90 laboratories even between the rounds in the same year. It was common that laboratories did not participate in every EQA round per year. The success of the other European laboratories varied between 9%–100%.

The correctly reported EQC results for *Salmonella* sp. were 47%–100%, while they were 60%–88% for *Shigella* sp., 11%–55% for *Campylobacter* sp. and *Yersinia* sp. with success rates varying from 45%–78%, and 9%–96% when there were two pathogens in the same sample Atypical *S.* Infantis and samples with a low cell count of *S.* Typhimurium were reported successfully in 82% and 47% of the other European laboratories.

5.3 INVESTIGATION METHODS USED IN EQA ROUNDS BY THE PARTICIPATING LABORATORIES

According to the collected data from the EQA rounds, the investigation methods varied between the participating laboratories. Additionally, some differences between large and small laboratories were detected in the methods used (see below and Table 19).

EQC samples for quantitative urine cultures were cultured in participating 335 laboratories either on dip-slides or on agar-plates with a 1 µl loop. The dip-slide method was used in 79 laboratories (Table 16.). The plate culture method was used in 246 laboratories, from which non-chromogenic (CLED or Brolacin) was used in 169 laboratories and commercial chromogenic media designed for urine culture were used in 77 laboratories. The dip-slide method was more common among the small laboratories. The growth of bacterial pathogens was determined in both methods quantitatively in terms of CFU/ml. The plate culture method users reported 86% and 87%, and dip-slide users 70% correctly of the urine EQC results. The results by the latter method differed significantly from both of the plate methods ($p<0.001$).

Table 16 *EQC results of quantitative urine cultures according to the used culture method.*

Method	No. of laboratories	No. of results	Success rate %
Dip-slide	79	1,416	70
Plate culture, non- chromogenic medium	169	3,618	86[1]
Plate culture, chromogenic medium	77	1,761	87[1]

[1] $p<0.001$ compared with dip-slide

In faecal bacterial cultures, no methodological differences were detected. During the study period the used culture methods were similar in all the participating laboratories. The laboratories used selenite broth for the enrichment of *Salmonella* before culturing the samples on selective agarplates. Samples were cultured on xylose-lysine-deoxycholate (XLD), cefsulodin-irgasan-novobiocin (CIN), Blood free charcoal-cefoperazonedeoxycholate agar (CCDA) plates and in some cases on Önöz and Cystinelactose- electrolyte–deficient (CLED) plates. Suspicious colonies were selected for further analyses. Potential bacterial pathogens were identified by appropriate biochemical and serological tests.

In EBV IM POC rounds participating laboratories used altogether 17 different test kits to investigate the EQC samples (Table 17.). The test kits were assigned to three groups, latex agglutination tests, immunochromatographic tests, and immunofiltration tests according to the method used. The overall success of the laboratories was 99.3%. The success in obtaining the correct result from EQC samples varied between 94.3 for immunofiltration assays to 99.4% for immunochromatographic assays and 99.6% for latex agglutination tests. Two of the most commonly used test kits Clearview and InstAlert comprised 62% and 25% of the 18,885 results, respectively. Test kits with fewer than 50 results during the study period were analysed together in group "other". In the laboratories, four test kits, Monogen, Monospot, Clearview and InstAlert, were used for the whole eightyear study period. The Monospot test kit was used only in large laboratories. The Mononucleosis and Nadal Mononucleosis test kits were used in only small laboratories. All of the test kits were CE-marked for professional use.

Table 17 *EQC results of EBV IM POC according to the used test method and test kit.*

Method (target)	Test kit (manufacturer)	No. of results	Success rate %
Latex agglutination method (heterophile antibodies)	Monogen (Biokit)	311	99,4
	Monospot (Meridian)	166	100
	Other [1]	27	100
Immunochromatographic method (heterophile antibodies)	Clearview (Unipath/ Alere)	11,766	99,5
	InstAlert (Innovacon)	4,792	99,4
	Mononucleosis (Sure Screen Diagnostics)	694	99,3
	Mnitop (All. Diag)	249	100
	Nadal Mononucleosis (Nal von Minden)	138	97,8
	OSOM Mono Test (Sekisui Diagnostics)	95	100
	QuickVue (Quidel)	76	88,2
	Other [2]	149	99,3
Immunofiltration method (IgM antibodies, EBV VCA recombinant antigen and IEA-ZEBRA peptide)	RDT EBV IgM Assay (Bio-Rad) [3]	422	94,3

[1] Avitex-IM (Omega Diagnostics), M.N.I Test (Fumouze). [2] Mnitop optima IM (Biosynex), Diaquick Mononucleosis Cassette (Dialab), Mono Rapid Test Cassette (Hangzhou AllTest Biotech), Immunocard Stat Mono (Meridian), Mononucleosis Test Card (ulti med). [3] Manufacturers' validation only for the serum samples.

