

# Infected total hip arthroplasty

Bacteriology and the role of operating room ventilation in the reduction of postoperative infection

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Håkon Langvatn

Avhandling for graden philosophiae doctor (ph.d.)  
Universitetet i Bergen  
2020

UNIVERSITETET I BERGEN



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## Abbreviations and terms

<b>ACH</b>	Air Changes per Hour
<b>CFU</b>	Colony Forming Units
<b>CoNS</b>	Coagulase Negative Staphylococci
<b>CRP</b>	C-Reactive Protein
<b>CV</b>	Conventional mixing Ventilation
<b>DAIR</b>	Debridement, Antibiotics and Implant Retention
<b>DTT</b>	Difficult-To-Treat
<b>ESR</b>	Erythrocyte Sedimentation Rate
<b>HEPA</b>	High-Efficiency Particulate Air
<b>LAF</b>	Laminar Airflow
<b>MRSA</b>	Methicillin Resistant Staphylococcus Aureus
<b>MRSE</b>	Methicillin Resistant Staphylococcus Epidermidis
<b>NAR</b>	Norwegian Arthroplasty Register
<b>PCR</b>	Polymerase Chain Reaction
<b>PJI</b>	Prosthetic Joint Infection
<b>SSI</b>	Surgical Site Infection
<b>THA</b>	Total Hip Arthroplasty
<b>UDF</b>	Unidirectional Airflow
<b>VFR</b>	Volume Flow Rate
<b>WBC</b>	White Blood cell Count
<b>WHO</b>	World Health Organization

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## Scientific environment

This project was commenced in 2007 when I, as a medical student at the University of Bergen, started a pilot study under the supervision of Professor Lars Birger Engesæter who at that time was a professor and consultant surgeon in the orthopaedic department of Haukeland University Hospital, and leader of the Norwegian Arthroplasty Register (NAR). The work continued when I took up my position as a resident in the orthopaedic department of Haukeland University Hospital in 2012. Most of the basic work was conducted in my position as a medical doctor and researcher in the department of orthopaedic infection and rehabilitation in the period 2014-2016. The work was finalized when I began to work as a resident in the orthopaedic department of St. Olav's University Hospital in Trondheim in 2018, where I was funded for 50% research and 50% clinical work from March 2019. I have received supervision from personnel at the Norwegian Arthroplasty Register, with Håvard Dale as my main supervisor. The project has been funded by scholarships from the NAR, the Norwegian Orthopaedic Association, the Norwegian Association for Hip and Knee Surgery and Ortomedic, in addition to funding from the orthopaedic departments of Haukeland and St. Olav's University Hospitals. The thesis is a part of the PhD programme of the departments of clinical medicine and clinical dentistry at the University of Bergen.



**ORTOMEDIC**



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Family – by far the most important. My best friend and wonderful wife Stine, as well as my kids and executive producers: Ida, Herman and Live. My dad Hogne and my mum Wenche who at an early stage in my life taught me lessons about hypothermia as a possible risk factor for infectious disease (“put your jacket on!” etc.). Thank you for teaching my kids the same lessons by being of indispensable help during busy working days. My big brother Christian – thank you for not killing me, just making me stronger.

Co-authors, employees at the NAR and all the surgeons trying to report stuff to them. A special thanks to my main man Dr. Håvard Dale who has shown great tolerance. We are a couple of weirdos and we have been an awkward duo, but regardless of our differences, I believe both you and I have learned from our cooperation and appreciated it. A bunch of thanks for your broad knowledge and subsequent sharp and precise feedback. I owe you one. Thanks to Jan Schrama and Lasse Engesæter who took me under their wings and initiated the whole thing. Olav Lutro who was my inspiration and portal into the world of microbiology and internal medicine. Thank you also for being a culinary inspiration at the annual meetings of the European Bone and Joint Infection Society (EBJIS) - which, by the way, we won in 2019. Just thought I'd mention it. Huge thanks to Ove Furnes, Kjell Matre, Jonas Meling Fevang, Ivar Rossvoll and Tina Wik who, by virtue of their positions as heads of department at Haukeland University Hospital and St. Olav's University Hospital, gave me time and funding to finalize this project in parallel to clinical and surgical practice. Lasse Engesæter, Leif Havelin and Ove Furnes who through their positions as leaders of the NAR gave me the opportunity to use data from the register.

Thank you all, and be excellent to each other.

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## English abstract

Each year approximately 7,000 patients receive a total hip arthroplasty (THA) in Norway. The most common indication is osteoarthritis and most patients experience substantial pain relief postoperatively. A rare but much feared complication after arthroplasty surgery is postoperative prosthetic joint infection (PJI). This is a huge burden for patients and a technical challenge for surgeons, generating huge costs for the health care system and society. Knowledge of how and why these infections arise is essential in order to provide the best possible prophylaxis against and treatment of PJI. The aim of the first part of this thesis was to assess what kind of bacteria cause revisions due to infection after THA (*Paper I*). We also wanted to assess correlations between bacteriology and haematological findings (*Paper I*) and antibiotic resistance amongst the bacteria found in THA revisions due to infection (*Paper II*).

We used the Norwegian Arthroplasty Register (NAR) and supplemented this with bacteriological findings including antibiotic resistance patterns and preoperative blood samples including parameters of infection, collected from patient records. As expected, we found a large proportion of Staphylococci, a commensal organism known to be part of normal human skin flora. Coagulase negative staphylococci (CoNS) showed increased resistance to several antibiotics that are used both as prophylaxis and in empirical and definitive treatment of PJI. As the staphylococcus aureus (*S. aureus*) species led to significantly higher biochemical parameters of infection compared to CoNS, our results might inform the choice of empirical treatment based on haematological status in cases of arthroplasty infection with an unknown causative pathogen.

In the second part of the thesis (*Papers III and IV*), we wanted to enhance understanding of the origin of these infections by assessing operating room ventilation as a prophylactic measure against revision due to infection. The air in the operating room is, in addition to other surgery- and patient-related factors, a possible risk factor for postoperative infection. In Norwegian hospitals there are mainly two ventilation principles that are used to increase the cleanliness of the air: conventional, turbulent,

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mixing ventilation (CV) and unidirectional airflow (UDF) ventilation, formerly known as laminar airflow (LAF) ventilation, where the latter has in recent years been recommended on a disputed scientific basis. Lack of evidence for reduction in postoperative infection has led to the implementation of UDF systems being questioned as a prophylactic measure against postoperative infection. The NAR holds surgeon-reported data on the type of ventilation used during primary THA. We validated these ventilation data by performing a comprehensive assessment of the historical and present ventilation systems in 40 hospitals in Norway during the period 1987-2015 (*Paper III*). This was done in cooperation with knowledgeable surgeons and engineers at the relevant hospitals. This assessment showed that not all surgeons knew exactly what kind of ventilation system they performed the THA in, and accordingly may have reported inaccurate data to the register. This might have led to erroneous conclusions in earlier register studies on this topic. A series of such studies using data on ventilation reported by the surgeon or surgical department contributed to the scientific basis for a report on infection reduction from the World Health Organization (WHO) from 2016. This report concluded that UDF systems should not be installed in new operating rooms where arthroplasty is performed.

We continued the project by conducting new analyses on the risk of revision due to infection after THA using validated ventilation data (*Paper IV*). This included sub-analyses of technical specifications of the different systems. We concluded that UDF systems do not increase the risk of infection, as recent literature seems to imply. By performing a sub-classification based on technical specifications, we show that there is substantial variation between the different UDF systems and that the more modern and large UDF systems, offering high volumes of air, show a slight reduction in the risk of revision due to infection after THA compared to CV. This is in concordance with other studies showing that UDF/LAF systems are able to create cleaner air than CV systems.

When taking our results into account, considering also the finding of increased antibiotic resistance amongst common causative bacteria of THA, it would be erroneous to discontinue the use of large, high volume, vertical UDF systems in the

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operating room of the future. We hope and believe that the results of this thesis will have an impact on the ongoing international discussion on operating room ventilation and perioperative care.

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## Sammendrag

Hvert år opereres omtrent 7,000 pasienter med total hofteprotesekirurgi (THA). Den vanligste indikasjonen er artrose (slitasjegikt), og de aller fleste opplever bedret funksjon i etterkant. En sjelden, men fryktet komplikasjon etter protesekirurgi er infeksjon. Dette er en stor belastning for pasientene, en teknisk utfordring for kirurgene og en meget kostbar hendelse for helsevesenet og samfunnet. For å kunne gi pasientene den best mulige profylakse og behandling mot proteseinfeksjon er det essensielt å ha kjennskap til hvordan og hvorfor infeksjonene oppstår. For å kunne bidra til økt forståelse ønsket vi i det første delprosjektet å kartlegge hvilke typer bakterier som fører til infeksjon etter innsetting av totale hofteproteser (*Artikkel I*). I tillegg ville vi se om vi fant noen korrelasjon mellom bakteriefunn og hematologiske infeksjonsparametere (CRP og SR) (*Artikkel I*), og i tillegg vurdere forekomst og eventuell endring av antibiotikaresistens blant bakteriene (*Artikkel II*).

Vi tok utgangspunkt i data fra Nasjonalt Register for Leddproteser (NRL) som vi supplerte med bakteriologiske prøvesvar fra sykehusjournaler, inkludert antibiotiske resistensbestemmelser og preoperative blodprøvesvar, inkludert infeksjonsparametere. Som forventet fant vi en stor andel av stafylokokker. Dette er bakterier som er en vanlig bestanddel av menneskers normale hudflora. De hvite stafylokokkene viste økt resistens mot flere typer antibiotikum som brukes både i behandling og forebygging av proteseinfeksjon. Gule stafylokokker gav signifikant høyere infeksjonsparametere enn hvite stafylokokker, og i Norge kan derfor disse resultatene gi støtte til valg av empirisk behandling i tilfeller med ukjent bakterie, men kjent blodprøvestatus.

I det andre delprosjektet ønsket vi forsøksvis å belyse noe av forklaringen på hvor slike infeksjoner har sitt opphav, ved å se på effekten av operasjonsstueventilasjonen som et forebyggende tiltak mot proteseinfeksjon (*Artikkel III og IV*). Luften i operasjonssalen er sammen med andre pasient- og operasjonsrelaterte faktorer, antatt å være en risikofaktor for postoperativ infeksjon. I norske sykehus er det hovedsakelig to ventilasjonsprinsipper som brukes for å bedre renheten av luften: Konvensjonell, turbulent blandingsventilasjon (CV) og unidireksjonell luftstrømsventilasjon (UDF)

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(tidligere kjent som laminær luftstrømsventilasjon (LAF)), hvor sistnevnte de senere år har vært anbefalt på et noe kontroversielt vitenskapelig grunnlag. Manglende bevis for reduksjon i insidens av postoperativ infeksjon har satt spørsmålstegn ved implementeringen av UDF-systemer som beskyttelse mot infeksjoner i nye operasjonsstuer. I NRL finnes det kirurgrapporterte data på hvilken type ventilasjon som ble brukt under primæringrepet. Vi validerte disse dataene ved å gjøre en grundig gjennomgang av de aktuelle og historiske ventilasjonsforholdene på 40 inkluderte sykehus i perioden 1987-2015 (*Artikkel III*). Dette ble gjort i samråd med kirurger og ingeniører med kunnskap om ventilasjonssystemene på de aktuelle sykehusene. Denne gjennomgangen viste at kirurgene ikke var helt klare over hvilken type ventilasjon de faktisk opererte i. Dette kan ha medført at tidligere registerstudier gjort på den profylaktiske effekten av ventilasjonssystemer, kan inneholde feil. En rekke slike registerstudier med ventilasjonsdata rapportert fra kirurger eller kirurgiske avdelinger, bidro i 2016 til en ny rapport fra verdens helseorganisasjon (WHO) angående infeksjonsreduksjon. Denne konkluderer med at UDF-systemer ikke bør installeres i nye operasjonsstuer hvor protesekirurgi skal utføres.

Prosjektet vårt ble videreført ved å gjøre nye analyser på risiko for revisjon på grunn av infeksjon etter THA med validerte ventilasjonsdata, inkludert subanalyser på ulike tekniske spesifikasjoner av ventilasjonssystemene (*Artikkel IV*). Alt i alt viser vi at UDF-systemer ikke øker faren for infeksjon, slik som nyere litteratur har antydnet. Ved å gjøre en inndeling av UDF-systemene basert på tekniske spesifikasjoner, viser vi også at det er betydelige forskjeller mellom de ulike UDF-systemene hvor moderne, store systemer, som tilbyr høyt luftvolum, viser en viss reduksjon i revisjon pga infeksjon etter hofteproteseoperasjon sammenliknet med CV. Dette er i overensstemmelse med andre studier som viser at UDF-/LAF-systemer kan gi renere luft enn CV-systemer.

Når man tar våre resultater med i betraktningen, sammenholdt også med funn av økende, antibiotisk resistensgrad blant de vanligste bakteriene som fører til infeksjon etter THA, synes det feilaktig å ikke implementere store, høyvolum vertikale UDF-systemer i fremtidens operasjonsrom. Vi håper og tror at resultatene fra denne



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avhandlingen vil bidra til den internasjonale diskusjonen angående operasjonsstueventilasjon og perioperativ håndtering av pasienter på operasjonsstuer hvor ultraren kirurgi foregår.

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## List of publications

### *Paper I*

Langvatn H, Lutro O, Dale H et al. Bacterial and Hematological Findings in Infected Total Hip Arthroplasties in Norway. The Open Orthopaedics Journal 2015; 9: 445-9.

### *Paper II*

Lutro O, Langvatn H, Dale H, et al. Increasing Resistance of Coagulase-Negative Staphylococci in Total Hip Arthroplasty Infections: 278 THA-Revisions due to Infection Reported to the Norwegian Arthroplasty Register from 1993 to 2007. Advances in Orthopedics 2014; 2014: 580359.

### *Paper III*

Langvatn H, Bartz-Johannessen C, Schrama JC et al. Operating room ventilation -Validation of reported data on 108 067 primary total hip arthroplasties in the Norwegian Arthroplasty Register. Journal of Evaluation in Clinical Practice 2019; doi 10.1111/jep.13271.

### *Paper IV*

Langvatn H, Schrama JC, Cao G, et al. Operating room ventilation and the risk of revision due to infection after total hip arthroplasty – Assessment of validated data in the Norwegian Arthroplasty Register. Journal of Hospital Infection 2020; doi 10.1016/j.jhin.2020.04.010.

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## 1 General background

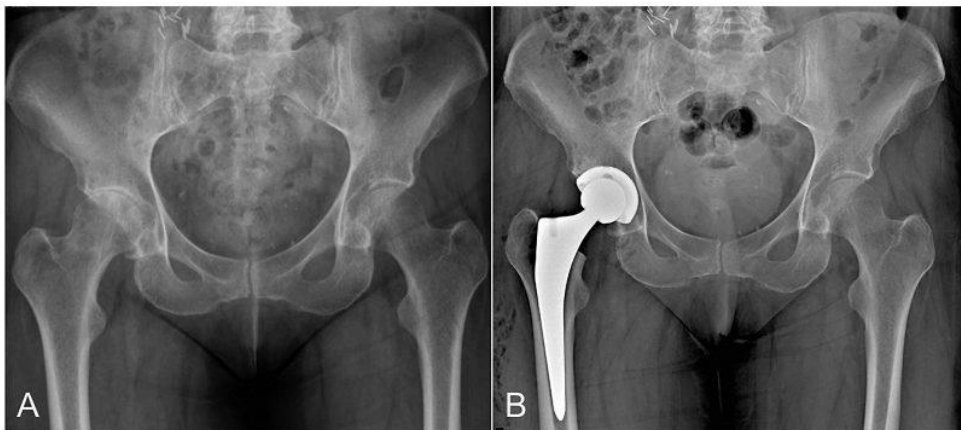
In total hip arthroplasty (THA) the injured or worn hip is substituted by an artificial joint. More than 7,000 patients receive a THA each year in Norway and the main indication is osteoarthritis. Most prostheses are made of surgical steel or various titan alloys, and together with occasional polyethylene inserts and bone cement they constitute a large foreign body that is introduced into a presumptive sterile, biological environment. Such foreign bodies are subject to both adhesion of bacteria and the protective immune system of the host. The “race for the surface” is described in the literature as a struggle between the tissue integration process of the host and the colonization and biofilm formation of bacteria on the surface of the foreign body (1). If the bacteria win this race, a fulminant prosthetic joint infection (PJI) might develop. This is a much feared complication that in most cases necessitates reoperations and prolonged antibiotic treatment. For patients this involves prolonged hospital stays, loss of function due to repeated surgery, and potential complications of both the surgical and medical treatment. The mortality risk of patients with a revision for PJI is approximately double the risk of that in a reference population (2). The five-year pooled mortality is by some estimated to be around 20% (3), which is comparable to the pooled mortality of colorectal cancer and uterine cancer (4). Further, it is estimated that an infected THA will cost up to four times more than uncomplicated primary THA (5, 6).

Optimal prophylaxis against and treatment of PJI depends on knowledge of what causes the infection and from where the infection originates. This thesis aims to assess the bacteriology of PJI after THA, the antibiotic resistance patterns and the possible correlation between bacteriology and haematological infection parameters. A further aim is to assess the importance of air cleanliness indirectly by evaluating the ventilation system of the operating room (OR) as a potential risk factor for revision due to infection after THA.

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## 1.1 Total hip arthroplasty

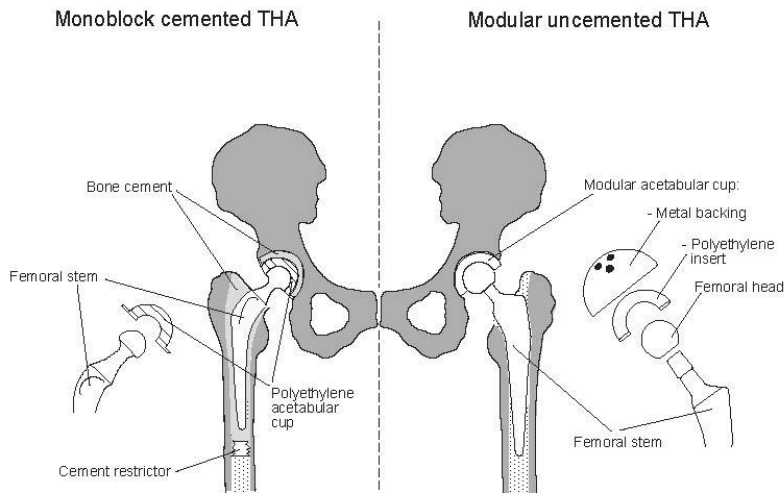
In total hip arthroplasty the whole hip joint including the proximal femur and the articular acetabulum is substituted. A total hip prosthesis consists of a femoral stem, a head at the top of the stem and an acetabular cup substituting the acetabulum of the pelvis. Figure 1 shows a hip joint with osteoarthritis before and after THA. Osteoarthritis is the most common indication for THA with other indications being complications to inflammatory disease, hip fracture, complications after hip fracture, and complications after childhood hip disease, among others. The surgery is quite standardized with regards to patient handling, surgical approach, surgical technique, duration of surgery, etc. This makes THA favourable for comparative research.



*Figure 1: Osteoarthritis of the right hip before (A) and after (B) an uncemented THA*

There are many different producers and designs of hip prostheses, but basically two main principles of prosthesis design dominate (Figure 2). The most common one today

is the *modular* prosthesis where the stem and the head are separate parts. The acetabular cup may also be modular with a separate liner in a metal shell. In the *monoblock* prosthesis the stem and the head come in one piece, as also in the *monoblock* acetabular cup.



*Figure 2: Prosthesis concepts and methods of fixation (by courtesy of Geir Hallan)*

There are also two main principles of prosthesis fixation to the bone: with the use of bone cement or without (Figure 2). The uncemented prosthesis has a surface of either hydroxyapatite or titanium that allows growth of bone into the structure of the prosthesis. Combinations of fixation methods are also utilized, where the most common combination consists of a cemented acetabular cup and an uncemented femoral stem. This combination is called a reverse hybrid fixation. The combination of a cemented stem and an uncemented cup is referred to as a hybrid fixation, but is little used in Norway today.

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## 1.2 Infection after total hip arthroplasty

Postoperative infections after THA are often classified according to the time of symptom debut. This is a simple classification that is widely used, where *early* infections are defined as symptoms occurring <3 months following primary THA, while *delayed* refers to 3-24 months and *late* >24 months after primary THA (7, 8). This classification is based on several approximations: early infections are acquired at implantation with virulent bacteria leading to an acute presentation, delayed infections are acquired at implantation with less virulent bacteria causing a more subtle clinical presentation, and late onset infections are predominantly acquired by haematological seeding.

A more clinically directed classification scheme was presented by Tsukayama in the 1990s (9). This classification is also based partly on the time since prior implant surgery, as well as other clinical aspects, and divides arthroplasty infections into four categories. The first category, *positive intraoperative culture*, includes revisions due to presumed aseptic loosening where culturing of intraoperative tissue samples reveals microbial growth. *Early postoperative infection* occurs within one month of implant surgery with an acute presentation, while *late chronic* infection occurs *after* one month with a more insidious course. The last category, *acute haematogenous infection*, might appear at any time after implant surgery, presenting with an acute onset of symptoms and documented or suspected bacteraemia.

There are numerous additional classifications used in different publications. Worth mentioning is the classification by McPherson (10), which also assesses different clinical aspects of PJI, but a further description of this is beyond the scope of this thesis.

The different types of infection are often classified into two main groups: surgical site infection (SSI) and prosthetic joint infection (PJI). SSI after arthroplasty is divided by the Centres of Disease Control and Prevention (CDC) into three categories (11-13): *superficial incisional SSI*, which involves only skin and subcutaneous tissue of the incision, *deep incisional SSI*, which involves deep soft tissue of the incision, and

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*organ/space (bone/joint) SSI*, which involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure.

The criteria for PJI were postulated in the aftermath of the Philadelphia international consensus meeting held in 2013 (14), where delegates of 51 different nationalities and various disciplines came together to evaluate the available evidence. Based on the main criteria in the consensus report, PJI is defined as two positive periprosthetic cultures with phenotypically identical organisms, or a sinus tract communicating with the joint, or cases having three of the following minor criteria:

- Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR)
- Elevated synovial fluid white blood cell (WBC) count, OR ++ change on leukocyte esterase test strip
- Elevated synovial fluid polymorphonuclear neutrophil percentage
- Positive histological analysis of periprosthetic tissue
- A single positive culture

#### *THA revision due to deep infection*

The endpoint of postoperative infection in the NAR has been defined as THA revised due to presumed infection with the removal or exchange of parts or the whole of the prosthesis. The infection diagnosis is reported immediately after surgery by the surgeon based on perioperative assessments and clinical evaluation, and reported accordingly. From 2011 all reoperations due to infection were to be reported, including cases treated with debridement without the removal or exchange of parts. However, the operations included in this thesis only include revisions with removal or exchange of parts or the whole of the prosthesis due to deep infection.

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### 1.3 Diagnostics of prosthetic joint infection

The diagnosis of PJI is set by the surgeon based on clinical findings, haematology, radiology, and bacteriological assessments conducted pre- and/or peroperatively. As all investigations are of varying sensitivity and specificity, it is essential to perform a broad evaluation and to assess the situation accordingly.

Depending on various patient-related factors and the virulence of the causative pathogen, the clinical presentation of PJI might vary from isolated pain as the only symptom, to more acute, severe infections with extensive soft tissue involvement and sepsis.

The clinical findings can be supported by the evaluation of haematological infection parameters. The most commonly used parameters from blood samples are C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white blood cell (WBC) count, the results of which also depend partly on microbial virulence (15). They have high sensitivity, and are cheap and easily accessible, but due to low specificity, these markers cannot be used alone in diagnostics of PJI (16, 17). Different biomarkers in blood serum such as D-dimer, interleukin-6 and procalcitonin have been proposed as substitutes in first line diagnostics of PJI, but they have not shown any significant increase in specificity (17). Different biomarkers in joint fluid like  $\alpha$ -defensin and leukocyte esterase have also been proposed as substitutes due to increased specificity (18). But with joint aspiration being a much more invasive method than blood sampling, and as the sensitivity is lower, this has not been introduced as a standard.