5.4 EQA SUCCESS OF EBV IM POC (STUDY III)

The overall success rate in the EBV IM POC rounds was 99.3%. No difference in the success rates between large and small laboratories were observed. The most significant factor regarding the correctness of the results was the clinical classification of the sample. The samples that represented old EBV immunity were the most difficult to interpreted with a 98.9% success rate (Table 18.). Another important factor associated with the success rate was the test kit used (see Chapter 5.2. and Table 14.).

Table 18 *EQC results of EBV IM POC divided according to the expected findings and clinical status.*

Expected finding	No. of samples	No. of results	Success rate %
Positive (recent EBV infection)	36	7,258	99,6
Negative (no EBV antibodies)	23	4,456	99,5
Negative (old EBV immunity)	37	7,717	98,9[1]

[1] *p < 0.001 compared with results in other categories of clinical status*

Table 19 *Success in EBV IM EQA compared with the test methods and laboratory size.*

Test method	Total laboratory success %	Large laboratory success %	Small laboratory success %	p-value
Latex agglutination method	99,6	99,5	100	1,000
Immunochromatographic method	99,4	99,5	99,4	0,433
Immunofiltration methodl	94,3	94,4	93,7	0,769
All test methods	99,3	99,3	99,3	0,539

[1] *The test kit only included the manufacturer's validation for serum samples.*

6 DISCUSSION

According to Kalra (2004), the error rate of clinical laboratories in the literature varies between 0.1% to 9.3% (184). Because laboratory results play an important role in clinical decision making and the total number of laboratory investigations is considerably large, efforts should be made to reduce the error rate and ensure that it is as low as possible. EQA is one of the tools to monitor the quality of laboratory investigations and help to direct corrective actions to where the impact is most effective.

6.1 PARTICIPATION AND SUCCESS IN EQA ROUNDS

In the Finnish licensing system participation in EQAs on a quarterly basis is mandatory. The most commonly used EQA provider in Finland is Labquality Ltd. The Finnish laboratories that were enrolled on the EQA schemes named in this study participated in all four rounds per year.

During the EQA process not all of the laboratories responded to the EQA tasks in all cases. However, the laboratories replied by sending their EQC results to the assessors from 95% to almost 100% of the time. The response rate was highest in the faecal bacterial pathogens EQA rounds, where all participants were specialised clinical microbiology laboratories, and it was the lowest in the quantitative urine culture EQA rounds, where most of the participants were smaller, non-specialised clinical laboratories and testing sites. This sort of neglect may mean that the importance of the EQA was not properly noted in some laboratories. Leaving paid EQC specimens unanalysed and unreported means wasted money and missed educational opportunities.

6.1.1 QUANTITATIVE URINE CULTURE

In the quantitative urine culture tests, the numbers of bacteria were correctly reported in 83% of EQC results. The correct results were more often obtained from samples containing Gram-negative bacteria (91%) than from samples containing Gram-positive bacteria (68%). The most common bacterial pathogens such as *E. coli* (93%), *Staphylococcus saprophyticus* (89%), *Enterococcus* sp. (84%) *Klebsiella* sp. (80%) were more often detected and correctly quantified, than the rarer ones such as *Aerococcus urinae* (31%) and *Streptococcus agalactiae* (23%). During the 3 year study period improvement in the success of these EQC results was not observed.

The data of the EQC results showed that the test method had influenced the results of the urine cultures. Namely, the laboratories using the plate culture method succeeded statistically significantly better (correctly answering 86% of the time) than those using the dip-slide method (69%). Dip-slides were preferred in the smaller laboratories, while plate cultures were more common in larger laboratories. In previous studies on quantitative urine culture and dip-slide devices by Morandi et al. (2007), Swiss EQC results indicated that specialised

laboratories achieved better results when compared to results in medical practices (185). In this study the laboratory size did not have an effect on success in the EQA rounds. In this study the difference between methods was most evident with EQC results from the samples containing Gram-positive bacteria and in these cases the culture method had more of an effect on the success than the laboratory size.