Conventional X-rays might provide support, especially in cases with a diffuse clinical presentation and sparse haematological findings, as in low grade infections with low-virulence bacteria. The findings that an X-ray might reveal are osteolysis surrounding parts of the prosthesis and possibly periosteal reaction on the surrounding bone tissue (19, 20). Images must be interpreted in relation to other findings. These include prior radiology to evaluate possible progression as current images themselves can rarely distinguish between true infection and aseptic loosening. To evaluate soft tissue



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involvement and periosteal reaction, a computed tomography (CT) scan might be a better alternative (21).

If the diagnosis remains unclear, preoperative aspiration with assessment of joint fluid with cell counts, bacteriological culturing, Gram staining or polymerase chain reaction (PCR) might be indicated (22-24). This might be valuable to help define the need of surgical intervention in cases of doubt, or to identify the causative pathogen in cases where antibiotic suppression treatment might be indicated.

At revision, the recommendation is to take at least five tissue samples for bacteriological and histological examination. Despite this, the share of culture negative infection is substantial, often due to perioperative antibiotic treatment (25, 26). Sonication of the removed prosthetic parts with culturing and/or PCR of sonicate fluid might help to identify the causative pathogen (27, 28).

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## 1.4 The microbiology of infected THA

### 1.4.1 Bacteriology

The main basis of optimal prophylaxis and treatment of PJI is knowledge of the microbiology and the causative pathogens (7). In the following, a short introduction to the bacteriology of hip PJI will be given. Each bacteria is initially presented by the way it appears in a Gram-stained smear under a microscope, either Gram-negative or Gram-positive, or if the bacteria appear as spherical cocci, elongated rods or as filamentous bacilli, appearing singularly or in couples, chains or clusters.

#### *Staphylococci*

Staphylococci are Gram-positive cocci often seen in clusters, which constitute a normal component of human skin and mucosal flora. Staphylococci are the most common bacteria in PJI and are the cause of 50-60% of prosthetic hip infections (29, 30).

*Staphylococcus aureus* (*S. aureus*) are known to be more virulent than coagulase negative staphylococci (CoNS), mainly due to the production of bound or free coagulase enzymes (31). They usually lead to a more severe presentation and are often associated with severe, invasive infection. PJI caused by *S. aureus* often presents as acute or early infection (32), but may also appear later on with a more diffuse presentation (33). It is speculated that derivatives of *S. aureus*, so-called “small colony variants” might be the cause of both the change in presentation and resistance to treatment (34, 35). Such derivatives might evolve by mutations in metabolic genes, which gives sub-populations with a less virulent phenotype, but one that can remain viable within the host cells.

*CoNS* is a group of staphylococci historically often evaluated as pollutants due to their relatively low virulence and prior difficulty of identification (36). For the same reason, the sub-groups of CoNS have not been studied in detail and they are often referred to

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as one large entity. Unlike *S. aureus* they rarely lead to severe, invasive infection, as the most common route of infection is by foreign body adhesion and biofilm formation. *Staphylococcus epidermidis* (*S. epidermidis*) is the most common type of CoNS. Other sub-groups of CoNS known to cause PJI are *S. simulans*, *S. caprae* and *S. lugdunensis*. PJI with CoNS can occur at any time after THA, but is often found in delayed and late infections where pain might be the only symptom.

*S. lugdunensis* differs from other CoNS in virulence and antibiotic resistance. They produce less  $\beta$ -lactamase and are therefore more susceptible to penicillins (37). They also have a bound form of coagulase and show greater virulence than other CoNS. Infections with *S. lugdunensis* might therefore mimic infections with *S. aureus* with a more acute presentation with pain and swelling (38).

### *Cutibacteria*

*Cutibacterium acnes* (*C. acnes*), formerly known as *Propionibacterium acnes* (*P. acnes*) are anaerobic Gram- positive rods that also constitute part of the normal skin flora, especially in areas with abundant sweat and sebaceous glands, such as the groin and the axilla (39). They are anaerobic and slow growers with a relatively low virulence, and the presentation is often mild with pain as the only symptom. Cases of *C. acnes* PJI are therefore often difficult to distinguish from aseptic loosening and as with CoNS, the identification of *C. acnes* has historically often been evaluated as pollution.

### *Streptococci*

Streptococci are Gram-positive cocci that often occur in couples or chains. The main classification is the differentiation between  $\alpha$ - and  $\beta$ -haemolytic streptococci depending on their ability to perform lysis on haemoglobin.  $\alpha$ -haemolysis is a partial decomposition of the haemoglobin of the erythrocytes, whereas  $\beta$ -haemolysis leads to a complete breakdown of the haemoglobin. The  $\beta$ -haemolytic streptococci are further subdivided by surface antigens into A, B, C, D, F and G. The most common types of

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streptococci found in PJI are  $\alpha$ -haemolytic viridans streptococci and  $\beta$ -haemolytic group A (*Streptococcus pyogenes*), group B (*Streptococcus agalactiae*) and group G (*Streptococcus dysgalactiae*) streptococci, often due to bacteraemia from other infection foci in patients with comorbidity (40-42). The majority of streptococcal PJIs present as late, haematogenous infections with acute onset and invasive infection with pain and swelling (43).

#### *Enterococci*

Enterococci are also Gram-positive cocci in couples or short chains. For this reason, they might be difficult to distinguish from streptococci. Monomicrobial enterococci infection after THA has been sparsely studied in detail, but is thought to originate from haematogenous seeding from infections of the gastrointestinal or urinary tract (44). Enterococci are relatively low virulent and often lead to late infections with pain as the main symptom. Occasionally they are also seen as part of polymicrobial infections with a different clinical presentation (45).

#### *Enterobacteriaceae*

Enterobacteriaceae is a large family of Gram-negative rods where the most common one causing hip PJI is *Escherichia coli* (*E. coli*). They show a relatively high virulence that often leads to an acute presentation in early infection, and are often associated with polymicrobial infection (46). Enterobacteriaceae in the normal human flora are found in the gastrointestinal tract, and the proximity to the hip is proposed as a potential explanation for the higher proportion of enterobacteriaceae in infected THA relative to other types of infected arthroplasty (47).

#### *Other pathogens*

There are some other, rarer pathogens that will not be described in further detail in this thesis. These rare infections mainly occur in immunosuppressed patients or older patients with severe comorbidities. Worth mentioning here are anaerobic bacteria

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such as bacteroides and peptostreptococci, fungi such as different types of candida, other bacteria, e.g. Pasteurella spp., Pseudomonas spp. and mycobacteria such as Mycobacterium tuberculosis.

#### *1.4.2 Biofilm*

Many of the different bacteria are capable of biofilm formation. Biofilm is a protective matrix consisting of glycocalyx fibres, protecting the bacteria from the patient's immune system in addition to any prophylaxis and/or antibiotic treatment. This might complicate the identification and treatment of biofilm-embedded bacteria (48). The bacteria encapsulated within the biofilm might also lead to a milder grade of infection compared to cases with free planktonic bacteria, which could result in a false diagnosis and insufficient treatment (8, 35). To increase the accuracy of the diagnosis, sonication of the removed implant has been proposed to make the biofilm bacteria available for culturing. But the method is disputed and has not been implemented as a standard in the diagnostics of arthroplasty infection in Norway (28).

#### *1.4.3 Antibiotic resistance*

The susceptibility of the bacteria to antibiotics is of utmost importance in curative treatment of PJI. Development of antibiotic resistance is a much feared problem worldwide and poses a growing challenge in the treatment of PJI (49). A brief summary of the most important trends of antibiotic resistance among the different bacterial groups will be presented in the following.

#### *Staphylococci*

A majority of staphylococci are producers of penicillinase, which makes them partially resistant to penicillins. In recent decades, staphylococci have also shown increased production of  $\beta$ -lactamase, and *S. aureus* has also shown increased resistance to

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antibiotics in the methicillin group, including penicillinase-resistant penicillins and  $\beta$ -lactam antibiotics including oxacillin, kloxacillin and dicloxacillin. These *S. aureus* are called methicillin-resistant *S. aureus* (MRSA) and constitute an increasing threat worldwide (50). The same trend is also seen amongst CoNS in the shape of methicillin-resistant *S. epidermidis* (MRSE). Due to restrictive use of antibiotics and precautions regarding bacterial import as described by national guidelines (51), the proportion of MRSA/MRSE in Norway has traditionally been quite low, although the resistance seems to be evolving (52).

### *Streptococci*

Streptococci have traditionally been quite sensitive to most kinds of relevant antibiotics, e.g. penicillins, macrolides and lincosamides such as clindamycin.

### *Enterococci*

Enterococci are genetically resistant to penicillinase-resistant penicillins and  $\beta$ -lactam antibiotics like cephalosporins, but are mostly sensitive to ampicillin. They are also showing increased resistance to aminoglycosides and vancomycin, probably due to chromosomal genes transferred between bacteria (53).

### *Enterobacteriaceae*

These Gram-negative bacteria are mostly sensitive to relevant antibiotics such as aminoglycosides, quinolones and carbapenems. There seems to be an increase in resistance to cephalosporins, mostly due to increased occurrence of extended spectrum  $\beta$ -lactamase (ESBL) variants (54). There are also reports of increased resistance to quinolones and carbapenems in Europe (55), but carbapenem resistance is still considered a rarity in the Norwegian bacterial flora.

## 1.5 Treatment of infection after THA

PJI treatment depends on the severity of the infection and ranges from soft tissue debridement (debridement, antibiotics and implant retention (DAIR)) in early postoperative infections to extensive revisions in several stages in patients with severe, deep infections with “difficult-to-treat” (DTT) bacteria. The choice of treatment is based on the type of infection, type of bacteria, time since prior surgery, anatomy and the extent of patient comorbidity (Figure 3) (8, 56).

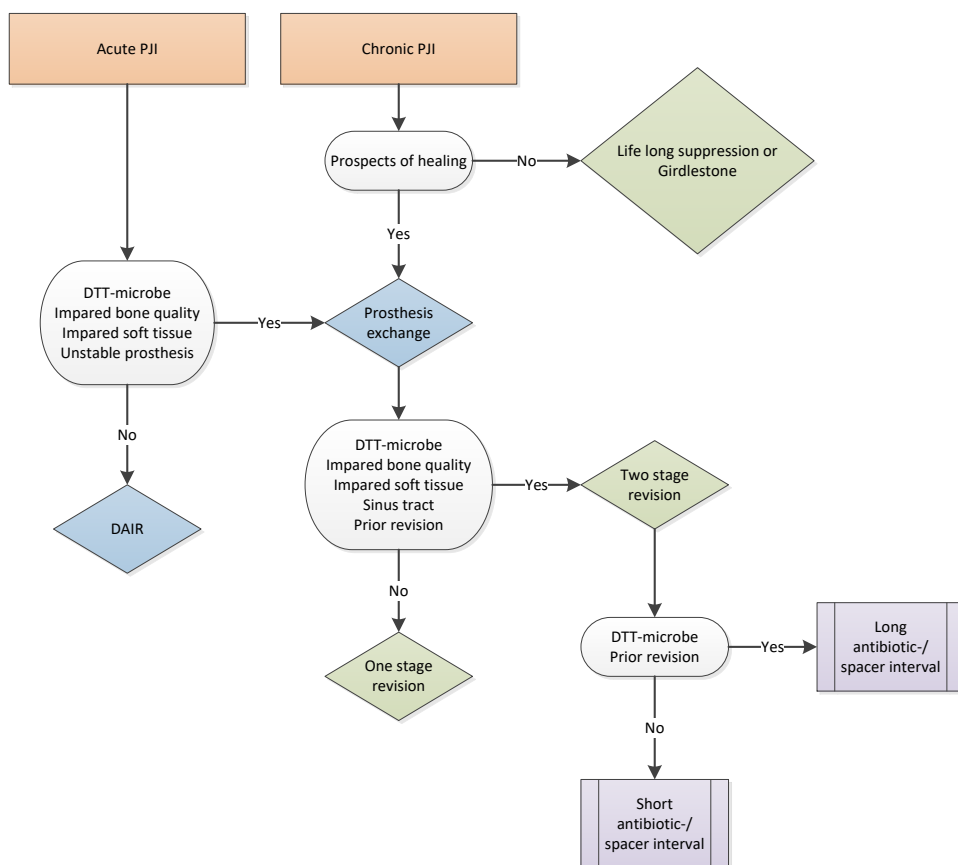


Figure 3: Simplified flow chart illustrating treatment selection in THA PJI (56)

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### 1.5.1 *Soft tissue debridement*

More recently this choice of treatment has been described as “debridement, antibiotics and implant retention” (DAIR). In the case of acute PJI with duration of symptoms <3 weeks in patients with viable soft tissue and relatively sensitive microbes, good results have been shown for DAIR treatment (57-60). Extensive debridement of the soft tissue is performed by removal of necrotic soft tissue, debris, and excision of sinus tracts, followed by a thorough irrigation of the wound before closure. In cases with a modular prosthesis, removable parts are exchanged. Historically this type of surgery has been withheld for acute postoperative infections. Due to good results, the indication span has by many been extended to three months and even longer after primary surgery, if the implant is well fixated. The outcomes of such an approach have not been studied in detail. DAIR treatment in Norway generally involves 12 weeks of postoperative antibiotic treatment.

### 1.5.2 *One-stage revision*

In cases of later/chronic PJI in patients with viable soft tissue and sensitive microbes, a one-stage revision with a complete removal of the prosthesis, soft tissue debridement and reimplantation can be performed in one surgery with relatively good results (61-63). The advantages of one-stage revision over two-stage revision are earlier mobilization of patients and improved functional outcome. It also leads to reduced trauma due to only one, although slightly more extensive, surgery and subsequently reduced costs. One-stage revision in Norway is usually followed by 12 weeks of antibiotic treatment.

### 1.5.3 *Two-stage revision*

In acute or chronic PJI in patients with compromised soft and/or bone tissue or a loose prosthesis, traditional treatment has been a two-stage revision with initial removal of the prosthesis, followed by an interval of intravenous antibiotics. In the first surgical



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stage, a cement spacer containing antibiotics may be implanted to secure the soft tissue and stabilize the joint, and to provide dead space management through elution of high doses of local antibiotics. Figure 4 illustrates a cement spacer containing a steel rod. Reimplantation is performed at a later stage when the infection is cured and the soft tissue is restored.

With sensitive bacteria, the antibiotics/spacer interval can be reduced to 2-3 weeks. With DTT microbes the interval should be 6-8 weeks. A long antibiotics/spacer interval should also be implemented in cases of chronic PJI in patients with several prior revisions with compromised soft or bone tissue with unknown or resistant bacteria. The antibiotic treatment may be followed by an antimicrobial-free interval of approximately two weeks before reimplantation. As with one-stage revisions, a total of 12 weeks of antibiotic treatment is usually administered. In general, good results are also achieved with two-stage revisions (63-66).



*Figure 4: X-ray of a cement spacer in the right hip*

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#### 1.5.4 *Suppression treatment/resection arthroplasty*

If the treatment is unsuccessful, the patient does not approve of further surgery and/or revision is associated with great risk to patient health and safety, lifelong suppression treatment with antibiotics may be an option if the microbes are known and susceptible to relevant antibiotics (67). If the patient approves and is expected to tolerate surgery, a resection arthroplasty (Girdlestone procedure) might be performed. This involves extraction of all prosthetic components and thorough debridement of the periprosthetic tissue without subsequent reimplantation (Figure 5), and without the need of lifelong antibiotic treatment.



*Figure 5: X-ray after a Girdlestone procedure in the right hip*

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### *1.5.5 Antibiotic treatment*

Antibiotic treatment is only curative when used as a supplement to surgical treatment. All antibiotic treatment should be long-term with a total treatment duration from 6 to 12 weeks after revision surgery. The total duration of the antibiotic treatment is disputed, as recent studies have questioned the additional effect of treatment beyond 6-8 weeks (68, 69). The most common procedure until recently has been the administration of intravenous antibiotics for two weeks, followed by six weeks or more of oral treatment. A recent trial, however, found that appropriately selected oral antibiotic therapy was just as effective as intravenous therapy when used during the first six weeks in the management of “complex bone and joint infection” (70). This has led to a shortening of the intravenous period in Norway, although national guidelines are yet to be updated. The choice of antibiotics is based on the bacteriology and associated susceptibility panels.

### *Empirical treatment*

Infections with an acute and critical presentation might require initiation of antibiotic treatment for a life-threatening indication. Such empirical treatment without knowledge of the causative microbe should cover the most probable microbes. This requires knowledge of the suspected bacteriology. Cloxacillin is the drug of choice in Norway, with addition of vancomycin in cases of low- grade, chronic infection, until bacterial cultures are ready. If Gram-negative microbes are suspected as in cases with intravenous drug abuse, immunosuppression or in elderly patients with substantial comorbidity, empirical treatment with cefuroxime or cefotaxime is recommended (71).

### *Bacteria-specific treatment*

This section mainly serves to give an overview of the most common types of antibiotics used to treat THA infections in Norway. The recommendations in this section are

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conditional, and should be adjusted on the basis of resistance patterns, type of surgical approach and clinical response (71).

### *Staphylococci*

The most common causative bacteria in Norway have been found to be methicillin-sensitive *S. aureus* and *S. epidermidis*. The recommended treatment for these infections is intravenous cloxacillin for 1-2 weeks after revision surgery. The proportion of methicillin-resistant CoNS is shown to be increasing (72), and if methicillin resistance is suspected or proven, cloxacillin should be substituted by vancomycin. Intravenous treatment is followed by a combination of oral rifampicin and ciprofloxacin for a total treatment of three months. Rifampicin is added as a biofilm-active supplement to increase biofilm penetration (60, 73, 74), even though the true additional effect of rifampicin is disputed (75). In case of resistance to or intolerance of ciprofloxacin, it might be substituted with clindamycin, co-trimoxazole, fusidic acid, linezolid or other antibiotics, depending on the pattern of resistance.

### *Streptococci*

The majority of streptococci are known to be susceptible to most relevant antibiotics. The recommendation in Norway is intravenous benzylpenicillin for two weeks if the clinical response is good, followed by oral phenoxymethylpenicillin or ampicillin, giving a total treatment duration of 6-12 weeks.

### *Enterococci*

Most enterococci are susceptible to ampicillin. This is the main choice, administered intravenously for 4-6 weeks due to the high rate of treatment failure (76). Intravenous vancomycin or oral linezolid are alternatives in the rare case of ampicillin resistance.

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### *Enterobacteriaceae*

Most enterobacteriaceae in Norway are susceptible to aminoglycosides, cephalosporins and quinolones. The recommended treatment is intravenous cefuroxime or cefotaxime for two weeks, followed by oral ciprofloxacin for 4-6 weeks.

#### *1.5.6 Antibiotic prophylaxis in Norway*

All patients receiving a THA in Norway today are given systemic antibiotic prophylaxis (77). The effect is well documented even though the choice of antibiotics and the timing of administration is disputed (78-80). Until lately, cephalothin has been the drug of choice in Norway. The first dose is administered 30-60 minutes prior to surgery, followed by every 90th minute in a total of four doses. Due to problems with supplies, a different first generation cephalosporin has been substituted for cephalothin in most hospitals in Norway. *Cephazoline* is administered in the same dose and in a total of four doses, but is administered 15-30 minutes prior to surgery with intervals of three hours as it has twice the half-life of cephalothin. In cases of penicillin allergy, clindamycin is used as a substitute, administered 30-60 minutes preoperatively, followed by every sixth hour in a total of four doses (71). In cemented THA it has been shown that antibiotic-loaded bone cement in addition to systemic antibiotic prophylaxis might increase prosthesis survival (81, 82). Administration of other local, antibiotic prophylaxis has not been shown to provide any additional effect, at least not in hemiarthroplasty (83).

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## 1.6 Risk factors and preventive measures for infection after THA

Studies have implemented different definitions in their analysis of data sets with varying content, and have thereby identified different risk factors (23, 84-88) relevant to predict the risk of infection after THA. Risk factors common to the majority of studies are comorbidity (American Society of Anesthesiologists (ASA) class, Charlson comorbidity index (CCI)), obesity, diabetes, THA due to femoral fractures and prolonged duration of surgery.

Risk factors for infection after THA known from the NAR and other similar surveillance registries are high ASA class, male sex, diabetes, THA due to necrosis of the femoral head or hip fracture, cemented implants without antibiotics and prolonged duration of surgery. Some have also identified the use of laminar airflow ventilation systems in the operating theatre as being a potential risk factor for postoperative infection (81, 89-91).

From a hospital point of view, the patient-related risk factors are difficult to modify in the form of simple preventive measures related directly to the surgery, although optimization of diabetic control, weight loss, pausing smoking and administration of anticoagulants should be encouraged and planned from the outpatient clinic. However, some of the surgery-related risk factors can be directly addressed. Based partly on different studies on risk factors for infection after THA, systematic reviews and guidelines on preventive measures have been published (92-94). The measures are supported by inconclusive scientific proof, and the use of systemic antibiotic prophylaxis seems to be the only factor with sufficient evidence (94). Nevertheless, there is a wide consensus that thorough preoperative patient washing, short preoperative hospital stay, use of antibiotic-loaded bone cement, use of double surgical gloves and face masks, adequate surgical technique and gentle soft tissue handling are effective measures to help reduce the incidence of postoperative infection (82, 95-97).

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Systematic measures to reduce the incidence of infections following arthroplasty were first introduced by Dr. Charnley in the early 1970s. Charnley and colleagues achieved a reduction of postoperative infection after THA from approximately seven to one percent (98). In his study, multiple measures were implemented including systematic iodine skin wash, use of surgical drapes, double disposable gloves, and suture of subcutaneous fat. The air in the operating room, however, was considered one of the major factors, and Dr. Charnley's implementation of a "greenhouse" ventilation system led to an increased focus on the cleanliness of the air. Operating room ventilation turned out to be a hotly disputed topic in the following decades, and the last part of this thesis will discuss this in further detail.

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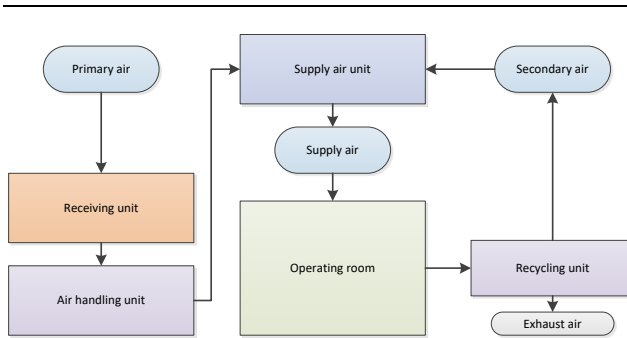
## 1.7 Operating room ventilation

One of the main functions of operating room (OR) ventilation is to offer adequate oxygen levels to patients and personnel, and to eliminate air pollutants from medical equipment, e.g. anaesthetic gas contamination. In addition, the air in the operating room is thought to be a possible risk factor of postoperative infection due to airborne particles that might serve as carriers of bacteria, often measured as colony forming units (CFUs). The cleanliness of the air is a debated topic in relation to infection reduction, but ventilation systems are now to a greater extent constructed as a prophylactic measure against postoperative infection.

Two main principles are implemented to increase air cleanliness: conventional, turbulent, mixing ventilation (CV) and laminar airflow (LAF) ventilation, the latter more recently termed unidirectional airflow (UDF). CV systems use the dilution principle to reduce the concentration of air contamination. This is in contrast to the UDF systems, which implement the displacement principle and work by sending parallel streams of filtered air directly towards the operating field. The two different functional principles will be discussed in more detail in the following sections.

The air supplied to the operating room (supply air) may be a mixture of filtered air from the outside (primary air) and recirculated and filtered air from the operating room (secondary air) (Figure 6), although most CV systems do not use recirculated air. Primary air is necessary to adequately withstand  $O_2$  pressure and is often supplied in quantities of 1000-2000m<sup>3</sup>/h to fulfil the requirement of at least 50m<sup>3</sup>/h of fresh air per person under physically demanding work (99). The total volume flow rate (VFR) of supply air is important to achieve an adequate reduction of contamination for both CV and UDF systems. Modern ventilation systems today often have a VFR of 10,000m<sup>3</sup>/h or more. This is to achieve adequate air velocities in UDF systems with large ventilation canopies, which will be discussed later in this thesis.