In this study EQC results with overly low CFU/ml values were reported significantly more often in laboratories using the dip-slide (69%) method than the plate culture (86%) method. Similar results have been shown by Aspevall et al (2000) and Morandi et al (2007) (185,186). However, the opposite results have been published by Petterson et al. (1995) (187). In the data analysed in this study the difference was greatest in the EQC samples containing Gram-positive bacteria. In addition to the incorrect CFU/ml measurements there were also high numbers of laboratories that reported the EQC samples as negative. Because the medium commonly used in quantitative urine cultures are designed to support the growth of Gram-negative rods, Gram-positive bacteria can be left undetected and unreported because of their week growth and small colony size.

In this study one EQC sample contained a high concentration of *S. agalactiae*. Of the dip-slide users, 37% reported the sample as negative, compared to the 6% of the plate culture users. The poor growth of *S. agalactiae* on dip-slides has been observed previously (185,186,188) and small colonies are difficult to detect from the agar surface (189). In European urinalysis guidelines (190) it is recommended to use a sensitised urine culture with 10 µl loop and a non-selective medium such as blood agar in addition to the selective agar in quantitative a urine culture. Based on the findings of this study if the routine culture from a symptomatic patient remains negative or the patient is pregnant, a urine culture with blood agar should be available. According to the data of the EQC samples evaluated in this study, chromogenic media were shown to be equal to non-chromogenic media in the determination of the abundance of growth, and even significantly better in the case of *S. agalactiae*.

6.1.2 FAECAL BACTERIAL PATHOGENS

For the faecal bacterial culture tests, the results were correct for 92% of the cases. Of the 48 EQC samples, 67% were correctly reported by all laboratories. Common findings such as *Salmonella* sp. and *Campylobacter* sp. were found reliably. False negative *Salmonella* results were given for two of the 18 samples. One of these contained an atypical *Salmonella* strain and the other had a low count of *Salmonella* cells. False negative Shigella reports were given for six of the seven samples. False positive results were rare, two of them were due to a possible mix-up with the samples and one was the false suspicion of an *E.coli* EHEC strain.

EQC sample containing *Salmonella* Infantis strain was successfully reported only by 67% of the participating Finnish clinical microbiology laboratories. This strain is an atypical H_2S negative *Salmonella* strain. Because of the ability to produce hydrogen sulphide (H_2S) *Salmonella* strains usually produce black colonies on selective plates such as XLD (191). Some non-typical H_2S negative *Salmonella* strains exist and can be missed in culture and screening the samples only by the production of H_2S (192,193). Chromogenic media for *Salmonella* have been developed (194), according to the data collected in this study they have not been introduced in clinical microbiology laboratories in Finland.

One EQC sample with a low count of *Salmonella* cells was successfully reported in 33% of the participating laboratories. Often in patients with symptoms of gastroenteritis, *Salmonella* cell counts in stool sample are high. In Finland, food workers are screened for asymptomatic *Salmonella* carriage (195), especially in these cases where the bacterial count in stool samples is low, enrichment procedures are important. In Finland a commonly used selenite enrichment broth inhibits the growth of many contaminating bacteria such as *E. coli* and enterococci in stool samples in the first 6-12 hours and then the inhibitory effect gradually declines. When incubated for too long, contaminating bacterial growth can overgrow the low cell count pathogen. Selenite is also slightly inhibitory to *Salmonella* and pathogens can be missed if a low cell count containing sample is plated only after enrichment.

13 false negative *Shigella* EQC results were reported by nine of the 17 participating laboratories. *Shigella* is a known bacterial pathogen which should be looked for in faecal bacterial cultures (139,196). There were differences in the success of reporting different *Shigella* species correctly. *S. flexneri* as a single pathogen was reported correctly in 89% and *S. sonnei* as single pathogen in 71% of the EQC samples. This could be due to the differences in the colony morphology of the control strains used in these EQC samples. While *S. flexneri* produces very small clear red colonies on commonly used XLD -plates, *S. sonnei* produces larger, opaque colonies on XLD plates (197), which are more easily missed as normal faecal growth.

If the prevalence of a rare bacterial pathogen in patient samples is low and the identification is done with expensive reagents, one option is to send the suspected pathogen to a reference laboratory for further investigation. At the moment this is done in some laboratories, for example, in the case of *Salmonella* and *Shigella* serotyping. All *Shigella* and *Salmonella* isolates of domestic origin are sent to the reference laboratory at THL for further pheno- and genotypic characterization. In the EQA rounds in this study, an acceptable result was a finding of *Salmonella* sp. and *Shigella* sp. with the comment that the suspected bacterial pathogen strain would have been sent for further investigation at the reference laboratory. In the case of two *Salmonella* species, *S.* Enteritidis and *S.* Agona in the same EQC sample, only a few laboratories identified the pathogens to the serogroup level. Because the identification of the pathogen to the genus level was acceptable the EQC result was correct if either one was found and reported as *Salmonella* sp. In

the case of this particular EQC sample, it was possible to succeed better with the genus level result than the more detailed EQC result. Because only a pure culture of a suspected pathogen is sent to the reference laboratory, the serotyping result could be from just one of the findings if two strains were not originally suspected.