*Figure 6: Simplified presentation of the operating room ventilation circuit*

The primary air is often treated in an air receiving unit containing a louver and a pre-filter. The air is then passed through an air handling unit which contains the first filter stage, a temperature regulator, a humidity regulator (not required in Norway), and the second filter stage. Before the air is supplied to the operating room, it is passed through a supply air unit where it is filtered through high- efficiency particulate air (HEPA) filters before it enters the room through the supply air diffuser/canopy. The air in some systems, primarily UDF systems, is then extracted from the OR through a recycling unit with yet another filter stage before some of the air is sent out as exhaust air, and some of it is returned to the supply air unit as secondary air (Figure 6). The way the primary air and secondary air are processed may vary between different systems in regards to the degree of heat recovery as well as whether the processing is centralized or separated, but the details of this will not be discussed further in this thesis.

### *1.7.1 Conventional ventilation*

Conventional ventilation (CV) is also known as turbulent ventilation, mixing ventilation, diluting ventilation or a combination of these. This reflects the functional principle which is to dilute the polluted air using turbulent, mixing airflows of clean and filtered air. The supply air is discharged from the supply unit in different directions, creating a turbulent airflow to mix the polluted air with clean air, thereby diluting the pollutants present. An important parameter of airborne particle removal in CV systems is the air exchange rate/air changes per hour (ACH), usually in the range of 12-25, and also to what degree dilution actually takes place (100). This depends on the geometry

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of the OR as the diluting effect is not uniformly distributed throughout the room. As the degree of protection also partly depends on overpressure, this adds vulnerability to the CV systems in terms of door openings and sudden episodes of pollution (101).

### *1.7.2 Unidirectional ventilation (UDF)*

LAF/UDF systems work by supplying linear and parallel streams of air with constant velocity directly towards the operating field. This is supposed to create a column or plug of fresh air displacing polluted air away from the surgical field (plug flow) (Figure 7a). True laminar airflow can only be created in optimal surroundings, and no system is able to do this consistently under real-life conditions (102-104). Lately the term UDF has been implemented to more realistically describe the functionality, and UDF will be the preferred term throughout this thesis. Technological developments have been substantial in recent decades, mainly in regard to increased canopy size and increased VFR to achieve increased air velocities in large protected areas. Studies have shown the impact of canopy size on the microbial load within the protective zone, and the minimum size of an UDF canopy has been recommended to be 320 x 320 cm (105-107). There are numerous variations of these systems with regard to airflow distribution configuration. Figure 7(a-d) shows the most commonly used systems in Norwegian hospitals.

An important parameter for UDF systems is “recovery time” (108). Recovery time defines the ability of the system to reduce the concentration of air pollutants in a defined range of time in a defined area of the operating room. This describes the time it takes for the system to achieve “steady state” in the protected area after an episode of air pollution. Recovery time is theoretically lower in UDF systems than in CV systems, meaning that the effect of door openings, sudden movements, etc. could be less pronounced in UDF systems, at least in the protected zone (99).

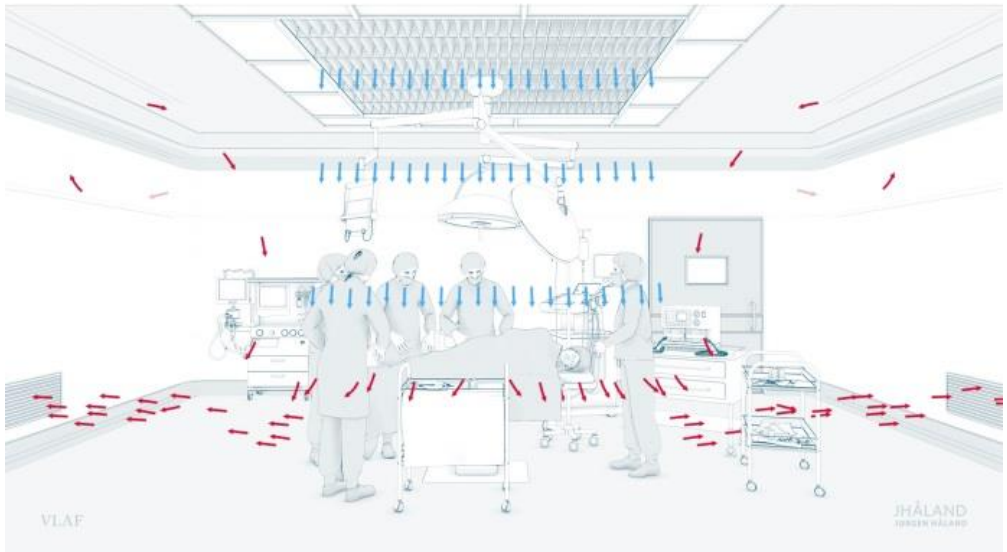


Figure 7a: Standard vertical UDF without side walls surrounding the canopy

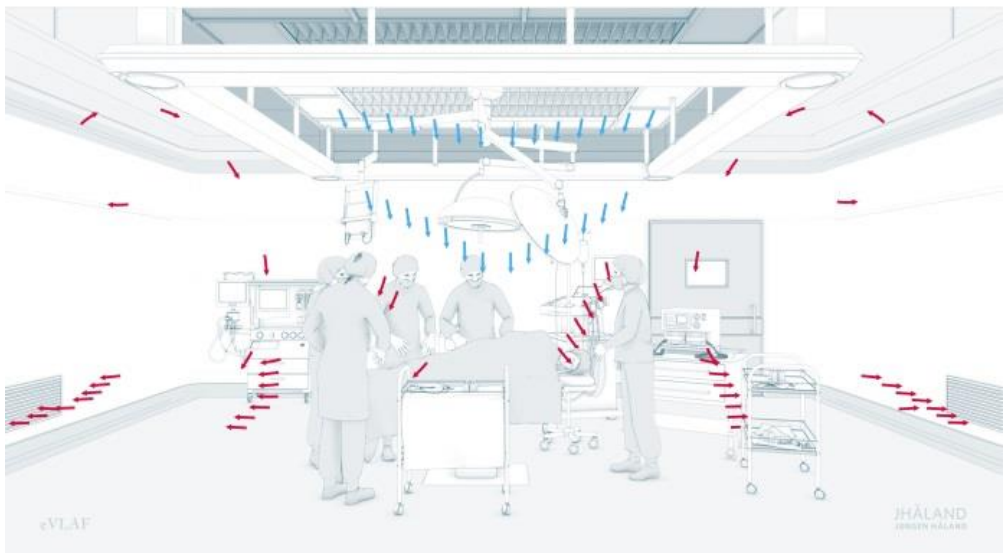


Figure 7b: Exponential vertical UDF with short side walls surrounding the canopy

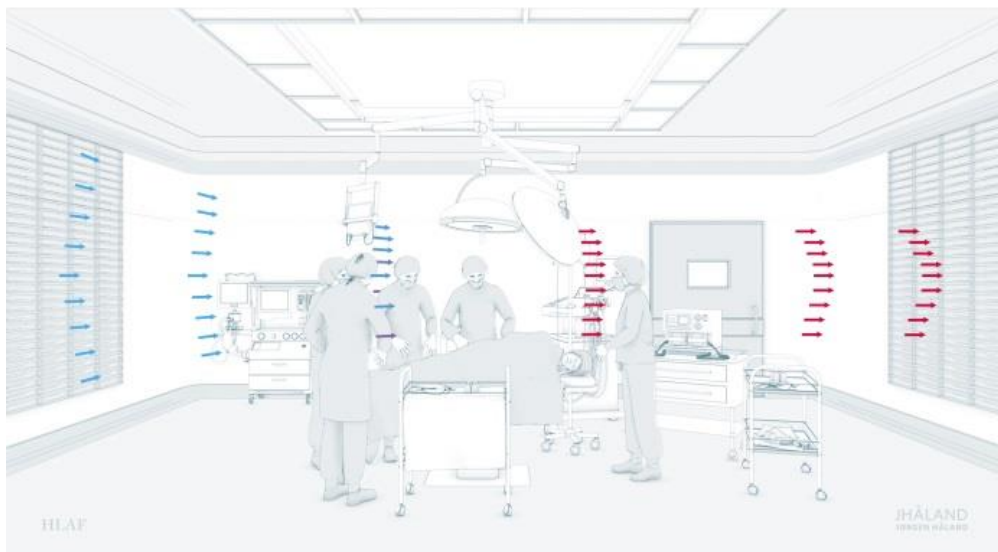


Figure 7c: Horizontal UDF

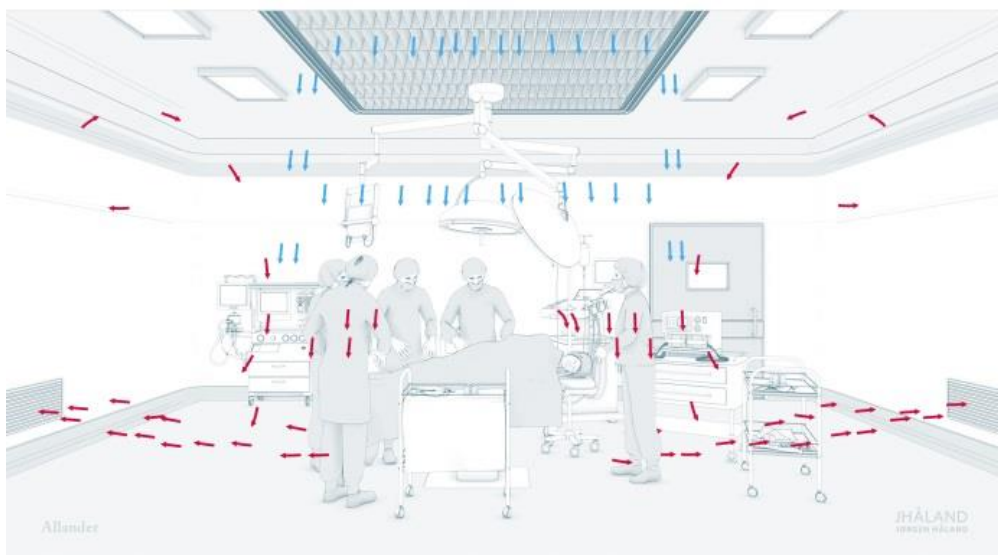
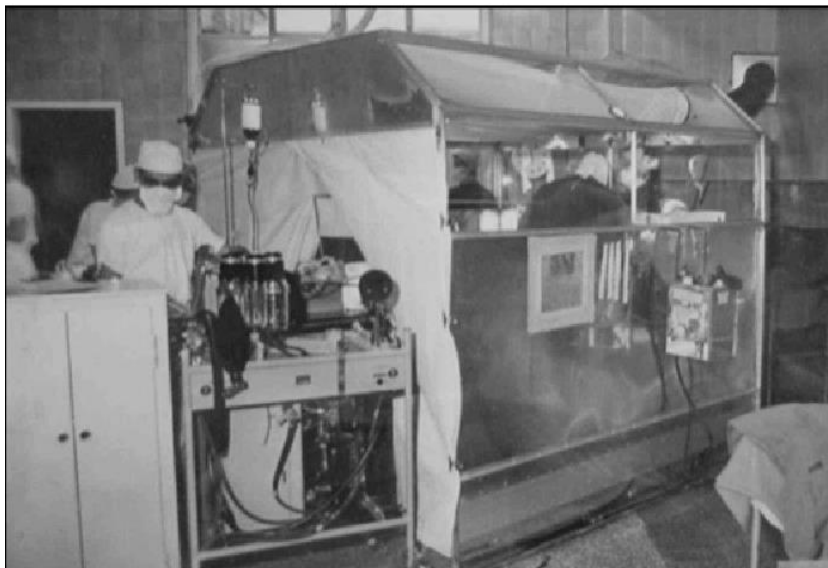


Figure 7d: Allander roof with intentional air curtains in the periphery of the supply canopy

There is an ever evolving development of new UDF system variations. Systems with local and transportable UDF diffusers have been tested out in small cohorts, but have not been implemented as standard, as their vulnerability to wrong implementation and subsequent adverse effects is a potential hazard (109, 110). A new concept involving undercooling of the central part of the plug flow has shown few but promising results in reducing the concentration of CFUs (111). A detailed presentation of new, experimental ventilation systems will not be provided, being beyond the scope of this thesis. In the following, the main focus will be on the prophylactic effect of the main categories of existing and well established ventilation systems in Norway.

### *1.7.3 Ventilation as infection prophylaxis*

In the 1950s, Dr. John Charnley revealed an infection rate of around seven percent after arthroplasty in a conventionally ventilated operating theatre. As mentioned in Section 1.6, he implemented numerous measures to reduce the incidence of postoperative infection during the 1960s. This led to a reduction of the infection rate from seven to almost one percent. One of these measures was the implementation of an ultraclean air (UCA) system to reduce the concentration of air pollutants. The first prototype system was known as the “greenhouse” system (112). This involved a separate enclosure within the OR where filtered air was introduced through the ceiling and extracted through slits along the floor of the enclosure (Figure 8). Air from the rest of the OR was thus separated from the surgical field, and exhaled air from the surgeons was extracted by the use of respiratory masks. Together with Harry Graven and Hugh Howorth, Dr. Charnley further developed the system with ever increasing VFR. The results were good regarding the cleanliness of the air (98), but the restriction of movement due to the enclosure was a matter of concern. In the 1970s, the system was further developed by Howorth into what must be considered the predecessor of UDF systems as we know them today. The supply air unit was installed in the roof of the OR and the canopy was encircled by partial walls as illustrated in Figure 7b. Dr. W. Whyte evaluated such a system and compared it to a full wall system (113).

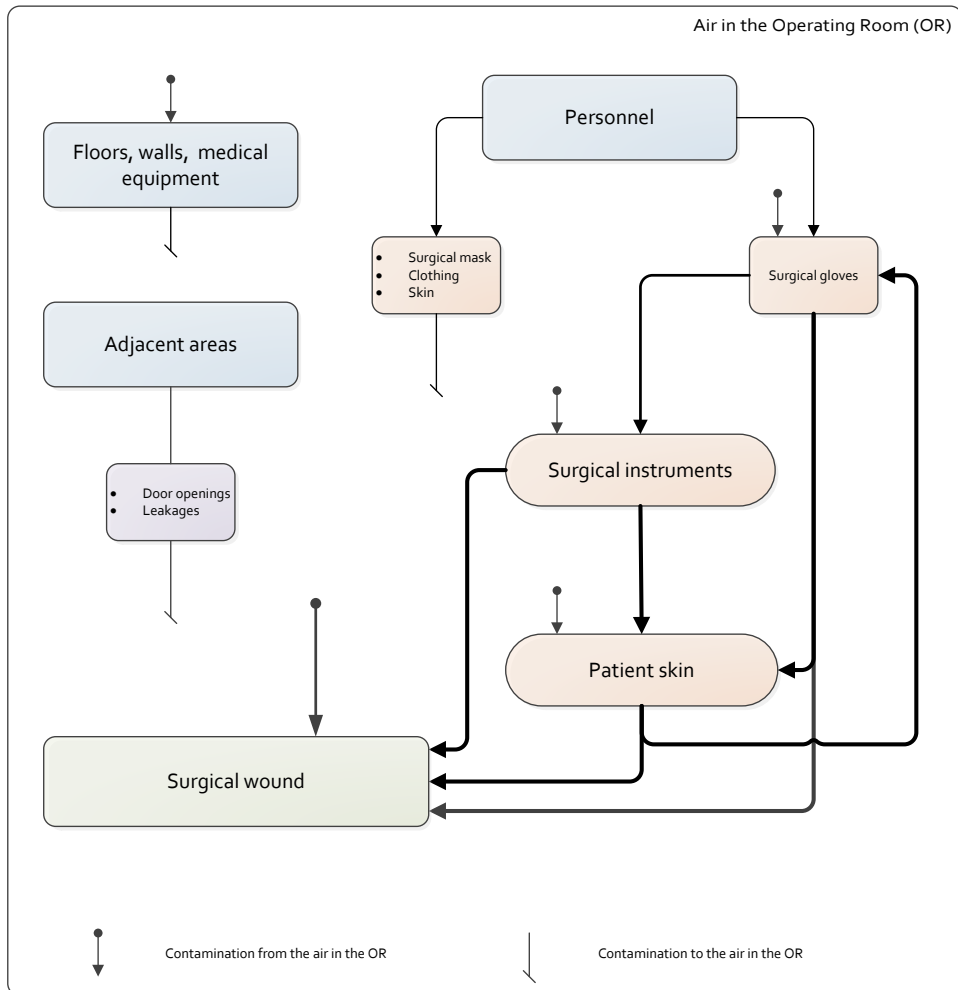


*Figure 8: Sir John Charnley's "greenhouse".*

The results were good and due to increased freedom of movement, these systems set the standard for the development towards the UDF systems as we know them today.

The prophylactic goal of the OR ventilation systems is to reduce the concentration of bacteria in the air. The size of the bacteria is less than  $1\mu\text{m}$  but they rarely exist as free planktonic bacteria in the air. Most microbes in the air of ORs exist in small colonies on skin flakes in the size range of  $4\text{-}20\mu\text{m}$  (114). These bacteria-carrying particles are filtered out in the air handling and supply air units of the ventilation systems where HEPA filters remove particles larger than  $0.3\mu\text{m}$ . The supply air is thus more or less particle-free, and the main source of CFUs in the OR is assumed to be people present (114-117). Without going into detail on this issue, it is worth mentioning four main mechanisms by which airborne bacteria may impact the surgical site by direct contamination: gravitational forces, electrostatic forces, Van der Waal forces or by inert impact. Gravitational forces dominate as the causative mechanism of colonization of operating wounds (118). Indirect contamination might also occur via surgical gloves, the patient's skin or surgical instruments, the latter potentially contaminated to a greater

degree via electrostatic forces (119, 120). Figure 9 shows potential routes of contamination focusing on the air as the source of bacterial pollution.



*Figure 9: Mechanisms for contamination of the surgical wound (modified with approval from Dr. Traversari) (99)*

The importance of air cleanliness in the reduction of postoperative infection has nevertheless been debated. Studies have shown that UDF systems are superior in

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reducing CFUs in the air and in the proximity of the surgical field (111, 121-125). The main reference in recommendations of UDF systems has been a clinical randomized controlled trial conducted by Dr. Lidwell and colleagues in the 1970s and 1980s (126). The results have been debated due to some methodological issues and the fact that the assessment of the true effect of air cleanliness is hard to isolate (127). In summary, Lidwell concluded that ventilation systems which were able to maintain a CFU concentration below 10 per m<sup>3</sup> reduced the incidence of “deep joint sepsis” by roughly 50%. This has been supported by other studies showing a relation between the concentration of CFUs and the incidence of SSI (98, 128-130).

Recent observational studies, however, show that UDF systems might actually *increase* the risk of SSI and revision due to infection (91, 131-133). A suggested mechanism behind this increase has been that the increased air velocity might lead to patient hypothermia and bacterial impingement, predisposing for infection. Increased turbulence in fringe areas and areas around the surgeon, surgical lamps, etc. has also been proposed as possible negative mechanisms. The quality and validity of these results have also been disputed due to several methodological weaknesses (134, 135); this will be discussed in further detail in Section 5.4, where all aspects of the true effect of OR ventilation in the reduction of postoperative infection will be assessed.

*The study of the literature in this thesis was completed in February 2020.*



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## 2 Project aims

### *2.1 General aims*

The overall aim of the project was to survey the bacteriology and antibiotic resistance patterns of microbes causing revision due to infection after THA in Norway, and to assess whether there was any correlation between bacterial findings and haematological infection parameters. As our microbiological findings substantiated the likelihood that contamination during primary surgery might lead to clinical infection several years later, and as the cleanliness of the air in the operating room is a possible risk factor of postoperative infection, we also wanted to validate the type of ventilation reported to the Norwegian Arthroplasty Register and to assess whether these corrected ventilation data affected the risk of revision due to infection after THA with several years of follow-up.

### *2.2 Specific aims*

#### *Paper I:*

To survey the bacteriology and haematological infection parameters in cases of revision due to infection after THA in Norway.

#### *Paper II:*

To survey antibiotic resistance patterns and their evolution in bacteria causing revision due to infection after THA in Norway.

#### *Paper III:*

To validate data on ventilation systems in the Norwegian Arthroplasty Register.

To correct and supplement ventilation data in the Norwegian Arthroplasty Register with true data including technical specifications of the different ventilation systems.

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*Paper IV:*

To evaluate the true effect of different types and sub- classifications of ventilation systems on the risk of revision due to infection after THA in Norway.

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## 3 Material and methods

### 3.1 *The Norwegian Arthroplasty Register (NAR)*

The Norwegian Arthroplasty Register was established in Bergen in 1987 and has since then registered data on THA and THA revisions. The registration form is filled in by the surgeon immediately after surgery and contains information on patient identity and characteristics, indication for surgery and several other patient- and surgery-related variables, including information on the type of ventilation in the operating room (Appendix 1). Revision is defined as removal or exchange of the whole or parts of the prosthesis, and revision cause (e.g. infection) is also determined immediately after surgery based on perioperative evaluations. Since 2011, all reoperations, including DAIR procedures without removal or exchange of parts, are to be reported. The patients' identity number is used to link subsequent revision to the primary THA.

### 3.2 *Data collection and supplementing the NAR data*

In *Papers I and II* we identified the ten hospitals with the highest number of reported revisions due to infection in the period 1993-2007. We used the NAR to identify the date of revision due to infection, and each hospital was visited by the main author (HL), who studied the hospital notes and electronic health records for all these patients. The date and type of surgery were verified and perioperative bacteriological test results including antibiotic resistance patterns as well as preoperative haematological infection parameters related to the revision were collected. The data from the revision were then linked to the primary surgery through the patients' personal identity number. The laterality of the THA (right/left) was also noted in order to eliminate errors in patients with bilateral arthroplasty.

In *Papers III and IV* we used the NAR to identify first revisions due to infection and the type of ventilation reported by the surgeon from the primary surgery, i.e. CV, LAF or greenhouse ventilation, being the three alternatives on the register form (Appendix

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I). To validate the information reported by the surgeon, all present and historical ventilation systems in the period 1987-2015 in the 40 selected hospitals in Norway were evaluated in cooperation with the hospital's head engineer, the register contact person (a surgeon) and/or personnel from the department of infection prevention. Six of the hospitals were visited in order to gain knowledge of the different ventilation systems. The actual ventilation conditions were identified by using a detailed questionnaire as guidance in the direct correspondence (Appendix II). The questionnaire included questions on the period of use of each individual OR ventilation system, physical measurements like the floor area and roof height of each OR, details such as air velocity, type of surgical lamps and types of filters, and questions on different aspects of maintenance. This information was linked to each hospital in the NAR based on year of primary surgery and the hospital's unique register number. In *Paper III* the existing ventilation data in the NAR were compared to the new validated data. In *Paper IV* we assessed the effect of validated OR ventilation on the risk of revision due to infection.

### 3.3 Statistics

The endpoint of all papers in this thesis is revision due to deep infection after THA with removal or exchange of prosthesis parts as reported to the NAR (Appendix 2). In *Paper I* we used Pearson's chi squared test for linear trend to compare time periods and bacterial groups. In *Paper II* we used the same method to compare the prevalence of antibiotic resistance between time periods.

In *Paper III* we compared the reported OR ventilation data with the new validated data. On the basis of the sensitivity, specificity and positive and negative predictive values of the reporting, we calculated the misreporting rate as a measure of the preciseness of the data reported by the surgeon.

In *Paper IV* patients were followed until revision due to infection, emigration, death or the end of follow-up. We used simple, descriptive statistics in the presentation of

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patient and surgery characteristics. To estimate the relationship between revisions due to infection after THA and OR ventilation in the period 2005-2015, we used a multivariate Cox regression model to calculate relative risks with 95% confidence intervals. P-values below 0.05 were considered significant. Adjusted survival rates and Kaplan-Meier survival rates were also calculated. Cumulative survival curves were constructed with OR ventilation system as strata.

Analyses were conducted using SPSS version 22 (Papers I and II) and version 24 (Papers III and IV). Supplementary analyses were conducted with R (R Foundation for Statistical Computing, 2014) (Papers III and IV).

### *3.5 Ethics and conflicts of interest*

The data registration and assessment were performed confidentially based on patient consent and according to Norwegian and EU data protection rules. In Papers I and II we applied for an extension of the existing approval in the NAR from the Regional Ethics Committee (REK number 2009/856b). The studies were fully financed by the NAR and the orthopaedic departments of Haukeland and St. Olav's university hospitals. No conflict of interest was declared.

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## 4 Summary of Papers I-IV

### *Paper I*

#### ***Bacterial and hematological findings in infected total hip arthroplasties in Norway***

**Aim:** To assess the bacterial findings in infected total hip arthroplasties (THAs) in Norway. We also wanted to investigate the relationship between causal bacteria and haematological findings.