Previous studies conducted on 27 and 26 Finnish clinical microbiology laboratories taking part to the UK Neqas general bacteriology rounds during in 1994–1997 (55) and 1998–2003 (198) showed similar difficulties in faecal bacterial culture investigations as were found in this present study. In both of those previous studies EQC samples containing *Shigella*, *Campylobacter* and *Vibrio* strains were the most difficult. This present study, however, found that the success with EQC samples containing *Campylobacter* had improved but difficulties with *Shigella* still existed.

As a comparison to Finnish clinical microbiology laboratories, the EQC results from faecal bacterial pathogens rounds of other European laboratories were also reviewed. Because the Finnish Communicable Diseases Act applies only to Finnish laboratories, the data of other European laboratories was collected from Labquality's EQA round reports. The success of these laboratories varied between 9%–100%. In addition to the same difficulties, *Shigella* sp. and two pathogens in the same sample, as seen in the data collected from Finnish laboratories. Other European laboratories had difficulties with *Campylobacter* sp. and *Yersinia* sp. with success rates varying from 11%–55% and 45%–78%, respectively. A possible explanation for this is that *Campylobacter* sp. requires specific culture conditions including a microaerobic atmosphere (139,141) and *Yersinia* sp. do not belong to the basic panel for faecal bacterial pathogens panels in some European countries (199,200). Atypical *S.* Infantis and samples with low cell counts of *S.* Typhimurium were reported successfully in 82% and 47% of the other European laboratories, which was slightly better than in the Finnish laboratories.

Finnish laboratories have invested in the introduction of PCR-based methods (145,146), and it remains to be seen whether these will improve the discovery of faecal bacterial pathogens from diarrhoeal stool samples. Some indication of increased recovery rates can be seen in the EHEC findings reported to the NIDR in recent years (162,167). The target of the PCR-based methods, the invasion plasmid antigen H (IpaH) is carried by *Shigella* as well as by enteroinvasive *E. coli* (EIEC) (201). For this reason, in order to successfully isolate *Shigella* strains from patient samples reliably, a working culture method is still needed (202,203).

6.1.3 EBV IM POC

Heterophile antibody tests are widely used to test for EBV IM, partly because they are cheap, rapid, and easy to use. These tests have improved over the past decades (204–207). Even though POC tests are designed to be easy to use, the visual reading and interpretation of the test results requires skills and experience from the personnel conducting the investigation. According to Fox et al. (2006) and Nissinen et al. (2009), laboratory personnel were better at producing the

right answer with POC tests for Group A *Streptococcus* (GAS) antigen detection than nursing staff (54,208). As the results are often qualitative, it makes the interpretation of the test results even more important. There are some recorded cases of mononucleosis pseudo epidemics due to falsely interpreted test results (209,210). In this study, no laboratory stood out with a high number of false EQC results and 46 of the 130 reported false EQC result were from EQA rounds that yielded one or two false EQC results per round. The randomness of the scattered false results found when analysing the data from the EBV IM EQC samples might indicate that there were some troubles in conducting the test or interpreting the results at that particular time.

6.2 SOME LIMITATIONS OF EQC SAMPLES

It has been stated that a good EQA scheme should be suitable for a wide range of methods used in clinical laboratories, and that it should be traceable, cost-effective and appropriate for the intended purpose (79,211). An EQA gives an overview of the situation of a laboratory's quality at a given time. However, there are some limitations regarding EQAs and EQC samples that should be kept in mind. In order to get the most realistic assessment of the situation, EQC samples should be processed as normal patient samples. In real life this does not always happen, and in these cases the results from the EQC samples reflect the best possible quality of the laboratory (212). In order to assure the quality of the results all of the time, laboratories should also have a suitable IQC in place.

The sample matrix of EQC samples should be the same that is commonly in use in the participating laboratories (213), but in real life in order to guarantee a large enough range for all the participants, the EQA organisers are forced to use artificial simulated samples or samples with equivalent matrix-like serum and plasma. An example of compatibility was encountered in this study when the data for the EBV IM POC EQC results were being analysed. The EQC samples manufactured from single patch plasma were analysed in the participating laboratories with a test that had been validated by the test kit manufacturer to be used only for serum samples. In this case the success rate of this test was only 91% for the negative EQC samples and 100% for the positive EQC samples.

In microbiology there are also some restrictions on the bacterial strains which can be used in EQC samples, for example *Salmonella* Typhi and *E. coli* strains that can produce Shiga toxins (Stx) are not suitable for this purpose. As a substitute for Shiga toxin producing *E. coli* strains, in EQC samples non toxicogenic *E. coli* O157 strains have been used. After the introduction of new methods that are based on the toxin or stx-gene detection (214), these strains are no longer valid as EQC control strains.

6.3 TEST METHODS USED IN THE EQA ROUNDS BY THE CLINICAL LABORATORIES AND TESTING SITES

In Finnish microbiological laboratories test methods are selected by the laboratory's clinical microbiological experts and other personnel responsible for that particular laboratory. In the case of the EQA rounds in this study, the tests were done using commonly used microbiological methods and techniques (195).

6.3.1 URINE CULTURE TEST METHODS USED IN THE EQA ROUNDS

In clinical laboratories urine samples are commonly inoculated on agar plates using 1 µl calibrated plastic loops (215). Conventionally laboratories use non-chromogenic media such as CLED or Brolacin (127,150). Chromogenic media has been widely available since the 1990s (133,216). In Finland the first chromogenic media appeared in the results of quantitative urine culture EQC samples in 2005 and the number of users has gradually increased over the years. In the study period 2009–2011 77 laboratories used chromogenic media in quantitative urine culture investigations. Mixed growth is more easily seen from chromogenic media (217,218).

In addition to plate cultures, small laboratories especially use dip-slide devices containing two or more agar slides typically made from CLED, MacConkey and Eosin methylene blue (EMB) agar (185,217,219). Dip-slides and culture plates are commonly read after overnight incubation (220,221).

In order to relieve the large workload from culturing urine culture specimens, to standardise the inoculation step (215) and shorten the TAT, clinical laboratories have taken various methods into use. In Finland, laboratories have traditionally used so called graduated urine cultures, where samples are first screened in smaller laboratories closer to the patient, and only those that are positive or unclear are sent to a larger laboratory for further investigation (69). In this study only one quarter (72) laboratories identified the uropathogens with growth interpreted as significant. Of these, 23 were laboratories that analysed over 10,000 urine culture specimens per year. Large clinical laboratories can also screen samples using flow cytometry (156,222), or automation in culturing the samples (126,223), but this information was not included in the data that was analysed in this study.

6.3.2 FAECAL BACTERIAL PATHOGENS TEST METHODS USED IN THE EQA ROUNDS

All of the 17 participants in the faecal bacterial pathogen EQA rounds during the 6-year study period were specialised clinical microbiology laboratories,

and according to the accompanied questionnaire (data not shown), the culture methods in use were similar between laboratories. The methods were the same that are commonly used in clinical laboratories all around the world (138,224). All the participating laboratories used similar plates and broths to detect the four most common bacterial pathogens (*Campylobacter*, *Salmonella, Shigella* and *Yersinia*) from stool samples. Selenite enrichment broth, which is selective for *Salmonella* (225) was commonly used to enrichment for this particular pathogen. Samples were inoculated on plates before and after enrichment. For *Salmonella* and *Shigella*, plates such as XLD, Önöz and CLED were commonly used. For *Yersinia*, laboratories used CIN and for *Campylobacter* CCDA plates.

Routine laboratory techniques for identification of suspicious bacterial colonies picked from the primary culture plate are most commonly done by microscopy, while interpretation of bacteria phenotypic characteristics and biochemical reactions are tested using commercial methods including API20E (139,141), the VITEK 2 Gram-negative (GN) Identification Card (226) and for some instances an in-house carbohydrate fermentation test. These analyses are time-consuming and require lots of expertise from the laboratory personnel conducting them. The latest addition in typing methods in clinical microbiology is MALDI-TOF MS where the bacterial strains are identified according to a protein profile which is compared against a the reference database (142,143). The quality of the identification depends on the coverage of that database. Despite the methodology used in the 57 identification, EQA schemes should also cover this area of the investigation. In this study data on the identification method was not included in the data for the EQC false negative results. Because of this, the influence of the identification method on the success in the EQA rounds could not be analysed.