**Material and methods:** Revisions reported to the Norwegian Arthroplasty Register (NAR) due to infection after total hip arthroplasty from 1993 to September 2007 were identified. One single observer visited ten representative hospitals where clinical history, preoperative blood samples and the bacterial findings of intraoperative samples were collected. Bacterial growth in two or more samples was found in 278 revisions, and thus included.

**Results:** The following bacteria were identified: Coagulase negative staphylococci (CoNS) (41%), *Staphylococcus aureus* (*S. aureus*) (19%), streptococci (11%), polymicrobial infections (10%), enterococci (9%), Gram-negative bacteria (6%) and others (4%). CoNS were the most common bacteria throughout the period but in the acute postoperative infections (<3 weeks) *S. aureus* was the most frequent bacterial finding. We found no change in the distribution of the bacterial groups over time. *S. aureus* appears to be correlated with a higher C-reactive protein (CRP) value (mean 140 (95% confidence interval (CI): 101-180)) than CoNS (mean 42 (CI: 31-53)). *S. aureus* also correlated with a higher erythrocyte sedimentation rate (ESR) (mean 67 (CI: 55-79)) than CoNS (mean 47 (CI: 39-54)).

**Interpretation:** In this nationwide study, based on 278 revisions of infected THA, staphylococci were the most common bacteria in THA revision for infection in Norway. *S. aureus* was more common in acute postoperative infections and CoNS were more common in early, delayed and late infections. CRP and ESR may be of help in differentiating between infections caused by CoNS and *S. aureus*.

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*Paper II*

***Increasing resistance of coagulase-negative staphylococci in total hip arthroplasty infections***

**Aim:** We investigated bacterial findings from intraoperative tissue samples taken during revision due to infection after total hip arthroplasty (THA). The aim was to investigate whether the susceptibility patterns changed during the period from 1993 to 2007.

**Material and methods:** Reported revisions due to infection in the Norwegian Arthroplasty Register (NAR) were identified, and ten representative hospitals in Norway were visited. All relevant information on patients reported to the NAR for a revision due to infection, including bacteriological findings, was collected from the medical records.

**Results:** A total of 278 revision surgeries with bacterial growth in more than two samples were identified and included. Differences between three five-year periods were tested for linear trend using the chi-square test. The most frequent isolates were coagulase-negative staphylococci (CoNS) (41%, 113/278) and *Staphylococcus aureus* (19%, 53/278). The proportion of CoNS resistant to the methicillin group increased from 57% (16/28) in the first period, 1993-1997, to 84% (52/62) in the last period, 2003-2007 ( $P=0.003$ ). There was also a significant increase in resistance for CoNS to cotrimoxazole, quinolones, clindamycin, and macrolides. All *S. aureus* isolates were sensitive to both the methicillin group and the aminoglycosides. For the other bacteria identified no changes in susceptibility patterns were found.

**Interpretation:** We identified an increase in the proportion of PJI-causing methicillin-resistant CoNS over the study period. Adequate bacterial sampling is crucial for choosing the right antibiotic treatment. This is increasingly important given the emerging resistance of CoNS found in PJI in the present study.

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*Paper III*

***Operating room ventilation - Validation of reported data on 108,067 primary total hip arthroplasties in the Norwegian Arthroplasty Register***

**Aim:** To validate the information on operating room (OR) ventilation reported by orthopaedic surgeons to the Norwegian Arthroplasty Register (NAR).

**Material and methods:** 40 of the 62 public orthopaedic units performing primary total hip arthroplasty (THA) in Norway from 1987 to 2015 were included. The hospitals' current and previous ventilation systems were evaluated in cooperation with the head engineer of the hospital. We identified the type of ventilation system reported to the NAR, and compared the information with the actual ventilation in the specific ORs at the time of primary THA.

**Results:** 108,067 primary THAs were eligible for assessment. None of the hospitals performed THA in true "greenhouse" ventilation. 57% of the primary THAs were performed in ORs with LAF and 43% in ORs with CV. Comparing the reported data with the validated data, LAF was reported with a sensitivity of 86.4%, specificity of 89.4% and positive predictive value (PPV) of 91.6%, with an accuracy of 87.7%. CV was reported with a sensitivity of 89.0%, specificity of 86.7% and PPV of 83.5%, with an accuracy of 87.7%. The total mean misreporting rate was 12.3%.

**Interpretation:** Surgeons were not fully aware of what kind of ventilation system they operated in. This study indicates that conclusions based on ventilation data in the NAR should not be interpreted without considering the inaccuracies in the data.



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*Paper IV*

***Operating room ventilation and the risk of revision due to infection after total hip arthroplasty - Assessment of validated data in the Norwegian Arthroplasty Register***

**Aim:** To assess the influence of validated operating room (OR) ventilation data on the risk of revision surgery due to deep infection after primary total hip arthroplasty (THA) reported to the Norwegian Arthroplasty Register (NAR).

**Material and methods:** Forty orthopaedic units reporting THAs to the NAR from 2005 to 2015 were included. The true type of ventilation system in all hospitals at the time of primary THA was confirmed in a previous study (136). Unidirectional airflow (UDF) systems were subdivided into small, low volume, unidirectional vertical flow (lvUDVF) systems, large, high volume, unidirectional vertical flow (hvUDVF) systems, and unidirectional horizontal flow (UDHF) systems. These three ventilation groups were compared to conventional, turbulent, mixing ventilation (CV). The association between the end point, time to revision due to infection, and OR ventilation was estimated by calculating relative risk (RR) in a multivariate Cox regression model, with adjustments for several patient- and surgery-related covariates.

**Results:** 51,292 primary THAs were eligible for assessment. 575 of these had been revised due to infection. We found a similar risk of revision due to infection after THA performed in ORs with lvUDVF and UDHF, when compared to CV. THAs performed in ORs with hvUDVF had a lower risk of revision due to infection than CV (RR=0.8, 95% CI: 0.6-0.9, p=0.01).

**Interpretation:** THAs performed in ORs with hvUDVF systems had a lower risk of revision due to infection than those performed in ORs with CV systems. The perception that all UDF systems are similar and possibly harmful seems erroneous.

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## 5 Main results and general discussion

### 5.1 Bacteriology and serology of infected THA

CoNS (41%) and *S. aureus* (19%) were the most common bacteria causing revision due to infection after THA in Norway from 1993 to 2007 (*Paper I*). Other bacteria were streptococci (11%), polymicrobial infection (10%), enterococci (9%), Gram-negative bacteria (6%) and others (4%). The bacterial spectrum concurs with results in other publications, although our share of *S. aureus* is somewhat lower (29, 30, 137-145). A possible explanation is that soft tissue revisions without removal or exchange of prosthesis parts were not reported to the NAR during the study period. Such revisions are often due to early THA infections caused by *S. aureus*, meaning that the share of *S. aureus* might be underestimated in our material (Section 5.6.2).

Low grade, chronic infections with normal or low haematological infection parameters might be evaluated as aseptic loosening by the surgeon perioperatively, and might subsequently and erroneously be reported to the NAR as such. These low grade infections are probably dominated by low virulent bacteria such as CoNS and *Cutibacterium* spp., and the proportion of these might thus also be somewhat underestimated in our material (Sections 5.6.1 and 5.6.2).

The distribution of the different bacterial groups remained unchanged during the different periods. There was a trend towards more polymicrobial infections, which in the majority of cases involved CoNS and *Cutibacterium* spp. This might be due to improved diagnostics and awareness of such low virulent bacteria formerly assessed as pollutants, during the study period (146).

*S. aureus* were the most common bacteria in acute, postoperative infections and CoNS was the most prevalent in later infections, including infections over two years after primary THA. Haematological seeding of CoNS is theoretically possible, but less likely to occur as it has been shown to require substantial bacteraemia (147, 148). The finding of 40% CoNS in late infections may thus support the perception that direct

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contamination during primary surgery is the most common route of infection after THA, even in infections occurring several years after primary surgery.

Infections after THA caused by *S. aureus* yielded higher CRP (mean 140 (95% CI: 101-180)) than infections caused by CoNS (mean 42 (CI: 31-53)). Combined with the finding of high and increasing resistance amongst CoNS to methicillin and aminoglycosides (*Paper II*), this supports a practice where vancomycin is introduced in cases of infected THA with low infection parameters (CRP<50) and unknown causative microbes in Norway.

### *5.2 Antibiotic resistance in bacteria causing infections after THA*

There is a high and increasing resistance to antibiotics in the methicillin group amongst CoNS, from 57% in 1993-2007 to 84% in 2003-2007 (*Paper II*). This high prevalence of MRSE concurs with international findings (29, 30, 141, 142). CoNS also showed increased resistance to co-trimoxazole, quinolones, clindamycin and macrolides as well as a trend towards increased aminoglycoside resistance, as referred to earlier (Section 5.1).

There is no conclusive explanation for this general increase in antibiotic resistance. It has been shown that methicillin resistance among CoNS might reflect the general consumption of antibiotics (149, 150). The Norwegian Institute of Public Health has shown a generally increased use of cephalosporins and quinolones in the study period (1987-2007) (151), and it can be speculated that this might have contributed to the increase in resistance among CoNS in THA infections. Hospitalization related to surgery is shown to rapidly transform or displace sensitive skin colonies with more resistant strains (152-154), and the increase in resistance among CoNS infections after THA might potentially reflect an increased resistance in the nosocomial flora, which may be speculated to reflect the increased use of antibiotics in general practice.

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Another possible explanation for increased resistance in bacteria causing revision due to infection after THA might be that the use of antibiotic-loaded bone cement with subinhibitory concentrations of antibiotics might lead to a selection of resistant strains of bacteria. In our material (*Paper II*) both enterococci and CoNS revealed a high share of aminoglycoside resistance, 90% and 59% respectively. A study from the USA found the share of aminoglycoside resistance among CoNS to be as low as 13% (141). In Norway approximately 60% of THA patients receive cemented THA (77), the vast majority with aminoglycoside-loaded cement, as cemented THA without antibiotics has been shown to increase the risk of revision due to infection compared to antibiotic-loaded cement (81, 155). In the USA most patients receive uncemented THA and if cemented, bone cement without antibiotics is most commonly used (156). This might explain some of the differences in antibiotic resistance in these two materials. One study did not find increased gentamicin resistance in CoNS strains in groin colonization depending on whether or not bone cement was used (154); however, the authors emphasized that due to the small number of cases and assessment of skin colonization only, it was not possible to reject the hypothesis that gentamicin-loaded bone cement might increase the risk of THA infection with gentamicin-resistant CoNS.

The choice of fixation method is disputed and beyond the scope of this thesis, but in Norway cemented THA is widely used and especially in elderly patients (>75 years) due to higher general survival of the prosthesis (157-159).

We did not find any MRSA in our material. This might reflect the prophylactic measures implemented in Norway to reduce the spread of MRSA. Comparable measures have been implemented in the Netherlands with good results (160). All *S. aureus* were also sensitive to aminoglycosides, linezolid, rifampicin, co-trimoxazole and quinolones, which might reflect the general susceptibility of *S. aureus* in Norway.

There was no major change in antibiotic resistance in the other bacteria groups during the study period. All streptococci were susceptible to penicillins and some very few strains were resistant to clindamycin and macrolides. We found no vancomycin-resistant enterococci and all enterococci were also susceptible to linezolid. We found a

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high proportion of aminoglycoside resistance among enterococci, but this remained unchanged throughout the study period. The Gram-negative bacteria were susceptible to aminoglycosides, but many were, as expected, resistant to ampicillin.

The most common empirical treatment of severely ill patients with clinically suspected PJI in Norway has traditionally been a combination of cloxacillin and gentamicin. The latter is also the most common antibiotic in antibiotic-loaded bone cement (81). Our results reveal increased resistance to these antibiotics among CoNS, the most common bacteria in infected THA. In suspected low grade PJI in THA with unknown bacteriology but relatively low haematological infection parameters (CRP<50, *Paper I*), our results support the suggestion to add vancomycin as empirical parenteral treatment as well as a component in the cement in the case of revision.

Results from *Paper I* and *Paper II* were included as references in the recommendations from the Norwegian Directorate of Health, where vancomycin is recommended in the empirical treatment of PJI (71).

### 5.3 Ventilation data in the NAR

Not all surgeons are aware of what kind of ventilation system they are operating in, and this resulted in a misreporting rate of 12% for both LAF and CV (*Paper III*). The recommendation in *Paper III* is that studies based on ventilation data from surgeons and surgical departments should not be interpreted without considering inaccuracies in the data. This includes several registry studies included in a large review published in the Lancet in 2016 (161), where the majority of the studies concerning THA reveal an increased risk of revision due to infection for THA performed in LAF compared to CV (91, 131, 133, 162). These studies contributed to new WHO guidelines which do not recommend the installation of LAF systems in new operating theatres constructed for ultraclean surgery (163). In *Paper III* we question the validity of this conclusion, based

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on inaccuracies in the evaluated data in our material. Regarding orthopaedic surgery, Dr. Bischoff's review in the Lancet also includes a prospective, non-registry study which shows a protective effect of LAF, but this is a study on hemiarthroplasty (164).

#### *5.4 Ventilation as a risk factor for revision due to infection after THA*

In *Paper IV* we use the validated ventilation data from *Paper III* to assess the effect of different ventilation systems on the risk of revision due to infection after THA. We found no difference between undifferentiated UDF, assessed as a whole, and CV. Further, we sub-classified the UDF systems based on airflow direction (horizontal/vertical), canopy size, and VFR. The use of large, high volume, vertical UDF systems (hvUDVF) was associated with a lower risk of revision due to infection after THA compared to CV (RR=0.8, 95% CI: 0.6-0.9, p=0.01). The other systems, i.e. smaller, low volume UDF systems (lvUDVF) and horizontal UDF systems (UDHF) showed no difference from the CV systems regarding the risk of revision due to infection. In *Paper IV* we conclude that no UDF system is harmful, and that hvUDVF systems should be implemented for use in ultraclean operating rooms in the future.

The uncertain quality and validity of ventilation data has been presented as one of the main arguments against the results in previous registry studies. The limited follow-up time of the included patients has also been a matter of dispute as this has been both unspecified and limited to 6 to 12 months in prior studies (131, 132, 162). In *Paper I* we found that CoNS are the most common bacteria causing revision due to infection after THA and the most common bacteria in late infections, occurring several years after primary surgery. Haematological seeding of CoNS has been shown to be a relatively rare event (147, 148), and this substantiates that direct contamination is the main route of postoperative infection, even in late infections. This gave us the incentive to study end point revision due to infection after THA, with four years of follow-up, as in the Lidwell studies (up to four years, mean 2.5 years).

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Another factor included in our analysis is the canopy size of the different UDF systems, where some recommendations state a minimum size of 320cm x 320cm in order to safely include the patient, surgical staff and instruments within the protected area (99, 105, 106). The canopy size is directly related to the displaced volume of air and thus the size of the protected field. Together with air velocity, this is considered one of the most important predictors of the protective effect (107). Movement of personnel in the UDF zone, movement of surgical lamps, etc. have been shown to reduce the cleanliness of the air in the operating field, mainly in the areas between the plug flow and the air in the rest of the OR (102, 165). A larger canopy size/UDF zone reduces the risk of creating turbulence in these fringe areas. All surgical activity should therefore be conducted within the zone and the zone should be clearly marked on the floor.

The potential adverse effect of UDF systems has been speculated to be caused by bacteria being impinged in the surgical wound due to high air velocities, also speculated to cause local hypothermia due to disruption of the protective thermal plume of the wound (117, 131, 166, 167). Some have also shown that UDF might lead to general hypothermia, a known risk factor for infection (168). To counteract the hypothermic effect, many have implemented the use of “forced air warming” (FAW) (Bair Hugger system, etc.), which is again thought to disrupt the unidirectional airflow (169, 170). These findings are disputed, and the evidence is sparse (171-173). It has recently been shown that a sufficient air velocity at a level of 0.35 m/s of the unidirectional airflow counteracts the negative effect of the thermal plume of the FAW (174, 175). To achieve such air velocities and at the same time maintain a large enough protected area with the use of large area canopies, the UDF systems should have a sufficient VFR in the magnitude of  $> 10,000 \text{ m}^3/\text{h}$ . In *Paper IV* we show that hvUDVF systems with canopy size  $>10 \text{ m}^2$  and VFR  $>10,000 \text{ m}^3/\text{h}$  are associated with a lower risk of revision due to infection after THA than CV systems, while the lvUDVF systems did not show the same effect. These are comparisons in a rough format, but they clearly emphasize the importance of ventilation system differentiation based on a variety of technical specifications, as this is likely to reflect the actual performance of contaminant removal.

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In *Paper III* we show that many surgeons do not know what kind of ventilation system they are operating in. Maximal effect of UDF systems requires correct implementation, which may be speculated to be a weakness of these systems (176). If one is unfamiliar with one's own kind of ventilation system, it is difficult to use it in a correct matter. Discipline in the operating room has been shown to affect air cleanliness where the number of personnel in the room, activity level and the number of door openings are considered important variables (176-178). This applies to both UDF and CV systems, where UDF systems are known to have a lower recovery time and might deal with sudden emissions of pollutants more rapidly. This does not, however, imply that one can behave at will and that UDF can defuse any unwanted episode of pollutant emission (178, 179). A sense of false security might lead to inappropriate behaviour, which might nullify the protective effect of UDF systems. Knowledge of the ventilation conditions and correct use of the different systems may thus be essential in the operating room of the future. This is discussed in an annotation by Dr. Thomas in the *Bone and Joint Journal*, where correct implementation is emphasized as an important factor (135). Even without knowledge of the use and implementation of the different systems in our material, our findings in *Paper IV* still indirectly support this, as incorrect use and implementation would in theory and most likely have negatively affected our results regarding UDF systems. Despite this, we show that hvUDVF systems perform better than the other systems as a prophylactic measure against PJI.

Trends in operating room ventilation have gone through different phases. UDF systems entered the ORs after Lidwell's Medical Research Council (MRC) study, which found a relative risk of 0.4 when comparing ultraclean systems with non-ultraclean systems in arthroplasty surgery. The study has been disputed due to some methodological weaknesses, where the main arguments have been as follows: it is a randomized study on 19 hospitals in four countries, the authors do not thoroughly adjust for the use of systemic antibiotic prophylaxis, the randomization practice varies between the hospitals, one type of ventilation system (Allander systems) was transferred from the ultraclean group to the non-ultraclean group during the study period due to some unsatisfactory measurements, CFUs were measured by different means and without



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standardized intervals, Cox regression was not used to account for varying follow-up time and disappearance, and one of the hospitals accounted for 1/3 of the infections in both the ultraclean and control group. Because of this and conflicting results in studies from national surveillance registries, the new WHO guidelines in 2016 made a conditional recommendation that UDF systems should not be installed in future operating rooms in order to reduce the incidence of postoperative infection after arthroplasty (163). But the wind is about to change again. One of Lidwell's companions and co-authors, Dr. Whyte, has with others reevaluated the findings in the original MRC paper (134). They emphasize the importance of evaluating the degree of contaminant removal of the ventilation systems, rather than the schematic configuration, and they present in detail why the results from the MRC study should still be considered valid, which implies that the use of UDF systems should be encouraged. Although we did not include measurements of contaminant reduction of the various ventilation systems, the findings in our material seem to support this wind of change.

Despite this, there is a series of arguments implying that air cleanliness is not a dominating risk factor for postoperative infection. As mentioned, in the MRC study one hospital reported 1/3 of the infections in both the ultraclean group and the control group. This alone questions the importance of air cleanliness compared to other risk factors. Further, studies on the bacteriology of infected shoulder arthroplasty and infected spinal implants show a different bacteriological spectrum than in infected THA (39, 180, 181), with a high proportion of *Cutibacterium acnes*, a species known to be abundant in sebaceous glands in the follicles of the skin in such regions, thus indicating that the patient is the source of infection. This is supported by differences in infection rates between sexes, where men have twice the risk of revision due to infection after THA compared to women, as shown in *Paper IV*, and gene studies showing that SSI after elective orthopaedic surgery is more frequently caused by endogenous transmission than previously assumed (182). Two recent Swedish studies using multilocus sequence typing following PCR amplification when studying *S. epidermidis* in PJI show that the air in the operating room does contain substantial

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amounts of CoNS, but does not seem to contain the sequence types of *S. epidermidis* strains most likely to cause PJI (183, 184).

Nevertheless, UDF systems create cleaner air with regards to both particle and microbial load, and the contribution of airborne bacteria in postoperative infection cannot be ruled out (111, 121-125). Our studies on OR ventilation involve a scenario in which all patients received an effective antibiotic prophylaxis. In spite of this, we show a protective effect of the hvUDVF systems in validated surveillance data. Without any antibiotic effect, the situation would probably have been different, and the importance of air cleanliness might have been more substantial. In such a scenario, which is in fact not unlikely to occur (185), one must reduce the impact of all risk factors to a minimum in order to avoid postoperative infection. This includes the cleanliness of the air and correct implementation and use of UDF systems, which will be important in the operating room of the future.

### *5.5 Methodological evaluations and limitations*

Revision due to infection after THA is a relatively rare phenomenon with an incidence of 1.1% in our material. To study such a rare end point requires large amounts of data of a magnitude that can only be assessed in practice by using national surveillance databases. The data in the NAR have been shown to be of good completeness for both primary and revision surgery (186, 187). But large data registers have some inherent challenges that will be discussed in the following.

#### *5.5.1 Confounding*

Large register studies will be affected by residual confounding as the number of adjustment variables in the analyses will be limited. *Papers I, II and III* were not directly affected by statistical confounding, since we examined the bacteriology and the quality of reporting, and did not conduct large, multivariate analyses with numerous

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adjustment variables. However, the diagnostics have changed somewhat over time and this might have led to *time-dependent confounding* in *Papers I and II*. Increased awareness of low grade infections and diagnostics targeted at e.g. CoNS and *Cutibacterium* spp. in the later years of the study period might have led to an underestimation of such low virulent bacteria early in the study period due to insufficient identification methods. This is in addition to possible clinical underestimation of low grade infection with subsequent misreporting of such as aseptic loosening.

In *Paper IV*, we could only suggest the association between OR ventilation and revision due to infection as several unknown confounders were probably involved, e.g. physical behaviour in the OR, incorrect implementation and maintenance of the systems and many other factors that could have affected the functionality of the systems: we had no information on the number of personnel in the OR, the number of door openings, type of clothing, use of FAW, use of surgical drapes, etc. However, we do not believe that these factors have led to systematic errors. THA was chosen as the surgical reference as it is relatively standardized surgery, and as variations between hospitals regarding perioperative management of patients are assumed to be small. This also applies to the assumption that revision due to infection is somewhat underestimated (188-190). The reporting rate is assumed to be evenly distributed between the hospitals throughout the periods involved, as it is shown to be for general completeness in the NAR (186, 187).

We found an increased proportion of hvUDVF in recent years (*Paper IV*, Figure 1) and the use of uncemented THA is also increasing (77). These factors are parallel to an increased risk of revision due to infection after THA in Norway (155). Thus they are time-dependent confounders which we have addressed by adjusting for the year of primary surgery as well as type of ventilation and method of fixation.

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### 5.5.2 Bias

*Papers I and II* are subject to *reporting bias*. In *Paper I* we found that the bacteriology depended on the time passed since primary surgery. Only revisions with removal or exchange of prosthetic parts were reported to the register in the study period, and soft tissue debridement with retention of the prosthesis was therefore not included. Such infections are often early infections caused by *S. aureus* (*Paper I*), which might have led to an underestimation of these in our results. As some low grade infections might have been misreported as aseptic loosening, this might also have led to an underestimation of CoNS in our material, as pointed out earlier.

Modular THAs (Figure 2) contain removable parts which are exchanged during a DAIR procedure. Such revisions have thus been reported to the NAR throughout the study period of *Paper IV*. Monoblock THAs *do not* contain removable parts, and DAIR procedures for such prostheses were therefore not reported to the NAR until 2011, since when all THA reoperations were to be reported, regardless of whether prosthetic parts were removed/exchanged or not. This may have led to an underreporting of revision due to infection after monoblock THA. This reporting bias was addressed by adjusting for modularity.

In *Papers III and IV*, 40 hospitals reporting 66% of the primary THAs to the NAR were included for validation of ventilation data. Both the included hospitals and the 22 excluded hospitals had THA activity throughout most of the period and similar distribution between rural hospitals, regional/university hospitals and specialized elective hospitals. The hospitals in the two groups also had similar completeness of reporting of both OR ventilation and primary THA (77, 186). Thus, we believe that the impact of *selection bias* was minor.