6.3.3 EBV IM POC TEST METHODS USED IN THE EQA ROUNDS

In the Finnish licensing system EQA participation on a quarterly basis is mandatory. The most commonly used EQA provider in Finland is Labquality Ltd. The Finnish laboratories that were enrolled on the named EQA schemes in this study attended all four rounds per year. The most commonly used test methods were immunochromatographic methods (12 test kits, 17,959 EQC results), followed by latex agglutination methods (4 test kits, 504 EQC results) and one immunofiltration method (1 test kit, 422 EQC results). Two of the most common test kits, Clearview and InstAlert, comprised 88% of the total number of the EQC results. In this study there were also differences in the used test methods between large and small laboratories. According to the data for the EBV IM POC EQC results, five of the 17 EBM IM test kits were used either in large (Monospot, MNI test and Mnitop) or small (Mononucleosis and Nadal Mononucleosis) laboratories.

The lot-to-lot variation is a problem especially in POC testing where there are limited possibilities to use reagent controls and calibrators due to the nature of the testing process itself. Investigations are done one test at a time possibly during a long period of time and in some cases the reagents in the test kit are tested only

when opening a package for the first time. Additionally, the yearly volume of the investigations can be so low that a change in the results may be difficult to detect. In this study, a possible case of the lot-to-lot variation leading to false EQC results was noted. Unfortunately, this could not be confirmed because data on the lot information was not collected by the EQA organiser. In tests where lot-to-lot variation is a possibility, information regarding the test lot should be included in the EQC result reporting form. This information would be especially helpful for the participants when investigating the cause of discrepant EQC results (227). When there are enough participants and the EQC material is communicable enough, diagnostic test manufacturers can use the EQC results for post-market evaluation (228). There were differences between the test kits used in large and small laboratories. Monospot, the MNI Test and Mnitop were used only in large testing facilities. Mononucleosis and Nadal Mononucleosis were used only by small testing facilities. Monogen, Clearview, InstAlert, OSOM Mono Test, QuickVue and the RDT EBV IgM Assay were used in both large and small testing facilities. From the 17 test kits, only four were used during the whole eight-year study period. These test kits were Monogen, Monospot, Clearview Discussion 58 and InstAlert. All the test kits used in the EQA rounds evaluated in this study were CE-marked and were suitable for POC testing.

The used tests and testing methods have been changed in the clinical microbiology laboratories for many reasons. EBV IM POC test kits and test methods have improved during the past decades (203–205,229). Additionally, competitive tendering and user friendliness (182) have had effects on the used test kits and testing methods. In the study by Leinikki et al. (1998) the participating laboratories used10 tests in 1996. The most common of these was the latex agglutination method Monosticon Dri-Dot test and it was used in 60 of the evaluated 81 Finnish clinical microbiology laboratories (230). This test kit was not seen in this study, and the latex agglutination method was used only by a handful of participating laboratories.

6.4 CONSEQUENCES OF THE FALSE RESULTS OBSERVED FROM THE COLLECTED DATA

In the Finnish licensing system the participation in EQA on a quarterly basis is mandatory. The most commonly used EQA provider in Finland is Labquality Ltd. The Finnish laboratories that were enrolled on the named EQA schemes in this study attended all four rounds per year. The avoidance of the overuse, underuse, or misuse of the clinical investigations is important (231–234). This study found that of the urine culture EQC samples containing mixed growth, 66% of the testing sites reported false positive results. For these samples, the testing sites often reported growth but added the comment that in the case of a real patient sample they would have sent the growth to the reference laboratory for further investigation. The expected result in these cases, however, was negative mixed growth. Ideally, no medical decision is made without a reason and the same principle applies also in ordering clinical laboratory investigations. In routine daily practice, if a urine sample is taken without clinical symptoms from a patient just in case, this result can lead to unnecessary additional testing and antibiotic treatments (235–237).

The clinical laboratory investigations also have a public health aspect. For example, when examining clinical samples for faecal diarrhoeal bacterial pathogens, laboratories play an important role in the prevention of additional transmissions. The fact that so many *Shigella* positive EQC samples were reported as negative raises the question of what the performance of the cultures are in the case of real patient samples. It has been previously shown that laboratory diagnostics of *Shigella* are difficult and it remains to be seen whether new techniques will bring any improvements to the situation (197,238,239).

EBV IM is diagnosed based on clinical, haematological, and serological findings. Symptoms of EBV IM may resemble malignant haematological 59 diseases and therefore false positive results that were also seen in this study can cause delays in initiating the right treatment. In this study, the most significant factor in obtaining the correct EQC result was the clinical classification of the EQC sample. Negative EQC samples that represented old EBV immunity were the most difficult to interpret with a 99% success rate compared to the positive EQC samples representing recent EBV infections and negative EQC samples with no EBV antibodies with success rates of almost 100%.

6.5 FUTURE TRENDS AND THEIR EFFECT ON THE EQA ROUNDS

The selection of the test types that laboratories offer have been influenced by the increased knowledge on diseases, improvement in methodology, need for shorter TAT in the clinics, and the need to cut costs in laboratories. Good examples of this include the introduction of multiplex PCR in the detection of faecal bacterial pathogens (144,145), and the screening of the negative urine samples with flow cytometry before culturing the samples in a microbiological laboratory (240,241). Because quality comprises all the steps of the investigation, EQA schemes should be expanded to cover the whole laboratory process (28). In this study the EQC results covered only the bacterial culture part of the investigation.

In clinical microbiology, the technical part of testing process and the interpretation of the result are closely linked. For example *Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus saprophyticus* are common bacterial pathogens and their role in urinary tract infections is clear, but the role of *Streptococcus agalactiae* and *Enterococcus* sp. found in urine samples requires consideration of how the result is presented to the clinician (242). The less frequently encountered bacterial pathogens often caused identification problems for the participating laboratories in this study. *Aerococcus urinae* is a rare urinary tract pathogen, and it is rarely encountered in clinical specimens (243). In future the interpretation part will become increasingly important and the new methods such as MALDI-TOF MS and WGS that have improved the TAT and accuracy of identification of bacterial pathogens in clinical samples (244) an which have increased the information on the bacteria found in clinical samples should be taken into account in the EQA rounds. In this study the data on the EQC results contained only the information for the reported pathogen. Because of this, the determination of whether the pathogen in the EQC sample was not detected or whether it was falsely interpreted as insignificant was not possible.

Clinical laboratories are becoming larger and more centralised with fewer smaller laboratories and this is also the current situation in Finland (245,246). This trend can have both positive and negative impacts concerning the quality of clinical microbiology laboratory investigations. Larger laboratories can provide better equipment and more routine in the sample processing. In times when there is a shortage of an educated workforce in the laboratory field (90), larger laboratories might be able to guarantee educated and experienced staff to be present in the laboratory. In this study the concentration of the laboratory field was seen in declining a number of the participating laboratories in the EQA rounds, but no change in the EQC results was observed during the time. In addition to this, based on the data analysed in this study, the laboratory size did not have an effect on the success in the EQA rounds.

Distant central laboratories can also mean longer transportation times which can have negative effects on the quality of patient samples. Longer transport

times mean longer final response times, and because the TAT has an influence on patient care and management in the clinics POC-testing in testing sites outside the laboratory has started to increase. Smaller, near patient testing sites and larger, specialised clinical microbiology laboratories can use equipment and methods that differ from each other, even though the investigation carries the same name. The method used can have a significant effect on the results, as was seen in this study in the case of quantitative urine culture and EBV IM POC EQC results. An EQA is an important part of the quality management in both clinical laboratories and testing sites, and EQA organisers should keep an eye on the developing methodology in order to adjust the schemes to fit the purpose for as many of the potential customers as possible.

6.6 ROLE OF ACCREDITATION AND LICENSURE IN CLINICAL LABORATORY

Accreditation is important for clinical laboratories to show service users and stakeholders that the quality processes are organised properly. The mutual recognition and international status of accreditation improve the conformity and mobility of laboratory services. In addition to accreditation, there are national licensing systems and regulations to respond to differences in the organisation of clinical laboratories in different countries (234). A common feature of these national regulations are, that they are stricter, and they have more specific terms and criteria that clinical laboratories need to fulfil.

The accreditation standards and licensing specifications direct the clinical laboratories to participate regularly in relevant EQA rounds. In the Finnish licensing system, clinical microbiology laboratories are obliged to take part in at least four EQA rounds per year, if suitable rounds are available, though in the Finnish licencing system the level of success in these rounds is not defined. The EQC results can be used as a tool when evaluating and comparing the quality of the clinical laboratory services. Because the aim is the constant improvement of the process, setting a minimum level of success 6l in EQC samples in the Finnish context is not necessary. Based on the results of this study, false EQC results were not concentrated in certain participating laboratories.

At the time when the EQC samples whose data was analysed in this study were sent, many of the 25 large specialised clinical microbiology laboratories were already accredited, but the rest of the participating laboratories and testing sites were not. Because of this, in this study the difference in success between accredited and non-accredited laboratories was not evaluated. Accreditation of the large clinical laboratories has become more common during the centralisation of the laboratory field, but the trend is not the same in small laboratories and testing sites.