In *Paper IV*, only two hospitals reported the use of UDHF. In addition, these two hospitals had a higher proportion of uncemented THA. This adds selection bias to these results, also assessed by adjusting for method of fixation. In general, we nevertheless

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believe that the high grade of completeness in the NAR results in a relatively low impact of selection bias.

### *5.5.3 Internal and external validity*

With high completeness and coverage of the data in the NAR (77), we believe that the results in *Papers I-IV* are all of high internal validity. Bacteriology and antibiotic resistance patterns might vary with regards to population geodemography, thus perhaps limiting the direct external validity of *Papers I* and *II*. Indirectly, however, it is important to show that efforts in Norway to inhibit the development of antibiotic resistance and the spread of resistant bacteria have probably contributed to a low occurrence of e.g. MRSA in the Norwegian bacterial flora.

*Papers III and IV* must be considered of high external validity, as this is the first register study using validated ventilation data to assess technical sub-classifications of UDF systems with several years of follow-up. This is emphasized by the fact that existing WHO guidelines are mainly based on register studies of assumed lower validity.

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## 6 Conclusions

CoNS is the most common bacteria causing revision due to infection after THA in Norway, with increasing resistance to the antibiotics used in both prophylaxis and empirical treatment of PJI in Norway. Numerous risk factors influence the occurrence of PJI, and the type of ventilation system seems to be one of them. Currently, air cleanliness seems to be important up to a certain point beyond which other factors might be more influential. Nevertheless, with increasing antibiotic resistance amongst common causative bacteria, it is necessary to reckon with a reduced antibiotic effect in the future. All possible efforts to reduce the peroperative bacterial load to a minimum must therefore be implemented. This includes installation of large, high volume UDVF (hvUDVF) systems in ORs where ultraclean surgery is to be performed. This recommendation should be included in future international guidelines.

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## 7 Future directions

Antibiotic resistance is increasing and must be monitored in all medical disciplines dealing with infections. This is necessary in order to offer the best possible prophylaxis and treatment, and also to identify necessary measures to reduce specific challenges in the development of antibiotic resistance.

Technological advances and correct implementation and use of UDF systems will be essential to optimize the air cleanliness of ORs in the future. The microbiological effect of the ventilation systems should be evaluated in a more direct manner. It is challenging to isolate the air cleanliness close to the surgical wound as a risk factor for postoperative infection. Interdisciplinary cooperation between technical personnel, engineers, infection prevention personnel and surgeons will be of great value in enhancing knowledge of the field. Better methods of monitoring CFUs during real-life surgery should be developed and implemented in a manner that does not conflict with surgical activity. Further, methods for evaluating the microenvironment of the surgical wound with regards to humidity, temperature, and contamination in different stages of surgery should be developed and used to compare real-life surgery performed with different technical sub-classifications of ventilation systems. This could help in answering various questions about where the infections arise from and to what degree air cleanliness plays a part.

"Fortune favours the prepared mind."

-Louis Pasteur



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## Appendices



Nasjonalt Register for Leddproteser  
The Norwegian Arthroplasty Register

Spørreskjema – Ventilasjon av operasjonsstuer

- Stuenummer: .....
- Periode i bruk: fra..... til.....
- 1) Ventilasjonstype/luftstrømstype: Laminær (LAF)  Annet:.....  
Konvensjonell   
Greenhouse
- 2) Stuens areal: .....m<sup>2</sup>
- 3) Stuens takhøyde: .....m
- 4) Luftens utgangshastighet: .....m/s
- 5) Anleggets nominelle innluftsmengde: .....m<sup>3</sup>/h Friskluftsandel.....
- 6) Hvilken type filter/filterklasse er installert?: .....
- 7) Hvor ofte foretas: Filterbytte.....pr. år  
Rengjøring.....pr. år
- 8) Hvordan og hvor ofte foretas CFU-måling?: ...../.....pr. år
- Ingen rutiner
- 9) Har CFU-verdien vært målt til  $\leq 10\text{CFU/m}^3$ : Ja  Vet ikke   
Nei
- 10) Ventilene for ut-luft er plassert: Gulv  Tak   
Vegg
- 11) Benytter systemet underkjøling?: Ja  Vet ikke   
Nei
- For LAF-tak:
- 12) Takets størrelse: .....m x .....m
- 13) Takets luftstrøm er definert som: Delvegg  Spesifisering:  
Helvegg
- 14) Takets luftstrøm er: Vertikal  Skrå   
Horisontal
- 15) Er det montert sidevegger/skjørt?: Ja  Lengde:  
Nei
- 16) Er det installert spesial-operasjonslamper for LAF?: Ja   
Nei
- 17) Er det sonemarkering i gulvet?: Ja   
Nei



## Spørreskjema - Ventilasjon av operasjonsstuer - forklaringer

**Stuenummer og Periode i bruk:** Den aktuelle operasjonsstuens romnummer og perioden den ble brukt i intervallet 1987-2015. (dd.mm.åååå, mm.åååå, åååå eller dd (dagens dato)).

- 1) **Ventilasjonsstype:** Laminær luftstrøm (LAF), Konvensjonell (turbulent) overtrykksventilasjon, «Greenhouse» ventilasjon eller annet spesifisert tak (Allander, Weiss, Trox etc).
- 2) **Stuens areal:** Stuens areal i kvadratmeter (m<sup>2</sup>).
- 3) **Stuens takhøyde:** Stuens takhøyde i meter (m).
- 4) **Luftens utgangshastighet:** Snittverdi av luftens utgangshastighet i meter per sekund (m/s). For sonedelte tak er det også ønskelig at det oppgis én snittverdi. Størrelsesorden 0,15 - 0,5 m/s.
- 5) **Anleggets innluftsmengde:** Luftvolumet som systemet tilbyr per time (m<sup>3</sup>/h) (Størrelsesorden 1000-16000 m<sup>3</sup>/h) samt friskluftandel (primærluft).
- 6) **Filtertype/ -klasse:** Filtertype for innløpsluften. Det er ønskelig med informasjon om alle steg. For eksempel HEPA, 3 steg, Last H13.
- 7) **Filterbytte og rengjøring:** Frekvens for filterbytte (alle steg) og rengjøring av ventilasjonssystemet; 1 x , 2 x pr. år etc.
- 8) **CFU-målinger:** Gjøres målingene under pågående kirurgi («Intraoperativt») og i nærheten av operasjonsfeltet, eller på «tom stue»? Frekvens for CFU målinger; 1 x , 2 x pr. år etc.
- 9) **CFU-verdien:** Har CFU-konsentrasjonen noen gang vært målt til å være  $\leq 10\text{CFU}/\text{m}^3$  slik kravet fra statens helseetilsyn om ultrarene operasjonsstuer tilsier? Dette vil spesifiseres i korrespondanse med smittevernavdelingen.
- 10) **Ventiler for ut-luft:** Er slusene for luften som forlaster rommet plassert langs gulvet, på veggen (eventuelt som langstrakte sluser fra gulvet og opp på veggen), tak eller en kombinasjon (sett da flere kryss eller spesifiser)?
- 11) **Underkjøling:** Benyttes det underkjøling av innløpsluft?
- 12) **Takets størrelse:** Mål på selve ventilasjonsflaten (lengde x bredde)
- 13) **Takets luftstrøm:** Er det snakk om et helveggsystem med nokså jevn snitthastighet for luftsøylen i hele taket, eller er det snakk om et delveggsystem med ulike hastighetssoner. Ved delvegg er det ønskelig at prinsippet spesifiseres: eksponenssiell LAF e.l.
- 14) **Takets luftstrøm:** Er det vertikal luftstrøm, horisontal luftstrøm eller skrå luftstrøm?
- 15) **Sidevegger/skjørt:** Er det montert sidevegger/skjørt ned langs innløpet? Hvis ja, oppgi heist lengde på disse/dette.
- 16) **Spesiallamper:** Er det montert spesial-operasjonslamper til bruk sammen med laminær luftstrøm for å hindre dannelse av turbulens?
- 17) **Sonemarkering:** Er det markeringer i gulvet på stuen som indikerer luftsoner(e)?



**Nasjonalt Register for Leddproteser**  
Ortopedisk klinikk, Helse Bergen HF  
Haukeland universitetssjukehus, Postboks 1400  
Møllendalsbakken 11, 5021 BERGEN  
Tlf 55973742/55973743

F.nr. (11 sifre) .....

Navn: .....

(Skriv tydelig ev. pasientklarellapp – spesifiser sykehus.)

Sykehus: .....

## HOFTEPROTESER

Alle totale hofteproteseoperasjoner og hemiprotetser på annen indikasjon enn fraktur/fraktursekvele registreres her (hemiprotese for fraktur/fraktursekvele registreres på Hoftebruddskjema). Alle reoperasjoner skal registreres: skifte/fjerning av proteselever, kantplastikk, bløtdelsdebridement, og operasjoner for protesenær fraktur eller gluteal svikt.

### TIDLIGERE OPERASJON I AKTUELLE HOFTE (ev. flere kryss)

- Nei
- Osteosyntese for fraktur i prox. femurende
- Hemiprotese pga. fraktur
- Osteotomi
- Artrose
- Totalprotese(r)
- Annen operasjon .....

+

### AKTUELLE OPERASJON (ett kryss)

- Primæroperasjon (også hvis hemiprotese tidligere)
- Reoperasjon (totalprotese tidligere)
- Primær hemiprotese for annen indikasjon enn fraktur/fraktursekvele

OPERASJONSDATO (dd.mm.åå)      | | | | | | | |

### AKTUELLE SIDE (ett kryss) (Bilateral opr. = 2 skjema)

- Høyre  Venstre

### ÅRSÅK TIL AKTUELLE OPERASJON (KRYSS AV ENTEN I A ELLER B)

#### A. Primæroper. pga (ev. flere kryss)

- Idiopatisk coxartrose
- Rheumatoid artritt
- Sekvele etter frakt. coli. fem.
- Sekv. dysplasi
- Sekv. dysplasi med total luksasjon
- Sekv. Perthes
- Sekv. epifysiolyse
- Mb. Bechterew
- Akutt fraktura coli femoris
- Annet .....

(f.eks. caputnekrose, tidl. artrose osv.)

#### B. Reoper. pga (ev. flere kryss)

- Løs acetabularkomponent
- Løs femurkomponent
- Luksasjon
- Dyp infeksjon
- Fraktur i acetabulum
- Fraktur av femur
- Vancouverklassifikasjon, se bakside.
- A  B1  B2  B3  C
- Smertor
- Osteolyse i acetab. uten løsning
- Osteolyse i femur uten løsning
- Implantatfraktur femurdal
- Implantatfraktur caput
- Implantatfraktur kropp
- Implantatfraktur liner
- Implantatfraktur annet: .....

+

- Gluteal svikt
- Annet .....
- (f.eks. Girdlestone etter tidl. infisert protese)

+

### REOPERASJONSTYPE (ev. flere kryss)

- Bytte av femurkomponent
- Bytte av acetabularkomponent
- Bytte av hele protesen
- Fjernet protese og satt inn sementspacer
- Fjernet sementspacer og satt inn ny protese
- Fjernet protese (Girdlestone eller fjerning av sementspacer)
- Angi hvilke deler som ble fjernet .....
- Bytte av plastforing
- Bytte av caput
- Bløtdelsdebridement
- Ny protese etter Girdlestone
- Resutur av muskel
- Transposisjon av muskel
- Osteosyntese for fraktur
- Konvertering til hemiprotese
- Andre operasjoner .....

### TILGANG (ett kryss)

- Fremre (Mellom sartorius og tensor)
- Anterolateral (Mellom glut. medius og tensor)
- Direkte lateral (Transgluteal)
- Bakre (Bak glutoseus medius)
- Annen .....

MININVASIV KIRURGI (MIS)  Nei  Ja

LEIE  Sideleie  Rygg

TROCHANTEROSTEOTOMI  Nei  Ja

### BENTRANSPLANTASJON (ev. flere kryss)

- Acetabulum  Nei  Ja  Bepakking
- Femur  Nei  Ja  Bepakking a.m. Ling/Gie

### BENTAP VED REVISJON (Paprotsky's klassifisering se baksiden)

- Acetabulum  I  II  IIA  IIB  IIC  IIIA  IIIB
- Femur  I  II  IIIA  IIIB  IIV

### PROTESEKOMPONENTER (Bruk klarellapp på baksiden, eller skriv REF.NR.)

#### Acetabulum

- Navn/Type .....
- ev. REF.NR. ....
- Med hydroksylapatitt  Uten hydroksylapatitt
- Sement med antibiotika – Navn .....
- Sement uten antibiotika – Navn .....
- Usementert

+

#### Femur (+ ev. trokanterdel)

- Navn/Type .....
- ev. REF.NR. ....
- Med hydroksylapatitt  Uten hydroksylapatitt
- Sement med antibiotika – Navn .....
- Sement uten antibiotika – Navn .....
- Usementert

#### Caput (+ ev. halsdel)

- Fasttettende caput
- Separat caput - Navn/Type .....
- ev. REF. NR. ....
- Diameter .....

### ANTIBIOTIKAPROFYLAKSE Nei Ja

Navn	Dosering	Varighet i timer
Medikament 1 .....	.....	..... timer
Medikament 2 .....	.....	..... timer
Medikament 3 .....	.....	..... timer

### TROMBOSEPROFYLAKSE

- Nei  Ja. Første dose  Preoperativt  Postoperativt
- Medikament 1 .....
- Dosering opr.dag .....
- Medikament 2 .....
- Dosering videre .....
- Varighet .....
- Medikament 3 .....
- Dosering .....
- Varighet .....

### FAST TROMBOSEPROFYLAKSE

- Nei  Ja, type: .....

### FIBRINOLYSEHEMMER

- Nei  Ja, medikament: .....
- Dosering: .....

### OPERASJONSTUE

- "Green house"
- Operasjonstue med laminær luftstrøm
- Vanlig operasjonstue

+

OPERASJONSTID (hud til hud) .....

### PEROPERATIV KOMPLIKASJON

- Nei
- Ja, hvilke(n) .....

### ASA KLASSE (se baksiden for definisjon)

- Frisk  Livstruende sykdom
- Asymptomatisk tilstand som gir økt risiko  Morbund
- Symptomatisk sykdom

Lege .....

Legen som har fylt ut skjemaet (navnet registreres ikke i databasen).

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## Papers I-IV

# Bacterial and Hematological Findings in Infected Total Hip Arthroplasties in Norway

## Assessment of 278 Revisions Due to Infection in the Norwegian Arthroplasty Register

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**Abstract:** Our aim was to assess the bacterial findings in infected total hip arthroplasties (THAs) in Norway. We also wanted to investigate the relationship between causal bacteria and hematological findings. Revisions reported to the Norwegian Arthroplasty Register (NAR) due to infection after total hip arthroplasty during the period 1993 through September 2007 were identified. One single observer visited ten representative hospitals where clinical history, preoperative blood samples and the bacterial findings of intraoperative samples were collected. Bacterial growth in two or more samples was found in 278 revisions, and thus included. The following bacteria were identified: Coagulase-negative staphylococci (CoNS) (41%), *Staphylococcus aureus* (*S. aureus*) (19%), streptococci (11%), polymicrobial infections (10%), enterococci (9%), Gram-negative bacteria (6%) and others (4%). CoNS were the most common bacteria throughout the period but in the acute postoperative infections (< 3 weeks) *S. aureus* was the most frequent bacterial finding. We found no change in the distribution of the bacterial groups over time. *S. aureus* appears correlated with a higher C-reactive protein value (CRP) (mean 140 (95% Confidence interval (CI): 101-180)) than CoNS (mean 42 (CI: 31-53)). *S. aureus* also correlated with a higher erythrocyte sedimentation rate value (ESR) (mean 67 (CI: 55-79)) than CoNS (mean 47 (CI: 39-54)).

**Keywords:** Bacteriology, CRP, hematological findings, intraoperative bacterial samples, prosthetic joint infection, revision due to infection, staphylococci, total hip arthroplasty.

## INTRODUCTION

Approximately 7,000 primary total hip arthroplasties (THA) are performed annually in Norwegian hospitals [1]. Infection after primary THA is a relatively rare event, and large numbers of patients are therefore needed to assess bacteriology and trends. In recent years there have been indications of an increasing risk for revision due to infection after THA [2-4], and the question has been raised as to whether this might be due to changes in bacteriology [5]. The bacteria most frequently causing prosthetic joint infections (PJI) are staphylococci (i.e. Coagulase negative staphylococci (CoNS) and *Staphylococcus aureus* (*S. aureus*)), and biofilm formation and emerging resistance towards antibiotics represent a challenge in PJI treatment [6-8]. However, many different bacterial species may cause PJIs and there has previously been no nationwide assessment of bacteria causing revisions of THAs in Norway.

Identification and diagnostics of PJI may be challenging, and in addition to bacterial samples, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are important hematological markers in diagnostics [9].

Our aim was to investigate the bacterial findings in infected THAs in Norway by using the nationwide Norwegian Arthroplasty Register (NAR) to identify cases of revision due to infection, and then collect additional information on bacterial and hematological findings. We also wanted to assess whether CRP and ESR correlated with bacterial findings, and whether there were any time trends regarding the bacterial findings.

## MATERIAL AND METHODS

The NAR has since its inception in 1987 registered data on both primary THAs and THA revisions in Norway [10], and the NAR data has been validated as being of good quality [11, 12]. The register form is filled in by the surgeon immediately after surgery, containing information on reason for surgery and different patient and surgery related variables. A unique identification number of the patient is

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used to link the primary THA surgery to later revisions. Since the form is filled in immediately after surgery in the case of a revision, the diagnosis of *e.g.* deep infection or aseptic loosening is based on clinical, biochemical and radiological findings pre- and intraoperatively. The cause of the revision is reported to the NAR before the results from the intraoperative bacterial samples are ready, and may not be corrected later.

From January 1993 through September 2007, 62 hospitals reported 1,089 revisions due to infection after THA to the NAR. These included revisions where parts of or the whole prosthesis was removed or replaced due to infection. Also cases of re-revision that showed different bacterial findings to the prior revision were included. We performed a pilot study at three large university hospitals, before extending the study to include the ten hospitals with the highest number of reported THA revisions due to infection during the period. The ten hospitals were geographically spread throughout the whole country and had similar rates of revision due to infection as the national average (0.6%) [5]. So of all THAs performed in Norway, approximately 0.6% are revised due to infection and reported to the NAR. The hospitals were visited by the first author and information on bacterial findings of intraoperative samples was collected from the patients' medical records. Results from preoperative blood samples were not collected in the three hospitals in the pilot study, but were added from the seven hospitals in the main study. Preoperative CRP and ESR within three days before the revision due to infection were assessed and compared to the bacteriological findings.

For the revision to be included there had to be growth of the same bacteria in two or more periprosthetic tissue samples collected intraoperatively, according to the definition of PJI [13]. Preoperative joint aspirations were not included. On average five samples were taken. None of the removed parts were sonicated, as this has not been procedure in Norway. Polymicrobial infection was defined as infection with more than one species (at least two of each) in intraoperative samples.

The study period was divided into three 5-year time periods to assess for time trends. Time from index THA to subsequent revision due to infection was divided into acute postoperative (less than 3 weeks), early (3 weeks to 3 months), delayed (3 months to 2 years) and late infections (more than 2 years).

The ten hospitals reported 454 identifiable revisions due to infection to the NAR. 138 of these had no growth in intraoperative tissue samples and 38 of the revisions had growth in only one periprosthetic tissue sample and were therefore excluded (Fig. 1). Hence, 278 THAs reported to the NAR for revision due to infection and verified by bacterial cultures were included. Time from index THA to revision was addressed in only 227 of the cases, mainly due to missing registration of the index THA in the NAR. CRP and SR were addressed in 166 of the cases.

The patient characteristics are presented in Table 1 and shows that 98.4% of the patients are reported to have received systemic, antibiotic prophylaxis. From 2003 the prophylaxis has consisted mainly of Cephalotin according to

national guidelines. This is supported by a study from the NAR also showing a reduction in the use of  $\beta$ -lactamase resistant penicillin as prophylaxis after 1996 [14].

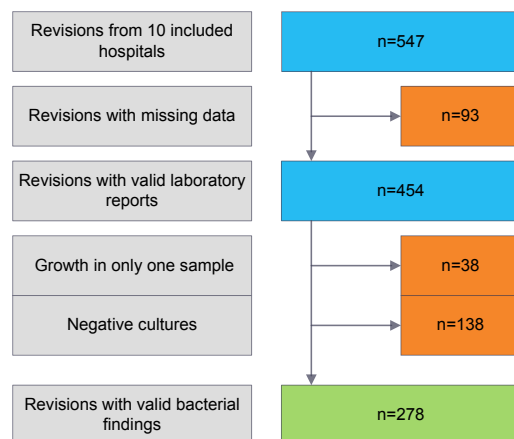


Fig. (1). Flow chart showing the patient selection.

Pearson's chi-squared test and linear-by-linear association were used to compare time periods and groups of bacteria. P-values less than 0.05 were considered significant. Statistical analyses were performed using SPSS version 22 (SPSS Inc., 2004). The study was approved by the Regional Committee for Medical Research Ethics (number 2009/856b).

Table 1. Patient characteristics.

<b>Sex</b>	
Male	32.4%
Female	67.6%
<b>Age</b>	
Mean	69.4
SD	10.9
<b>Diagnosis</b>	
Osteoarthritis	67.3%
Inflammatory	4.0%
Other	28.7%
<b>Antibiotic Prophylaxis Systemically</b>	
Yes	98.4%
No	1.6%
<b>Method of Fixation</b>	
Uncemented	11.1%
<b>Cement</b>	
With antibiotics	72.2%
Without antibiotics	16.7%

## RESULTS

### Bacteriology of THA Infection

The distribution of microbes is presented in Table 2. Staphylococci (60%) were the most common, followed by streptococci (11%) and enterococci (9%). 10% of the infections were polymicrobial. Table 3 presents the different CoNS species with *S. epidermidis* being the most common. Among the polymicrobial infections, staphylococci were involved in all except four. The combination of CoNS and corynebacteria was most common. Table 4 shows the combinations of bacteria for polymicrobial THA infections.

**Table 2. Bacterial findings throughout the 15-year period (n=278).**

	Frequency	Percent
<i>S. aureus</i>	53	19%
CoNS	113	41%
Streptococci	30	11%
Gram-negative	17	6%
Others	12	4%
Enterococci	26	9%
Polymicrobial	27	10%

**Table 3. CoNS subspecies in the bacterial findings (n=113).**

	Frequency
<i>S. epidermidis</i>	43
<i>S. capitis</i>	3
<i>S. lugdunensis</i>	3
<i>S. warneri</i>	1
<i>S. simulans</i>	1
Unspecified CoNS	46
<i>S. epidermidis</i> and unspecified CoNS	12
<i>S. epidermidis</i> , <i>S. xylos</i> and <i>S. lentus</i>	1
<i>S. epidermidis</i> and <i>S. hominis</i>	1
<i>S. haemolyticus</i> and <i>S. capitis</i>	1

### Bacterial Findings and Time After Index THA

Bacterial findings relative to time after index THA are presented in Fig. (2). The first 3 weeks all infections were either with Staphylococci or polymicrobial, and *S. aureus* was the most frequent bacteria. Later on the bacterial findings were more diverse.

### Bacterial Findings, CRP and ESR

*S. aureus* infections were associated with higher CRP (mean 140 (95% Confidence interval (CI): 101-180)) than infections caused by CoNS (mean 42 (CI: 31-53)) (Fig. 3a).

This was also found for ESR when *S. aureus* infections (mean 67 (CI: 55-79)) were compared to CoNS infections (mean 47 (CI: 39-54)) (Fig. 3b). *S. aureus* infections were also associated with higher CRP than infections caused by enterococci (mean 43 (CI: 19-68)).

**Table 4. Bacterial findings in cases with mixed bacteriology (n=27).**

	Frequency
CoNS and corynebacteria	6
CoNS and <i>S. aureus</i>	4
CoNS and Gram-negative	4
Enterococci and Gram-negative	4
<i>S. aureus</i> and streptococci	2
<i>S. aureus</i> and enterococci	2
CoNS and enterococci	1
CoNS, <i>S. aureus</i> and enterococci	1
CoNS, <i>S. aureus</i> and streptococci	1
Enterococci and peptostreptococci	1
CoNS, Gram-negative, enterococci and streptococci	1

### Time Trend of Bacterial Findings

The incidence of the different bacteria was mostly unchanged throughout the study period, but there was a trend towards more polymicrobial infection ( $p=0.1$ ).

## DISCUSSION

CoNS were the most common bacteria causing revision due to deep infection after THA. Since CoNS are regarded as commensal bacteria, this may support the idea that direct contamination is the most common mechanism of THA infection [15-17]. Our bacterial findings were similar to those in other publications [18-28], although the share of *S. aureus* was somewhat lower than in some of the publications.

*S. aureus* was the most frequent bacterium in acute postoperative infections, whereas CoNS were the most common cause of revision due to infection in early, delayed and late infections. As late infection is most prevalent in our study, it may be that suppressed and biofilm embedded CoNS infection can emerge even after 2 years postoperatively, or that CoNS are spread through hematogenous seeding.

*S. aureus* infections had higher CRP and ESR values than CoNS infections. Given high resistance to methicillin and aminoglycosides amongst CoNS [29], in empirical treatment of infected THA with low CRP (<50) in Norway, Vancomycin should be considered until results of intraoperative cultures are known.

The incidence of the different bacteria was mostly unchanged throughout the study period. There was a trend towards more polymicrobial infection and the combination

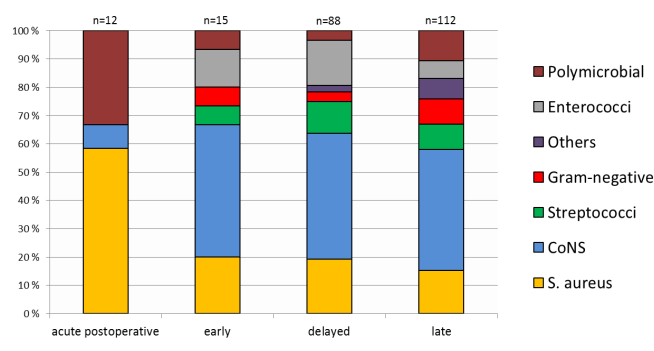


Fig. (2). Bacterial findings relative to time after index THA surgery (n=227).

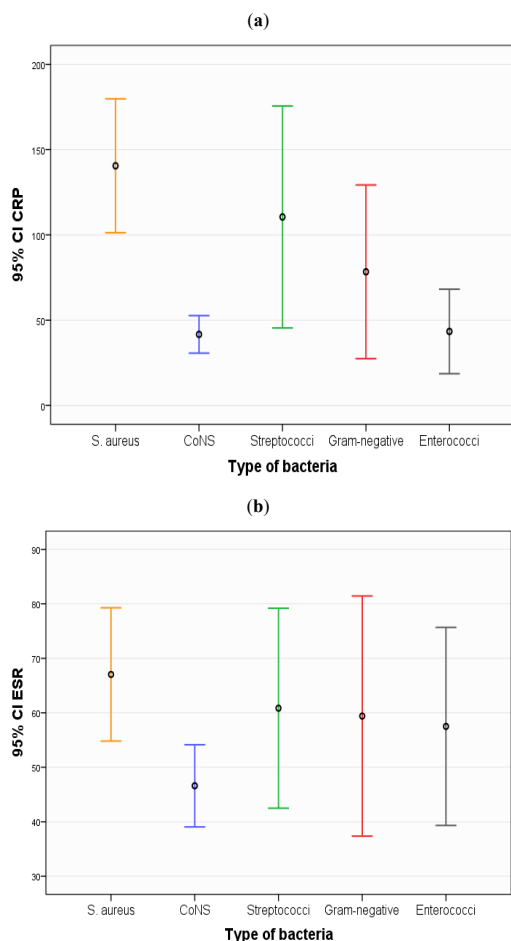


Fig. (3). (a, b) Mean values of ESR and CRP level with 95% confidence intervals (CI) for different species of bacteria cultured after revision surgery.

of CoNS and corynebacteria was most common. This may be explained by better sample handling, better culturing methods and increased attention to pathogens formerly considered as contamination by commensal bacteria, not able to cause infection (e.g. corynebacteria).

The retrospective nature of this study represents one of the major limitations of this paper. Another weakness of our study is that only revisions with removal or change of the whole or parts of the prosthesis are reported to the NAR. Accordingly, soft tissue debridement of infected THAs without exchange of prosthesis parts is not reported to the register. Consequently not all surgical site infections after THA are reported. This may have affected the distribution of the bacterial findings since surgical site infection is an early postoperative event [30], and it may have led to an underestimation of e.g. *S. aureus* in our study. Further, low grade infections with low or normal CRP or ESR may be evaluated by the reporting surgeon as an aseptic loosening and hence erroneously reported to the NAR as such. These low grade infections, not identified in preoperative diagnostics, will not be included in our study, and the prevalence of low-virulent bacteria such as CoNS may be underestimated.

**CONCLUSION**

In this nationwide study, based on 278 revisions of infected THA, staphylococci were the most common bacteria in THA revision for infection in Norway. *S. aureus* was more common in acute postoperative infections and CoNS were more common in early, delayed and late infections. CRP and ESR may be of help in differentiating between infections caused by CoNS and *S. aureus*.

**CONFLICT OF INTEREST**

The first author received a scholarship from OrtoMedic for his work on this study. We report no conflict of interest.

**ACKNOWLEDGEMENTS**

HL collected the data. HL, OL and BE performed the analyses. HL wrote the manuscript. All authors contributed in interpretation of the analyses and critical revision of the

manuscript. We would like to thank the NAR contacts at all ten hospitals for contributing to data collection. We also wish to thank Norwegian surgeons for persistently and thoroughly reporting primary THAs and revisions to the NAR.

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## Research Article

# Increasing Resistance of Coagulase-Negative Staphylococci in Total Hip Arthroplasty Infections: 278 THA-Revisions due to Infection Reported to the Norwegian Arthroplasty Register from 1993 to 2007

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We investigated bacterial findings from intraoperative tissue samples taken during revision due to infection after total hip arthroplasty (THA). The aim was to investigate whether the susceptibility patterns changed during the period from 1993 through 2007. Reported revisions due to infection in the Norwegian Arthroplasty Register (NAR) were identified, and 10 representative hospitals in Norway were visited. All relevant information on patients reported to the NAR for a revision due to infection, including bacteriological findings, was collected from the medical records. A total of 278 revision surgeries with bacterial growth in more than 2 samples were identified and included. Differences between three 5-year time periods were tested by the chi-square test for linear trend. The most frequent isolates were coagulase-negative staphylococci (CoNS) (41%, 113/278) and *Staphylococcus aureus* (19%, 53/278). The proportion of CoNS resistant to the methicillin-group increased from 57% (16/28) in the first period, 1993–1997, to 84% (52/62) in the last period, 2003–2007 ( $P = 0.003$ ). There was also significant increase in resistance for CoNS to cotrimoxazole, quinolones, clindamycin, and macrolides. All *S. aureus* isolates were sensitive to both the methicillin-group and the aminoglycosides. For the other bacteria identified no changes in susceptibility patterns were found.

## 1. Introduction

The development of bacterial resistance has been an emerging problem since the introduction of the first antibiotics [1]. Studies of prosthetic joint infections (PJIs) have shown a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), extended-spectrum beta-lactamase-resistant Gram-negative bacteria (ESBL), and other highly resistant bacteria in PJI [2, 3].

Norway has a lower incidence of highly resistant bacteria compared to most European countries, but in selected populations, such as intensive care unit patients with infected

foreign bodies (e.g., central venous catheters), an increasing proportion of infections are caused by MRSE [4, 5]. PJIs, such as an infected total hip arthroplasty (THA), impose a burden to the affected patients and are difficult to treat. An increased risk of revision due to deep infection after THA has been found in Norway as in the other Nordic countries [6, 7]. It has been suggested that increased bacterial resistance may have contributed to the increased risk of revision due to infection [8].

The aim in the present study was to investigate whether the susceptibility patterns had changed during the observation period from 1993 through 2007 for the bacteria causing deep infection after THA in Norway.

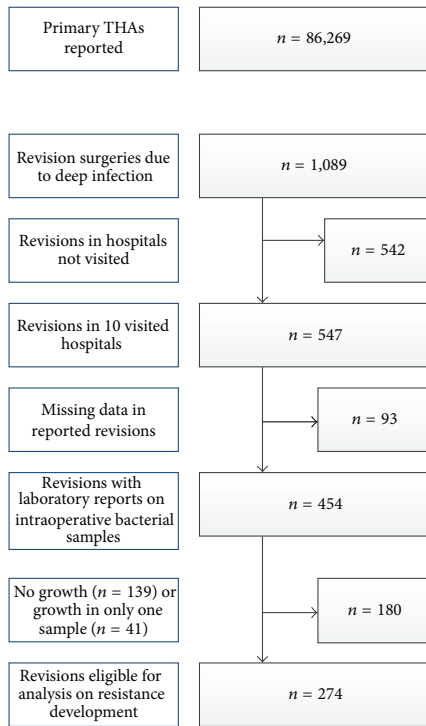


FIGURE 1: Flowchart showing the selection of patients.

## 2. Material and Methods

Since its inception in 1987, The Norwegian Arthroplasty Register (NAR) has collected individual information on primary and revision THA [9]. Based on preoperative clinical examinations, laboratory tests, and intraoperative findings, the reason for revision is reported immediately after surgery by the surgeon to the NAR. The patients in this study were reported as revisions for infections. Bacterial findings were not reported to the NAR.

Patients from the period January 1, 1993, to September 30, 2007, were included. The study period was divided into three 5-year periods, which were compared to evaluate possible changes of resistance during the study period.

Based on registrations in the NAR, the ten hospitals with most THA-revisions due to infection, spread all over Norway, were visited by a single observer. This reflects large volumes of surgery, not higher rates of infection. Revision was defined as exchange or removal of parts or the whole prosthesis.

For capacity reasons, we had to limit the number of visited hospitals to ten. These hospitals reported half of the revisions for infected THAs in the study period. Bacterial findings and susceptibility charts from the medical records were collected (Figure 1). To be included, the clinical diagnosis of infection had to be verified by two or more intraoperative tissue

TABLE 1: Patient characteristics.

Variable	
Sex (%)	
Male	32,4
Female	67,6
Age (mean) (SD)	69,4 (10,9)
Diagnosis (%)	
Osteoarthritis	67,3
Inflammatory	4,0
Other	28,7
Antibiotic prophylaxis systemically (%)	
Yes	98,4
No	1,6
Method of fixation (%)	
Uncemented	11,1
Cement	
With antibiotics	72,2
Without antibiotics	16,7

samples with valid growth of the same bacteria. Identification of the bacteria also had to include susceptibility panels. The tissue samples were handled fresh; mostly five samples were taken. There was no sonicated prosthesis included, as this method was, and still is not, in routine use in Norway. Thus, revisions reported as infections, but with no growth in intraoperative tissue samples, were not included ( $n = 139$ ). These were mostly cases in which the patients had received antibiotics prior to surgery.

278 patients met the inclusion criteria. Patient characteristics are described in Table 1.

In addition, a written survey from all Norwegian microbiology laboratories was performed, asking about their culture techniques and growth media, incubation time, susceptibility panels, and breakpoints. In 2007, all the microbiology laboratories followed the recommendations for susceptibility patterns and breakpoints determining S, I, and R (SIR = Sensitive, Intermediate, Resistant) for the different bacteria, as recommended by the AFA (the Norwegian workgroup for questions regarding antibiotics). However, during the study period, the laboratories changed the susceptibility panels from 1, 2, 3, and 4 to SIR. We transformed 1 as S, 2 and 3 as I, and 4 as R. SIR was dichotomized into either S or R, regarding I as R to separate the sensitive bacteria from the rest.

The laboratories had, to some extent, used different methods, susceptibility panels, and incubation times over the 15 years studied. The mean incubation period was 7 days in 2007.

In general, few of the cultures were tested against linezolid, carbapenems, and rifampicin because those antibiotics were not part of the standard susceptibility panels used in Norway during the study period. In addition, few staphylococci were tested against the quinolones because the Norwegian regulatory authorities do not want the quinolones available in Norway (ciprofloxacin and ofloxacin) to be used routinely in the treatment of Gram-positive infections, in order to avoid the development of resistance.

We chose to combine methicillin, oxacillin, and cloxacillin in one group called the methicillin group. The laboratories used one of the above as a marker for resistance towards cloxacillin, dicloxacillin, and all cephalosporins. Furthermore, we combined the aminoglycosides gentamicin, tobramycin, and netilmicin into one aminoglycoside group. Ciprofloxacin and ofloxacin were combined in the quinolone group. Imipenem and meropenem were combined in the carbapenem group. Ceftazidime, ceftriaxone, and cefotaxime were combined in the third generation cephalosporin group.

The study was approved by the Regional Committee for Medical Research Ethics (number 2009/856b).

The chi-square test for linear trend was used to evaluate changes over time in the distribution of resistance.  $P$  values less than 0.05 were considered significant. Statistical analyses were performed using SPSS version 20 (SPSS Inc., 2004).

### 3. Results

The distribution of bacteria isolates is presented in Table 2. Coagulase-negative staphylococci (CoNS) were the dominating bacteria (41%), followed by *S. aureus* (19%). The results for antibiotic susceptibility are summarized in Table 3.

**3.1. Coagulase-Negative Staphylococci.** We found a high proportion of resistant strains among CoNS. Resistance increased with time. All CoNS cultures retained full susceptibility only to linezolid (only tested the last years) and vancomycin.

Resistance significantly increased over time to the methicillin group ( $P = 0.003$ ), clindamycin ( $P = 0.048$ ), trimethoprim/sulfamethoxazole (cotrimoxazole) ( $P = 0.03$ ), quinolones ( $P = 0.03$ ), and macrolides ( $P = 0.03$ ). A trend of increased resistance was seen for aminoglycosides ( $P = 0.15$ ) (Figure 2). Only a few rifampicin-resistant strains were identified, and only during the last 5-year period.

**3.2. Staphylococcus aureus.** All *S. aureus* cultures were susceptible to aminoglycosides, the methicillin group, rifampicin, vancomycin, linezolid, and cotrimoxazole. A few strains were found to be resistant to fusidic acid, clindamycin, quinolones, and macrolides.

**3.3. Streptococci.** All streptococci were susceptible to penicillin. A few strains were found to be resistant to clindamycin and macrolides.

**3.4. Enterococci.** All enterococci were susceptible to linezolid and vancomycin, and only one was resistant to ampicillin. However, a large proportion of the enterococci were resistant to aminoglycosides throughout the study period. We did not have information on whether some of the enterococci were highly resistant, so-called high-level gentamicin-resistant enterococci (HLGRE).

**3.5. Gram-Negative Bacteria.** The Gram-negative bacteria were all but one susceptible to aminoglycosides. A few strains were resistant to quinolones; a large proportion of the strains were resistant to ampicillin.

TABLE 2: Type of bacteria.

	Frequency	Percent
Coagulase-negative staphylococci	113	41
<i>Staphylococcus aureus</i>	53	19
Streptococci	30	11
Enterococci	26	9
Gram-negative bacteria	17	6
Polymicrobial	27	10
Other microbes	12	4
Total	278	100

### 4. Discussion

We found a high proportion of resistant strains among CoNS, and we found that resistance increased with time.

For many years, CoNS were considered incapable of causing serious clinical infection and discarded as contamination when found in periprosthetic tissue cultures. However, CoNS are now considered a major cause of PJI [8, 10]. We found that CoNS was the most frequent bacteria causing infected THA in Norway.

The CoNS are skin commensals. When found in patients outside hospital settings, these bacteria exhibit less antimicrobial resistance than bacteria isolated from hospitalized patients and hospital personnel. Rapid transformation from susceptible to resistant strains has been shown soon after patients have been hospitalized [11–13]. Pre- and postoperative hospitalization for primary THA may have influenced the finding of a high proportion of multidrug resistant CoNS, as could the extensive use of cement containing antibiotics.

We do not know if the increased proportion of resistant CoNS is due to a general transformation of the bacterial flora, or if it only reflects a selection of bacteria causing THA infection. Epidemiologic surveys of CoNS susceptibility are absent in Norway.

The emergence of drug resistance in CoNS has been shown to reflect the consumption of antibiotics [14, 15]. We do not have data on the use of antibiotics for each individual patient, except for prophylaxis in primary THA as reported to the NAR. The Norwegian Institute of Public Health has found an increase in the use of both cephalosporins and quinolones in Norway during our study period [16]. This may also have contributed to the increased resistance of CoNS found in infected THA.

Other studies of PJI in hip- and knee arthroplasty have found the proportion of MRSE among bacterial infections to be 62–72% [2, 3, 17, 18]. Our findings of 70% MRSE are similar to these findings.

Dale et al. found a 3-fold increased risk of revision due to THA infection during the time period 2003–2007 compared to the time period 1987–1992 [6]. In an editorial comment to Dale's paper, Walenkamp raised the question of whether increased bacterial resistance could be part of the explanation [8]. Our findings support Walenkamp's opinion that increased prevalence of MRSE could be a part of the explanation.

TABLE 3: Susceptibility to selected antibiotics, given as number of tested isolates susceptible to the given antibiotic/total number tested.

Time period (years)	CoNS		<i>S. aureus</i>		Enterococci		Gram-negative		Streptococci			
	93-97	98-02	03-07	93-97	98-02	03-07	93-97	98-02	03-07	93-97	98-02	03-07
Aminoglycosides	10/19	13/26	14/45	5/5	8/8	22/22	0/8	0/2	3/10	4/4	7/8	11/11
Methicillin group	12/28	15/33	10/62	10/10	15/15	37/37						
Cephalosporins, 3rd generation												
Clindamycin	23/29	17/31	34/64	11/11	13/13	35/36				2/3	6/6	6/7
Quinolones	6/6	8/17	8/20	2/2	0/4	3/4				2/3	4/7	8/10
Carbapenems										3/3	4/5	8/8
Linezolid		3/3	38/38			11/11	1/1		10/10			
Rifampicin	4/4	3/3	22/26	1/1		6/6						
Fusidic acid	12/29	14/31	33/63	11/11	13/14	33/35						
Macrolides	16/20	9/22	29/57	7/7	11/12	32/33						
Cotrimoxazole	10/16	10/18	12/41	4/4	7/7	24/24				3/3	5/7	9/9
Ampicillin							9/9	3/4	20/20	1/4	4/9	1/10
Penicillin												
Vancomycin	26/26	23/23	51/51		8/8	7/7	10/10	6/6	3/3	15/15		

CoNS = coagulase-negative staphylococci.

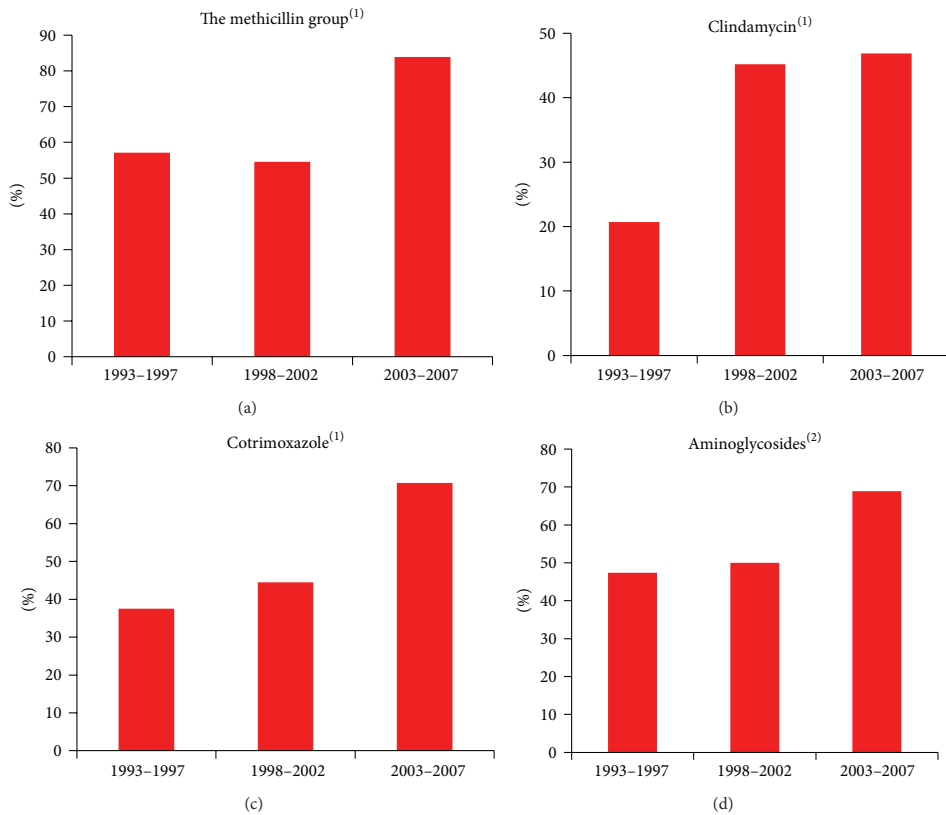


FIGURE 2: Development of resistance in coagulase-negative staphylococci towards selected antibiotics. Percent resistance is present on the y-axis, time period on the x-axis. (1) Significant increase in resistance for methicillin, clindamycin, and cotrimoxazole ( $P < 0.05$ ). (2) Not significant increase in resistance for aminoglycosides ( $P = 0.15$ ).

We found a high proportion of CoNS and enterococci resistant to the aminoglycosides. A trend towards increasing aminoglycoside resistance was found with CoNS, whereas the resistance was more or less unchanged for the other bacteria. Interestingly, Fulkerson found a higher rate of susceptible CoNS for aminoglycosides in a cohort from New York and Chicago (87%) compared to our Norwegian patients (51%) [19]. The explanation for this difference could be that in Norway gentamicin-loaded bone cement was used in most primary THAs. In contrast, in the United States cementless implants are predominant, and when bone cement is used in primary surgery, it mostly does not contain antibiotics [20].

We found no methicillin-resistant *S. aureus* (MRSA). In Norway, there is a very low incidence of MRSA compared to most other countries [4]. In an English study, an MRSA prevalence of 8% was found. In a study from Australia, a prevalence of 11% MRSA was found (6/53) [2, 3]. In a Swedish study of infected knee implants only 1/84 of the causal bacteria were MRSA, reflecting the low incidence of MRSA also in another Scandinavian country [17]. The favorable

resistance patterns of *S. aureus* are also reflected by the lack of resistance to aminoglycosides, linezolid, rifampicin, cotrimoxazole, and quinolones, and only sporadic cases of resistance to macrolides, clindamycin, and fusidic acid.

The incidence of methicillin resistance is higher for CoNS than *S. aureus*. In Norway, strict measures have been taken to prevent the spread of MRSA, similar to the Netherlands, and these programs have been successful thus far [21]. Preventing the spread of MRSE has proven more difficult [22].

**Limitations.** The present study has some limitations. It is a retrospective study based on data from a national registry.

However, our data on revisions due to infection after THA were prospective, and the NAR has been found to have good completeness [23, 24]. Since we used the NAR to identify cases of infection for the purpose of collecting bacteriological data, and the hospitals were different in types and spread all over the country, we expect the selection bias to be minor. Hence, we assume that our findings are representative for the

susceptibility patterns with bacteria causing infected THAs in Norway over the study period.

The diagnosis of infection was based on perioperative assessment by the orthopaedic surgeon, before culturing results of intraoperative tissue samples were available. Since only cases with growth of the same bacteria in two or more tissue samples were included, all revisions included in the present study should be true PJIs. However, these strict criteria led to a high amount of reported revisions disqualified due to no growth or only one positive sample. We did not include preoperative joint fluid collection, as we first and foremost wanted our included revisions to be true PJIs, and we wanted full susceptibility charts. Also, PJIs treated with debridement without change of liner or head, or antibiotic suppression therapy alone, were not reported to the NAR and thus not included in the present study.

**Clinical Implications.** In Norway, the common practice is to use cephalothin as systemic prophylaxis during surgery and gentamicin in bone cement as local prophylaxis for cemented THAs [25]. The most common empirical antibiotic therapy for suspected PJI has been a combination of cloxacillin and gentamicin. With 84% methicillin resistance and 67% aminoglycoside resistance for CoNS during the last time period, treatment failure could be the result of inadequate antibiotic coverage. Thus, preoperative sampling, such as aspiration or biopsy, is crucially important, especially in low-grade infections. Under these circumstances, the patients are normally nonseptic, and there is time to await the culture results before surgical and medical treatment of the infection. The second most common pathogen, *S. aureus*, is fully susceptible to both the prophylactic regimen and the empirical treatment.