According to the literature, the results of accreditation have been variable. According to Ehrmeyer and Laessig (2004), the activities leading to accreditation can improve quality-related processes in the clinical laboratory (247), and the

process was found to be beneficial in building up laboratory quality in Abu Dhabi (248) and Turkey (249). In Sub-Saharan Africa, Microbiology EQA results improved notably after accreditation (250), while in Singapore accreditation of cervicovaginal screening laboratories led to relatively minor improvements (251). In Finland, there were no differences in serum total-calcium and glucose measurement results between accredited and non-accredited laboratories (252). According to Strandén et al. (2004), in the study conducted on 26 Finnish clinical microbiology laboratories taking part to the UK Neqas General bacteriology rounds during years 1998– 2003 there were no differences in success between accredited and nonaccredited laboratories (197).

The real focus in EQA schemes should be on continual improvement where it is possible. According to Bartlett et al. (1994), success in EQA schemes should be regarded as achieving the minimum acceptable performance and the aim should not be to receive the accreditation status (253). Based on this study, the participation in the EQA rounds was regular, but no rising trend in success in EQA results was observed in these studies.

In this study the success in the EQA rounds between years and participating laboratories was stable. The same types of errors recurred during the study period. This can mean that the educational role of the EQC samples has not been exploited to the full extent in the participating laboratories and the idea of constant improvement has been forgotten for these investigations.

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Appendix I.

Helsingissä, heinäkuussa 2012

Asia: Labqualityn ulkoisen laadunarvioinnin tulokset vuodesta 2009 alkaen
Viite: Tartuntatautilain §10, 4 mom

Hyvä kliinisen mikrobiologian laboratorion vastuuhenkilö

Terveyden ja hyvinvoinnin laitoksen asettaman toimilupatyöryhmän asiantuntijasihteerinä olen tekemässä selvitystä laboratorioiden ulkoisen laadunarvioinnin tuloksista. Selvitystä varten pyydän saada nämä tulokset käyttööni. Käytännössä pyydän teitä valitsemaan, saako laboratorionne tulostiedot toimittaa sähköisesti suoraan Labqualitystä vai haluatteko toimittaa ne itse kirjeitse paperikopioina.

Tavoitteena on selvittää laboratoriotutkimusten laatua kansallisella tasolla ja siihen mahdollisesti vaikuttavia tuotannollisia tekijöitä. Ensimmäisenä tarkastelun kohteeksi on tarkoitus ottaa uloste- ja märkäviljelyt. Jatkossa tarkastelemme muidenkin kierrosten tuloksia. Labqualityä varten tarvitsen teiltä allekirjoituksen, jonka voitte antaa palauttamalla tämän kirjeen mukana tulevan liitteen täytettynä allekirjoittaneelle, halutessanne sähköpostinkin välityksellä. Pyydän vastaustanne mahdollisine tuloskopioineen 15.8.2012 mennessä.

Yhteistyöstä kiittäen,

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salla.kiiskinen@thl.fi tai 0295 247697

LABQUALITYn mikrobiologian ja immunologian ulkoiset laadunarviointikierrokset

Ulkoisen laadunarvioinnin mikrobiologian ja immunologian kierrosten tulokset

☐ saa toimittaa suoraan Labqualitystä

☐ ei saa toimittaa suoraan Labqualitystä, vaan toimitamme tarvittavat tulosteet itse

Mikäli laboratorionne ei anna suostumusta kaikkien kierrostulosten luovuttamiseksi suoraan Labqualitysta, alla mainittujen kierrosten tulokset

5180 Salmonellaviljely (2009-2011 Kierrokset 1-4)

5190 Ulosteviljely 1 ja EHEC-viljely (2009-2011 Kierrokset 1-4)

5080 Bakteeriviljely 1, aerobit ja anaerobit (2009-2011 Kierrokset 1-4)

☐ saa toimittaa suoraan Labqualitystä

☐ ei saa toimittaa suoraan Labqualitystä, vaan toimitamme tarvittavat tulosteet itse*

Päiväys:_____

Laboratorion nimi ja osoite:_____

_____

Labqualityn asiakasnumero:_____

Allekirjoitus, nimen selvennys ja asema:_____

_____

*Mikäli ette halua em. kierrostuloksia (5180, 5190 ja 5080 2009-2011) toimitettavan suoraan Labqualitystä, pyydämme ystävällisesti lähettämään niistä paperikopiot 15.08.2012 mennessä osoitteeseen

Toimilupatyöryhmä/ Salla Kiiskinen
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