The antibiotic treatment must be adjusted to the bacteriological findings. When MRSE is proven or likely the cause of infection, vancomycin should be added to bone cement or spacers if used in revision surgery and should also be part of the systemic treatment [26]. The newly published national guidelines for use of antibiotics in hospitals from The Norwegian Directorate of Health have now advocated the use of vancomycin as empirical treatment for PJI, partly based on data from our study [27].

## 5. Conclusion

We identified an increase in the proportion of PJI-causing methicillin-resistant CoNS over the study period. Adequate bacterial sampling is crucial for choosing the right antibiotic treatment. This is increasingly important given the emerging resistance of CoNS found in PJI in the present study.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Authors' Contribution

Olav Lutro and Birgitte Espehaug performed the analyses. Olav Lutro wrote the paper. Håkon Langvatn collected the data from the hospitals. All authors contributed in interpretation of the analyses and critical revision of the paper.

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# Operating room ventilation—Validation of reported data on 108 067 primary total hip arthroplasties in the Norwegian Arthroplasty Register

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## Abstract

**Rationale, aims, and objectives:** The true effect of laminar airflow (LAF) systems on postoperative infection is disputed, partly due to uncertainty regarding the validity of ventilation data in register studies. The aim of this study was to validate the information on operating room (OR) ventilation reported by the orthopaedic surgeons to the Norwegian Arthroplasty Register (NAR) after primary total hip arthroplasty (THA).

**Method:** Forty of the 62 public orthopaedic units performing primary THA in Norway during the period 1987-2015 were included. The hospitals' current and previous ventilation systems were evaluated in cooperation with the hospitals head engineer. We identified the type of ventilation system reported to the NAR and compared the information with the factual ventilation in the specific ORs at the time of primary THA.

**Results:** A total of 108 067 primary THAs were eligible for assessment. None of the hospitals performed THA in true "greenhouse" (GH) ventilation. Fifty-seven percent of the primary THAs were performed in ORs with LAF and 43% in ORs with conventional, turbulent ventilation (CV). Comparing the reported data with the validated data, LAF was reported with a sensitivity of 86%, specificity of 89%, and positive predictive value (PPV) of 92%, with an accuracy of 88%. CV was reported with a sensitivity of 89%, specificity of 87%, and PPV of 84%, with an accuracy of 88%. The total, mean misreporting rate was 12%.

**Conclusions:** Surgeons were not fully aware of what kind of ventilation system they operated in. This study indicates that conclusions based on ventilation data reported on THA in the NAR should not be interpreted without considering the inaccuracy of the data.

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**KEYWORDS**

conventional ventilation, laminar airflow, misreporting, operating room ventilation, The Norwegian Arthroplasty Register, total hip arthroplasty

**1 | INTRODUCTION**

Laminar airflow (LAF) systems have been used in operating rooms (ORs) for ultraclean surgery since the late 1950s. The intention is to reduce the incidence of postoperative infection by reducing the colony forming unit (CFU) density in the air of the OR.<sup>1,2</sup> The systems work by sending linear and parallel streams of clean air with constant velocity, directly on to the surgical field in order to, in theory, displace and reduce the flow of less clean air to the surgical field. In contrast, the conventional ventilation (CV) systems mostly use the dilution principle and work by creating an overpressure using turbulent air.<sup>3</sup> The LAF systems are, however, rarely able to create true LAF<sup>3</sup> and are therefore more recently designated as unidirectional airflow (UDAF or UDF) systems; but for simplicity, we will use the designation LAF in the present paper.

The existing recommendations of LAF as a prophylactic measure of postoperative infection, rest mainly on a randomized trial from a time when standards on antibiotic prophylaxis were not fully established, and was therefore not thoroughly adjusted for. The findings therefore may not apply for the current situation.<sup>4</sup> Subsequent observational studies from the same decade that adjusted for antibiotic prophylaxis demonstrated no influence of OR ventilation on the rate of postoperative infection.<sup>5,6</sup> Newer, registry-based studies have suggested that LAF actually increases the risk of postoperative infection.<sup>7-9</sup> A recent systematic review and meta-analysis in the Lancet, based partly on the above mentioned registry studies, concluded that LAF systems should not be installed in new ORs.<sup>10</sup> The conclusion is controversial and may be premature.<sup>11,12</sup> The Lancet review also includes a study from the Norwegian Arthroplasty Register (NAR), not studying the effect of LAF specifically, and which may be confounded by misreporting.<sup>13</sup>

Before concluding rigorously in systematic reviews and meta-analyses, it is of fundamental importance that ventilation data are valid and of good quality. The aim of the present study was to validate the data on OR ventilation reported on primary total hip arthroplasty (THA) cases to the NAR.

**2 | MATERIAL AND METHODS**

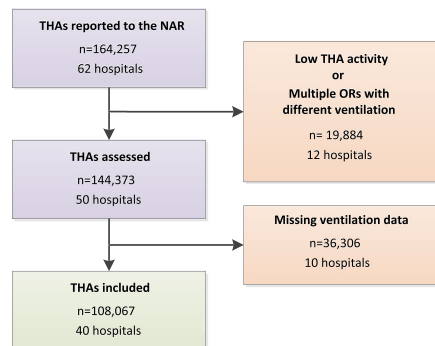
The NAR has registered individual data on primary THAs and THA revisions since 1987. The surgeon fills in a form immediately after surgery. The form contains information on patient identity, date of operation, the type of OR ventilation in addition to several other patient, and surgery-related factors. For each hospital, we used the NAR to identify the type of OR ventilation reported for the primary THA, ie,

CV, LAF, or greenhouse (GH) ventilation (register form, Appendix A). The period of inclusion was 1 September 1987 to 31 December 2015.

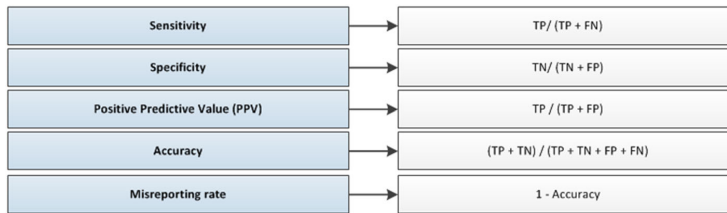
In order to validate the information on OR ventilation reported by the surgeon, the hospitals' current and previous ventilation systems were evaluated in direct contact and cooperation with the hospitals NAR contact-surgeon and the hospitals head engineer. Six hospitals in a pilot study were visited in order to gain knowledge on the different systems and method of data collection. The factual ventilation systems in the ORs were assessed using a detailed questionnaire regarding the configuration and specifications of the ventilation systems (Appendix B). The questionnaire was used as guidance in the correspondence with the engineers. Objective, technical specifications from manuals were retrieved in cases of doubt. To be classified as a LAF system, the ventilation set-up had to be confirmed to have been installed with a unidirectional diffuser array. These criteria are not sufficient to verify true LAF conditions, but in this paper, the main issue was whether the system was installed with a unidirectional diffuser array or not, in order to do a direct comparison with the reported data.

To assess the correspondence between the reported and validated ventilation data, we did a case-to-case comparison of the OR in which each reported, primary THA was performed. The accuracy of reporting, based on sensitivity and specificity for each ventilation group, was then calculated.

If the ventilation system had been out of function, exchanged, or updated, primary THAs reported from that year were excluded. Sixty-two public hospitals reported to the register in the period. Twelve hospitals were excluded due to low numbers of primary THAs or concurrent use of ORs with different ventilation systems. Fifty hospitals were selected for inclusion. Five hospitals were excluded due to missing contact with key personnel and five due to incomplete ventilation data (Figure 1). Forty hospitals had precise information on the



**FIGURE 1** Flow chart showing hospital and total hip arthroplasty (THA) selection



**FIGURE 2** Formulas for calculating measures. FP, false positive; FN, false negative; TN, true negative; TP, true positive

	Actual LAF	Actual CV	
Reported LAF	TP=53,253	FP=4909	PPV = 91.6%
Reported as CV or GH	FN=8402	TN=41,503	NPV = 83.2%
Sensitivity = 86.4%		Specificity = 89.4%	Accuracy = 87.7%

	Actual CV	Actual LAF	
Reported CV	TP=41,299	FP=8184	PPV = 83.5%
Reported as LAF or GH	FN=5113	TN=53,471	NPV = 91.3%
Sensitivity = 89.0%		Specificity = 86.7%	Accuracy = 87.7%

**FIGURE 3** Comparison between surgeon-reported ventilation data and validated ventilation data. CV, conventional ventilation; FN, false negative; FP, false positive; GH, greenhouse ventilation; LAF, laminar airflow; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive

OR ventilation, and these 40 hospitals reported 108 067 primary THAs available for validation.

## 2.1 | Statistics

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy of reported data, and misreporting rate were calculated as presented in Figure 2. Statistical analyses were performed using SPSS version 24 (SPSS Inc, 2004).

## 2.2 | Ethics

The registration of data and the study was performed confidentially on patient consent and according to Norwegian and EU data protection rules.

## 3 | RESULTS

A total of 108 067 primary THAs were included in the further analysis. These THAs constituted 66% of the THAs reported to the NAR during the study period; 57% of the surgeries were performed in a room with verified LAF, and 43% were performed in rooms with roof-mounted, verified CV. None of the THAs were performed in true GH conditions.

Figure 3 gives a summarized comparison between the reported OR-ventilation and the factual OR ventilation. LAF was reported with a sensitivity of 86%, specificity of 89%, and Positive Predictive Value (PPV) 92%. This gave an accuracy of 88%. CV was reported with a sensitivity of 89%, specificity of 87% and PPV of 84%, with an accuracy of 88%. This gave a total misreporting rate of 12% for both LAF and CV.

## 4 | DISCUSSION

We found 12% misreporting of the OR ventilation used during primary THA reported to the NAR.

Other registries have studied the preventive effect of LAF systems. All of these studies are included in the latest meta-analysis published in *The Lancet*.<sup>10</sup> Two studies based on data from The German KISS (Krankenhaus [hospital] Infections Surveillance System) registry showed an increased risk of severe surgical site infection (SSI) after THA operated in LAF conditions compared with CV.<sup>7,9</sup> They gathered information on the different ventilation systems by using a questionnaire, where data were provided by the surgical departments. To which degree these data were validated or from whom the data were reported remains unclear. The New Zealand Joint Registry reported an increased risk of revision due to deep infection after THA performed in an LAF theatre.<sup>8</sup> They validated the reported information by asking the hospitals to confirm what kind of ventilation system they used. It was not stated what kind of personnel answered these questions. Also included in the latest meta-analysis was a study from the NAR,<sup>13</sup> using invalidated, surgeon reported data on ventilation. In that NAR study, OR ventilation was used only as an adjustment variable in the study of time trends for revision due to infection. The relative risk of revision due to infection was found to be 1.3 (95% CI, 1.1-1.5) for LAF compared with CV. The above mentioned studies contribute to the basis for the new WHO-guidelines,<sup>14</sup> which recommend not to use LAF for arthroplasty. Taking the results of our study into consideration, this recommendation may be considered controversial, as the evidence is of uncertain validity and quality.

#### 4.1 | Strengths

The validated ventilation data, presented in the present study, is based on a large, national registry, with 100% coverage and 97% completeness in the reporting of primary THA.<sup>15-17</sup> It offers an opportunity to validate a majority of a national cohort from a long period of time.

The validated data were based on the information retrieved from the engineers responsible for the hospitals ventilation systems, and this information was verified by the NAR contact surgeon. In addition, in order to overcome possible reporting bias, we retrieved objective, technical data from manuals and specifications on the hospitals ventilation in cases of doubt. Only indubitable information was included, and hospitals with uncertain information were excluded.

#### 4.2 | Potential weaknesses

Only 40 hospitals, representing 66% of the primary THAs reported to the NAR, were eligible for validation of OR ventilation. Like the 40 included hospitals, the 22 excluded hospitals had THA activity throughout the majority of the time period and a similar distribution between local hospitals, regional hospitals, and elective centres. The excluded hospitals also had similar completeness of reporting of primary THA and OR ventilation.<sup>16,17</sup> Hence, we believe that the selection bias was minimal.

## 5 | CONCLUSION

Surgeons were not fully aware of what kind of ventilation system they operated in when performing primary THA. This resulted in a 12% misreporting rate for both CV and LAF systems. This indicates that conclusions based on ventilation data in the NAR should not be interpreted without considering the inaccuracy of the data as the subsequent evaluations of the prophylactic effect of ventilation systems against postoperative infection may turn out inaccurate.

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All authors have approved the final article. H.L., E.L., and H.D. conceived and planned the study. H.L. collected the data. H.L. and C.B.J. performed the analyses. H.L. wrote the manuscript. All authors contributed in interpretation of the analyses and critical revision of the manuscript.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## APPENDIX A



**Nasjonalt Register for Leddproteser**  
Ortopedisk klinikk, Helse Bergen HF  
Haukeland universitetssjukehus, Postboks 1400  
Møllendalsbakken 11, 5021 BERGEN  
Tlf 55973742/55973743

F.nr. (11 sifre).....  
Navn:.....  
(Skriv tydelig ev. pasientkistrelapp – spesifiser sykehus.)  
Sykehus:.....

**HOFTEPROTESER**

Alle totale hofteproteseoperasjoner og hemiproteser på annen indikasjon enn fraktur/fraktursekvele registreres her (hemiprotese for fraktur/fraktursekvele registreres på Hoftebruddskjema). Alle reoperasjoner skal registreres: skifte/fjerning av proteseleder, kantplastikk, blodtdelsdebridement, og operasjoner for protesenær fraktur eller gluteal svikt.

**TIDLIGERE OPERASJON I AKTUELLE HOFTE** (ev. flere kryss)

- Nei  
 Osteosyntese for fraktur i prox. femurende  
 Hemiprotese pga. fraktur  
 Osteotomi  
 Arthrode  
 Totalprotese(r)  
 Annen operasjon .....

+

**AKTUELLE OPERASJON** (ett kryss)

- Primæroperasjon (også hvis hemiprotese tidligere)  
 Reoperasjon (totalprotese tidligere)  
 Primær hemiprotese for annen indikasjon enn fraktur/fraktursekvele

**OPERASJONSDATO** (dd.mm.åå)    | | | | | | | |

**AKTUELLE SIDE** (ett kryss) (Bilateral opr. = 2 skjema)

- Høyre  Venstre

**ÅRSÅK TIL AKTUELLE OPERASJON (KRYSS AV ENTEN I A ELLER B)****A. Primæroper. pga. (ev. flere kryss)**

- Idiopatisk coxartrose  
 Rheumatoid artritt  
 Sekvele etter frakt. coll. fem.  
 Sekv. dysplasi  
 Sekv. dysplasi med total luksasjon  
 Sekv. Parthes  
 Sekv. epfyliolyse  
 Mb. Bechterew  
 Akutt fraktura coll. femoris  
 Annet.....  
(f.eks caputnekrose, tidl. arthrode o.l)

**B. Reoper. pga. (ev. flere kryss)**

- Løs acetabularkomponent  
 Løs femurkomponent  
 Luksasjon  
 Dyp infeksjon  
 Fraktur i acetabulum  
 Fraktur av femur  
Vancouverklassifikasjon, se baksiden.  
 A  B1  B2  B3  C  
 Smertor  
 Osteolyse i acetab. uten løsning  
 Osteolyse i femur uten løsning  
 Implantatfraktur femurdel  
 Implantatfraktur caput  
 Implantatfraktur kopp  
 Implantatfraktur liner  
 Implantatfraktur annet: .....

+

- Gluteal svikt  
 Annet.....  
(f.eks Girdlestone etter tidl. infisert protese)

+

**REOPERASJONSTYPE** (ev. flere kryss)

- Bytte av femurkomponent  
 Bytte av acetabularkomponent  
 Bytte av hele protesen  
 Fjernet protese og satt inn sementspacer  
 Fjernet sementspacer og satt inn ny protese  
 Fjernet protese (Girdlestone eller fjerning av sementspacer)  
Angi hvilke deler som ble fjernet.....  
 Bytte av plastforing  
 Bytte av caput  
 Blottdelsdebridement  
 Ny protese etter Girdlestone  
 Resutur av muskel  
 Transposisjon av muskel  
 Osteosyntese for fraktur  
 Konvertering til hemiprotese  
 Andre operasjoner .....

**TILGANG** (ett kryss)

- Fremre (Mellom sartorius og tensor)  
 Anterolateral (Mellom gl. medius og tensor)  
 Direkte lateral (Transgluteal)  
 Bakre (Bak gluteus medius)  
 Annen .....

**MINIVASIV KIRURGI (MIS)**     Nei     Ja  
**LEIE**     Sideleie     Rygg  
**TROCHANTEROSTEOTOMI**     Nei     Ja

**BENTRANSPLANTASJON** (ev. flere kryss)

**Acetabulum**     Nei     Ja     Børpakking  
**Femur**     Nei     Ja     Børpakking a.m. Ling/Gie

**BENTAP VED REVISJON** (Paprosky's klassifikasjon se baksiden)

**Acetabulum**     I     IIa     IIb     IIc     IIIa     IIIB  
**Femur**     I     II     IIIa     IIIB     IV

**PROTESEKOMponenter** (Bruk kistrelapp på baksiden, eller skriv REF.NR.)**Acetabulum**

Navn/Type ....., ev. REF.NR. ....  
 Med hydroksylapatitt     Uten hydroksylapatitt  
 Sement med antibiotika – Navn ....., ev. REF.NR. ....  
 Sement uten antibiotika – Navn ....., ev. REF.NR. ....  
 Usementert

+

**Femur (+ ev. trokanterdel)**

Navn/Type ....., ev. REF.NR. ....  
 Med hydroksylapatitt     Uten hydroksylapatitt  
 Sement med antibiotika – Navn ....., ev. REF.NR. ....  
 Sement uten antibiotika – Navn ....., ev. REF.NR. ....  
 Usementert

**Caput (+ ev. halsdel)**

Fastsittende caput  
 Separat caput - Navn/Type ....., ev. REF.NR. ....  
Diameter .....

**ANTIBIOTIKAPROFYLAKSE**     Nei     Ja

Navn	Dosering	Varighet i timer
Medikament 1.....	.....	..... timer
Medikament 2.....	.....	..... timer
Medikament 3.....	.....	..... timer

**TROMBOSEPROFYLAKSE**

Nei     Ja: Første dose     Preoperativt     Postoperativt  
Medikament 1..... Dosering opr.dag..... Varighet..... døgn  
..... Dosering videre..... Varighet..... døgn  
Medikament 2..... Dosering..... Varighet..... døgn

**FAST TROMBOSEPROFYLAKSE**

Nei     Ja, type: .....

**FIBRINOLYSEHEMMER**

Nei     Ja, medikament: ..... Dosering.....

**OPERASJONSTUE**

- "Green house"  
 Operasjonstue med laminær luftstrøm  
 Vanlig operasjonstue

+

**OPERASJONSTID** (hud til hud) .....min

**PEROPERATIV KOMPLIKASJON**


Nei  
 Ja, hvilke(n).....

**ASA KLASSE** (se baksiden for definisjon)

- Frisk     Livstruende sykdom  
 Asymptomatisk tilstand som gir økt risiko     Morbund  
 Symptomatisk sykdom

Legs.....  
Legen som har fylt ut skjemaet (navnet registreres ikke i databasen).

## APPENDIX B



Nasjonalt Register for Leddproteser

**Nasjonalt Register for Leddproteser**  
**The Norwegian Arthroplasty Register**

**Spørreskjema – Ventilasjon av operasjonsstuer**

---

Stuenummer: .....

Periode i bruk: fra..... til.....

1) Ventilasjonstype/luftstrømstype: Laminær (LAF)  Annet:.....  
Konvensjonell   
Greenhouse

2) Stuens areal: .....m<sup>2</sup>

3) Stuens takhøyde: .....m

4) Luftens utgangshastighet: .....m/s

5) Anleggets nominelle innluftsmengde: .....m<sup>3</sup>/h Friskluftsandel.....

6) Hvilken type filter/filterklasse er installert?: .....

7) Hvor ofte foretas: Filterbyte.....pr. år  
Rengjøring.....pr. år

8) Hvordan og hvor ofte foretas CFU-måling?: ...../.....pr. år

Ingen rutiner

9) Har CFU-verdien vært målt til  $\leq 10\text{CFU/m}^3$ : Ja  Vet ikke   
Nei

10) Ventilene for ut-luft er plassert: Gulv  Tak   
Vegg

11) Benytter systemet underkjøling?: Ja  Vet ikke   
Nei

For LAF-tak:

12) Takets størrelse: .....m x .....m

13) Takets luftstrøm er definert som: Delvegg  Spesifisering:  
Helvegg

14) Takets luftstrøm er: Vertikal  Skrå   
Horisontal

15) Er det montert sidevegger/skjørt?: Ja  Lengde:  
Nei

16) Er det installert spesial-operasjonslamper for LAF?: Ja   
Nei

17) Er det sonemarkering i gulvet?: Ja   
Nei

## Spørreskjema - Ventilasjon av operasjonsstuer - forklaringer

**Stuenummer og Periode i bruk:** Den aktuelle operasjonsstuens romnummer og perioden den ble brukt i intervallet 1987-2015. (dd.mm.åååå, mm.åååå, åååå eller dd (dagens dato)).

- 1) **Ventilasjonsstype:** Laminær luftstrøm (LAF), konvensjonell (turbulent) overtrykksventilasjon, «Greenhouse»-ventilasjon eller annet spesifisert tak (Allander, Weiss, Trox etc).
- 2) **Stuens areal:** Stuens areal i kvadratmeter (m<sup>2</sup>).
- 3) **Stuens takhøyde:** Stuens takhøyde i meter (m).
- 4) **Luftens utgangshastighet:** Snittverdi av luftens utgangshastighet i meter per sekund (m/s). For sonedelte tak er det også ønskelig at det oppgis én snittverdi. Størrelsesorden 0,15 - 0,5 m/s.
- 5) **Anleggets innluftsmengde:** Luftvolumet som systemet tilbyr per time (m<sup>3</sup>/h) (Størrelsesorden 1000-16000 m<sup>3</sup>/h) samt friskluftandel (primærluft).
- 6) **Filtertype/-klasse:** Filtertype for innløpsluften. Det er ønskelig med informasjon om alle steg. For eksempel HEPA, 3 steg, Last H13.
- 7) **Filterbytte og rengjøring:** Frekvens for filterbytte (alle steg) og rengjøring av ventilasjonssystemet, 1 x, 2 x pr. år etc.
- 8) **CFU-målinger:** Gjøres målingene under pågående kirurgi («Intraoperativt») og i nærheten av operasjonsfeltet, eller på «tom stue»? Frekvens for CFU-målinger, 1 x, 2 x pr. år etc.
- 9) **CFU-verdien:** Har CFU-konsentrasjonen noen gang vært målt til å være  $\leq 10\text{CFU}/\text{m}^3$  slik kravet fra statens helsestilsyn om ultrarene operasjonsstuer tilsier? Dette vil spesifiseres i korrespondanse med smittevernvedlingen.
- 10) **Ventiler for ut-luft:** Er slusene for luften som forlater rommet plassert langs gulvet, på veggen (eventuelt som langstrakte sluser fra gulvet og opp på veggen), tak eller en kombinasjon (sett da flere kryss eller spesifiser)?
- 11) **Underkjøling:** Benyttes det underkjøling av innløpsluft?
- 12) **Takets størrelse:** Mål på selve ventilasjonsflaten (lengde x bredde)
- 13) **Takets luftstrøm:** Er det snakk om et helveggsystem med nokså jevn snitthastighet for luftspalten i hele taket, eller er det snakk om et delveggsystem med ulike hastighetssoner. Ved delvegg er det ønskelig at prinsippet spesifiseres: eksponensiell LAF e.l.
- 14) **Takets luftstrøm:** Er det vertikal luftstrøm, horisontal luftstrøm eller skrå luftstrøm?
- 15) **Sidevegger/skjørt:** Er det montert sidevegger/skjørt ned langs innløpet? Hvis ja: oppgi helst lengde på disse/dette.
- 16) **Spesiallamper:** Er det montert spesial operasjonslamper til bruk sammen med laminær luftstrøm for å hindre dannelse av turbulens?
- 17) **Sonemarkering:** Er det markeringer i gulvet på stuen som indikerer luften(e)?





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# Operating room ventilation and the risk of revision due to infection after total hip arthroplasty: assessment of validated data in the Norwegian Arthroplasty Register

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## SUMMARY

**Background:** The air in the operating room is considered a risk factor for surgical site infection (SSI) due to airborne bacteria shed from the surgical staff or from patients themselves.

**Aim:** To assess the influence of validated operating room (OR) ventilation data on the risk of revision surgery due to deep infection after primary total hip arthroplasty (THA) reported to the Norwegian Arthroplasty Register (NAR).

**Methods:** Forty orthopaedic units reporting THAs to the NAR during the period 2005–2015 were included. The true type of OR ventilation in all hospitals at the time of primary THA was confirmed in a previous study. Unidirectional airflow (UDF) systems were subdivided into: small, low-volume, unidirectional vertical flow (lvUDVF) systems; large, high-volume, unidirectional vertical flow (hvUDVF) systems; and unidirectional horizontal flow (UDHF) systems. These three ventilation groups were compared with conventional, turbulent, mixing ventilation (CV). The association between the end-point, time to revision due to infection, and OR ventilation was estimated by calculating relative risks (RRs) in a multivariate Cox regression model, with adjustments for several patient- and surgery-related covariates.

**Findings:** A total of 51,292 primary THAs were eligible for assessment. Of these, 575 had been revised due to infection. A similar risk of revision due to infection after THA performed was found in ORs with lvUDVF and UDHF compared to CV. THAs performed in ORs with hvUDVF had lower risk of revision due to infection compared to CV (RR = 0.8; 95% CI: 0.6–0.9;  $P = 0.01$ ).

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**Conclusion:** THAs performed in ORs with hvUDVF systems had lower risk of revision due to infection compared to THAs performed in ORs with CV systems. The perception that all UDF systems are similar and possibly harmful seems erroneous.

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## Introduction

Infection after total hip arthroplasty (THA) is devastating for the patients and generates high public costs [1]. The air in the operating room (OR) is considered a potential source of contamination and subsequently a risk factor for surgical site infection (SSI) due to airborne bacteria and other viable microorganisms (colony-forming units (cfu)) shed from the surgical staff or from patients [2–7]. The number of cfu in the OR may be altered by staff behaviour such as the number of personnel, door openings, and physical movement, and by the use of other preventive measures such as impermeable gowns and space helmets [8–10]. Previous studies have postulated that the density of cfu is correlated with the rate of postoperative infection, but the findings are controversial as the isolated effect of air cleanliness is hard to assess [6,11–15]. Other studies show that air contamination is not directly associated with wound contamination and periprosthetic joint infection [16,17].

Unidirectional airflow (UDF or UDAF) systems (formerly known as laminar airflow (LAF) systems) have been used during ultraclean surgery since the late 1960s, as they were thought to reduce the incidence of SSI by reducing the cfu density [13]. UDF systems work by sending parallel, filtered air streams with constant velocity directly on to the surgical field to intentionally displace and reduce the flow of less clean air from the rest of the OR to the surgical field. This is in contrast to the conventional ventilation (CV) systems, which use the dilution principle. CV systems supply turbulent air in order to dilute airborne contamination, mixing polluted air with clean air, and are often termed turbulent and/or mixing ventilation systems [18].

Unidirectional airflow as a prophylactic measure against SSI has been supported ever since Lidwell and colleagues published their randomized, clinical trial in the 1980s [19]. For THA and total knee arthroplasty (TKA), they found lower risk of ‘deep joint sepsis’ after arthroplasty performed in ultra-clean air (UCA; cfu <10/m<sup>3</sup>) with a relative risk (RR) of 0.4 compared to a control group with non-ultra-clean air. The study has been criticized for having methodological weaknesses, but both historic and recent re-evaluations of the study confirm the validity of the findings [15,20–23]. Subsequent observational studies from the same decade, controlled for antibiotic prophylaxis, found no convincing influence of OR ventilation on the rate of SSI [24,25]. More recently, studies from surveillance registries have suggested that LAF actually may increase the risk of infection after arthroplasty [26–28]. Two recent systematic reviews, based partly on these registry studies, conclude that UDF systems should not be installed in new ORs [20,29]. One of the reviews includes an observational study from the Norwegian Arthroplasty register (NAR), not studying the effect of UDF specifically, using ventilation only as an adjustment variable in the study of infection trend [30]. In a

previous validation study, we found 12% misreporting of ventilation data to the NAR, questioning the validity of studies based exclusively on ventilation data reported from surgeons or surgical departments [31]. In addition, there are numerous different configurations of UDF systems, and when studying their effect on the rate of postoperative infections it is important to know the dissimilarities between the different UDF systems and that these have evolved over the decades.

Our aim in the present study was to assess the association between validated, factual OR ventilation systems and the risk of revision due to deep infection after primary THA.

## Methods

Since its inception in 1987, the NAR has registered data on primary and revision THAs in Norway. The register form is filled in by the surgeon immediately after surgery, containing information on patient identity, date of operation, indication for surgery and other surgery-related factors. In addition, certain patient-related factors such as sex, age, and comorbidity are registered. Primary THA and any subsequent revisions are linked through a unique person identity number that follows each citizen from birth to death. Revision is defined as removal or exchange of prosthesis parts, whereas revision cause, i.e. deep infection, is determined by the surgeon based on perioperative assessments and clinical evaluation. Cases of revision due to infection are thus reported to the NAR before the culturing of perioperative tissue samples is ready. The data is validated, with 97% completeness of reporting of primary THAs, 93% reporting of revisions, and 100% coverage of Norwegian hospitals [32].

The factual OR ventilation on each hospital was validated and either confirmed or corrected in a previous study [31]. To be included as a UDF system, it had to be verified that the system had been installed with a multistage high-efficiency particulate air (HEPA)-filtered, unidirectional diffuser array. Based on technical data collected, the following classification of ventilation systems was established for further analyses: small, low-volume, unidirectional, vertical flow systems (lvUDVF: volume flow rate (VFR; m<sup>3</sup>/h) <10,000 and canopy size (m<sup>2</sup>) <10); large, high-volume, unidirectional, vertical flow systems (hvUDVF: VFR ≥10,000 and canopy size ≥10); and unidirectional horizontal flow (UDHF). We did not have complete data on the volume of each OR, so we were unable to calculate the exact air changes per hour (ACH). As the ACH also might be dependent on other factors, we did not include ACH in the definition of the different UDF systems. The CV systems included in this study were verified to fulfil the requirement of multi-stage HEPA-filtered air with 20 ACH and positive pressurization [33].

The period of inclusion was 2005–2015, primarily due to the fact that the patients’ American Society of Anesthesiologists (ASA) class, a risk factor associated with infection, was only

reported to the NAR from 2005 and onwards [34]. All patients during this period received systemic, antibiotic prophylaxis.

A separate survey confirmed negligible use of space suits and/or helmets. Three of the hospitals used space suits in very short periods of time, but discontinued the use due to loss of spatial awareness.

Validated ventilation data were obtained for 40 out of 62 public hospitals reporting THAs to the NAR in the inclusion period [31]. Out of 60,298 THAs performed in these 40 hospitals, 2046 were performed in a period of ventilation system exchange or update, and were excluded. A total of 4313 THAs performed in UDFV ventilation were excluded due to lack of detailed information on certain ventilation covariates from parts of the inclusion period, essential for our main analyses, or due to the current UDFV system not fulfilling the defined criteria for lvUDVF or hvUDVF. In addition, 2647 THAs were excluded due to missing patient or procedure covariates. Hence, 51,292 THAs were eligible for analyses.

### Statistics

The association between OR ventilation and revision due to infection was estimated by Cox regression analyses. Relative risk (RR), as a measure of hazard rate ratios, was calculated with 95% confidence intervals (CIs). End-point was date of revision due to deep infection. Further, adjusted four-year survival rates were calculated, as well as Kaplan–Meier four-year survival rates, and cumulative survival curves with OR ventilation as strata. In the multivariate analyses, we adjusted for sex, age at primary surgery, indication for primary THA, ASA class, method of fixation, modularity of the prosthesis, and duration of surgery. Year of primary THA was included as an adjustment variable to account for unknown time dependent confounding. Additional analyses were made with one- and two-year follow-up. Further, additional assessments were performed to adjust for spatial orientation of the wound in the OR, whether the wound was oriented upwards or to the side, based on an evaluation of patient positioning and surgical approach as potential risk factors. The analyses were performed in concordance with the guidelines for statistical analyses of arthroplasty register data [35].  $P < 0.05$  and non-overlapping 95% CIs were considered statistically significant.

Statistical analyses were performed using SPSS version 24 (SPSS Inc., 2004) and R (R Foundation for Statistical Computing, 2014). The study was performed in accordance with the RECORD and STROBE statements.

### Ethics

The registration of data and further assessment were performed confidentially following patient consent and according to Norwegian and EU data protection rules.

### Results

Among the 51,292 eligible THAs, 575 (1.1%) had been revised due to infection. Demographics and distribution of risk factors in the different ventilation groups are presented in Table I. All patients received systemic antibiotic prophylaxis and all cemented THAs had antibiotic loaded bone cement. The distribution of the risk factors was similar for the four ventilation

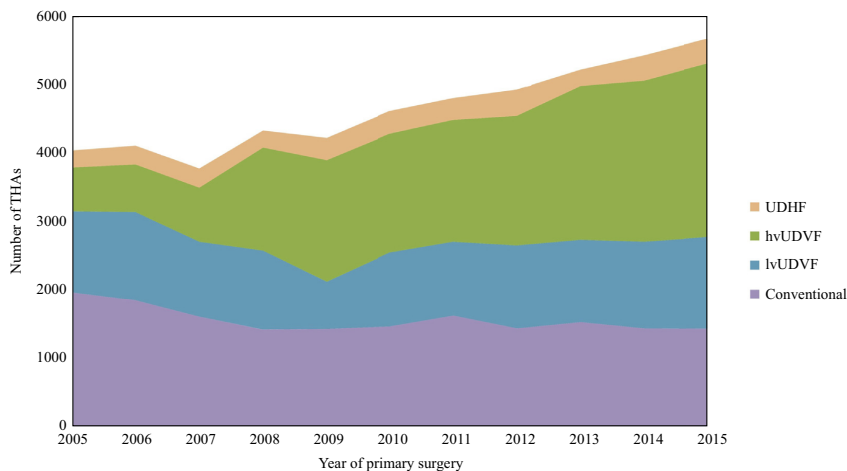
**Table I**

Baseline characteristics for the total hip arthroplasties performed in the different ventilation systems

Characteristic	Type of operating room ventilation			
	Conventional lvUDVF	lvUDVF	UDHF	UDHF
No. of THAs	17,297	12,639	17,960	3396
Sex				
Male	34%	33%	34%	33%
Female	66%	67%	67%	67%
Age group (years)				
<45	2%	3%	3%	3%
45–54	6%	7%	8%	7%
55–64	22%	23%	23%	22%
65–74	36%	36%	36%	35%
75–84	28%	27%	25%	28%
>85	5%	5%	5%	5%
Indication for primary THA				
Osteoarthritis	82%	75%	77%	83%
Inflammatory disease	3%	3%	2%	2%
Hip fracture	3%	2%	3%	1%
Complication after hip fracture	6%	6%	6%	5%
Complication after childhood hip disease	5%	12%	10%	6%
Necrosis of the femoral head	2%	2%	3%	3%
ASA class				
1	22%	18%	19%	19%
2	57%	63%	61%	62%
≥3	21%	19%	20%	19%
Method of fixation				
Uncemented	20%	9%	29%	64%
Cemented	80%	91%	71%	36%
Modularity of the prosthesis				
Monoblock	5%	5%	4%	0
Modular	95%	95%	96%	100%
Duration of surgery (min)				
<70	20%	20%	27%	18%
70–99	51%	41%	36%	48%
100–129	21%	28%	27%	27%
>130	8%	11%	10%	7%

lvUDVF, small, low-volume, unidirectional vertical flow systems; hvUDVF, large, high-volume, unidirectional vertical flow systems; UDHF, unidirectional horizontal flow systems; THA, total hip arthroplasty; ASA, American Association of Anesthesiologists.

groups, except for more uncemented THAs in the two hospitals using UDHF (one rural and one regional hospital). In the remaining three ventilation groups, rural, regional, university, and specialized elective hospitals were evenly represented. During the study period, four hospitals converted from CV to hvUDVF and one hospital converted from lvUDVF to hvUDVF between 2006 and 2009. From 2009, 16 hospitals used CV, nine used lvUDVF, and 13 used hvUDVF systems. The annual distribution of THAs within the different groups of ventilation system is presented in Figure 1. The risk factors and confounders in the adjusted analyses are presented in Table II. Sex, age, ASA class, and duration of surgery were associated with risk of revision due to infection.



**Figure 1.** Annual number of primary THAs in the four different ventilation groups during 2005–2015. UDHF, unidirectional horizontal flow systems; hvUDVF, large, high-volume, unidirectional vertical flow systems; lvUDVF, small, low-volume, unidirectional vertical flow systems.

Assessing the UDF group as one encompassing entity, primary THAs performed in ORs with such unclassified UDF had a risk of revision due to infection similar to that of CV (RR: 0.9; 95% CI: 0.7–1.2). The risk of revision due to infection after THAs performed in ORs with lvUDVF and UDHF was similar to those performed in CV (Table III, Figure 2). THAs performed in ORs with hvUDVF had a lower risk of revision due to infection than those performed in CV (Table III, Figure 2). No UDF system was associated with higher risk of revision due to infection after THA compared to CV.

Adjusting for wound spatial orientation and reducing follow-up time to one year and two years had only minor influences on the results. We did not have complete data on the spatial volume of all ORs in order to calculate the exact ACH, but adjusting for operating room volume in analyses of the available ORs had negligible impact on the results.

## Discussion

The risk of revision due to infection after primary THA performed in ORs with hvUDVF was 20% lower than after THA performed in CV, whereas THA performed in ORs with lvUDVF or UDHF had a risk of revision due to infection similar to that of THA performed in CV. No UDF system was associated with higher risk of revision due to infection after THA compared to CV.

Recent registry studies as well as systematic reviews and meta-analyses are questioning the effect of LAF/UDF as a prophylactic measure against postoperative infection, as they suggest for arthroplasty an increased risk of SSI and revision due to infection [20,26–30]. This is in contrast to the results from our study on validated ventilation data. Recent World Health Organization (WHO) guidelines, though conditional, recommend not to use UDF systems to reduce the risk of SSI in arthroplasty [36]. The WHO recommendation is based partly on

a few observational studies with some methodological issues: no UDF system differentiation or definition based on technical specifications, limited documentation of validation on the UDF systems, and limited information on coverage or completeness of reporting of the end-point SSI or revision due to infection [21,22,31,37]. Some of these studies had only six months to one year follow-up, and others had no systematic post-discharge surveillance. This has been a point of debate as low-grade infections caused by airborne contaminants might be excluded as they may present at a much later stage [21,22]. Coagulase-negative staphylococci (CoNS) are the most frequent bacterial cause of revision of infected THA [38]. Since CoNS are regarded as commensal bacteria and since CoNS have also been shown to be the most frequent bacterial cause of late infection, this may suggest that direct contamination from primary surgery is the likely mechanism of THA infection, even in infection more than two years after primary THA [38]. Haematogenous seeding of CoNS is possible, but is less likely to occur as this requires substantial bacteraemia [39,40]. We studied the effect of OR ventilation with four years follow-up, comparable to the Lidwell studies [21,41].

One possible explanation for the reported contrary effect of UDF could be improper positioning and movement of personnel, theatre lamps, etc. in the airflow [18,42,43], thereby abolishing the preventive effect by creating more turbulence. This might especially be the case in the boundary areas due to insufficient size of the protected UDF zone. Studies have shown impact of canopy size on bacterial counts in the surgical area, where the minimum size of a UDF ceiling distribution system has been recommended to be at least 320×320 cm for ultraclean surgery [44–46]. We studied the effect of canopy size on infection risk by defining cut-off for canopy size in accordance with this recommendation.

In addition, the potentially lower tissue temperature and bacterial impingement danger due to disruption of the

**Table II**  
Relative risks of revision due to infection after primary total hip arthroplasties in the Norwegian Arthroplasty Register

Risk factor	Included	Revised due to infection	Relative risk	95% CI	P-value
Sex					
Male	17,144	268	1.8	1.5–2.1	<0.001
Female	34,148	307	1		
Age group (years)					
<45	1334	15	1.2	0.7–2.1	0.5
45–54	3667	27	0.8	0.5–1.3	0.4
55–64	11,584	101	0.9	0.7–1.2	0.6
65–74	18,475	180	1		
75–84	13,669	202	1.5	1.2–1.8	<0.001
>85	2563	50	1.9	1.4–2.7	<0.001
Indication for primary THA					
Osteoarthritis	40,305	448	1		
Inflammatory hip disease	1293	18	1.3	0.8–2.1	0.3
Hip fracture	1180	17	1.3	0.8–2.1	0.3
Complication after hip fracture	2963	39	1.0	0.7–1.4	0.9
Complication after childhood hip disease	4342	31	0.8	0.5–1.2	0.2
Necrosis of the femoral head	1209	22	1.5	1.0–2.3	0.08
ASA class					
1	10,178	60	0.6	0.5–0.8	<0.001
2	30,837	347	1		
≥3	10,276	168	1.3	1.1–1.5	0.02
Method of fixation					
Uncemented	11,974	127	1.0	0.8–1.2	1.0
Cemented	39,318	448			
Modularity of the prosthesis					
Monoblock	2059	11	0.5	0.3–1.0	0.04
Modular	49,233	564	1		
Duration of surgery (min)					
<70	11,405	120	1.1	0.9–1.4	0.4
70–99	22,125	225	1		
100–129	12,935	147	1.1	0.9–1.4	0.3
>130	4827	83	1.6	1.3–1.8	0.002

CI, confidence interval; THA, total hip arthroplasty; ASA, American Association of Anesthesiologists.

Adjusted for sex, age, indication for primary THA, ASA class, modularity of the prosthesis, method of fixation, and duration of surgery, in addition to operating room ventilation and year of primary THA.

wound's own protective, thermal plume, is also claimed to disturb the effectiveness of the UDF [26,47–49]. One recent study identifies the use of UDF as a significant risk factor for hypothermia, thereby being subsequently a risk factor for infection of the wound [50,51]. To counteract these issues, forced air warming (FAW) systems have been used. These are also thought to disturb the laminar airflow [52,53]. However, recent reviews conclude that the evidence for this is sparse [54–56]. A recent experimental study found that the disturbing effect of FAW is counteracted by sufficient air velocity in the UDF systems [57]. As the air velocity of different UDF systems is adjustable, we could not use it as a constant adjustment variable in our analyses. It was therefore indirectly assessed by studying the VFR, varying in the range of 1000–5000 m<sup>3</sup>/h in older, low-volume systems and 10,000–20,000 m<sup>3</sup>/h in newer, high-volume systems. The latter is necessary to create velocities in the desired minimum range of 0.3–0.38 m/s through large area canopies [58].

UDF systems are able to create lower cfu concentrations than CV systems both in air and close to the operation site. This

is shown both in computational fluid dynamics studies and in experimental studies [44,59–66]. Studies have also shown an association between the cfu concentration and SSI, but the question remains whether other risk factors such as the patient's immunological status, bacterial virulence, antibiotic prophylaxis, surgical technique, etc., are indeed much more important [6,11–14]. The latter is supported by studies showing that SSI after elective orthopaedic surgery is more frequently caused by endogenous transmission than previously assumed [67,68]. Further indicating the patients' skin commensals as source of infection are studies on the bacteriology of infected shoulder arthroplasty and postoperative infections after spinal surgery, showing a high proportion of *Propionibacterium (Cutibacterium) acnes* [69–71]. This is a species known to be abundant in sebaceous glands of the skin in such regions, and as the bacteriology of infected total hip arthroplasties is different, dominated by staphylococci, this might indicate that the patients are their own source of infection. If the cleanliness of the air in the OR is the same during different types of prosthetic surgery and a significant source for postoperative infection, why does the bacteriological spectrum of

**Table III**

Relative risks of revision due to deep infection after primary total hip arthroplasty, adjusted four-year survival and Kaplan–Meier four-year survival for the four operating room ventilation systems

Operating room ventilation	THAs included	THAs revised due to infection	Relative risk	95% CI	P-value	Kaplan–Meier four-year survival	Adjusted four-year survival	Censored before four years	At risk at four years
Conventional	17,297	208	1			98.8 (98.6–98.9)	98.9 (98.7–99.0)	1627	12,914
lvUDVF	12,639	138	0.9	0.7–1.1	0.3	98.9 (98.7–99.0)	99.0 (98.9–99.2)	1081	9077
hvUDVF	17,960	175	0.8	0.6–0.9	0.01	99.0 (98.9–99.2)	99.1 (99.0–99.3)	1423	11,860
UDHF	3396	54	1.3	0.9–1.8	0.1	98.4 (97.9–98.8)	98.6 (98.2–99.0)	342	2366

THA, total hip arthroplasty; CI, confidence interval; lvUDVF, small, low-volume, unidirectional vertical flow systems; hvUDVF, large, high-volume, unidirectional vertical flow systems; UDHF, unidirectional horizontal flow systems.

Adjustments were made for sex, age, indication for primary THA, American Association of Anesthesiologists class, modularity of the prosthesis, method of fixation, duration of surgery, and year of primary THA.

infections vary between different regions of the body? This questions the extent of air cleanliness importance. Despite this, and with increasing antibiotic resistance taken into account, it seems logical to reduce the peroperative, bacterial load to a minimum. This will be increasingly important in an era with increasing microbial resistance to antibiotics [72,73].

Our finding of a 20% lower risk of revision due to infection after THA performed in hvUDVF compared to CV is minute, considering also that the incidence of revision due to infection is only around 1%. However, UDF systems can create cleaner air, and, taking our results into account, it seems erroneous to discontinue the use of large, high-volume, vertical UDF systems in the ORs of the future. Technological development and multidisciplinary co-operation with the focus on correct implementation and function of the ventilation systems should be encouraged [22,65,66].

Our study is based on data from the NAR with a large number of THAs, with good quality, coverage, and completeness [74–76]. This gives us a unique opportunity to study relatively rare events, such as deep infection after THA, with detailed information on surgery- and patient-related confounders.

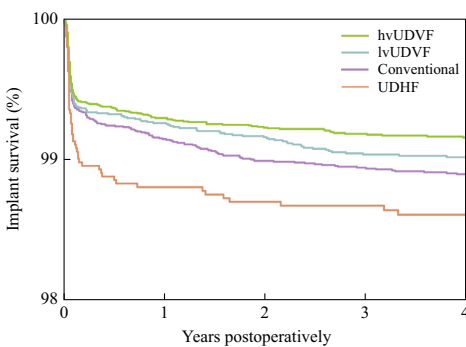
Other register studies on OR ventilation have been criticized for not making a thorough adjustment of antibiotic prophylaxis, for using surgeon- or surgical department-reported data on ventilation, for not differentiating the UDF systems on technical specifications, and for having a limited follow-up time [21]. All of our cases received systemic, antibiotic prophylaxis and the multivariate analyses were conducted on the basis of validated ventilation data. Further, we did sub-analyses on canopy size and VFR with four-year follow-up. All this adds strength to our study and makes it a substantial contribution to new knowledge in the field.

This study suggests merely the association between OR ventilation and revision due to deep infection after primary THA. There will be unknown confounding such as human behavioural factors in the OR, incorrect implementation and maintenance of the ventilation systems, and other factors potentially disturbing the UDF. We have no information on patient warming systems, use of surgical drapes, number of personnel in the room, number of door openings, etc., but we have no reason to believe that this would be different between the four ventilation groups in our study. In addition, revision due to infection may be underreported, but, as the under-reporting of revision is similar between the hospitals, this will add minimal selection bias and subsequent impact on our results [32,77–79].

There has been an increase in the share of hvUDVF systems over the last 20 years (Figure 1). This increase is parallel to the reported, increased risk of revision due to infection after THA [80,81]. This will necessarily be a time-dependent confounder in our analyses and we have addressed this by adjusting for year of primary surgery as a continuous variable in the analysis.

Only two of the included hospitals used UDHF. In addition, these two hospitals had a higher share of uncemented THAs. This may add selection bias, but the type of fixation was adjusted for.

The modularity of the prosthesis may affect the incidence of reported revision due to infection. Non-modular/monoblock THAs (i.e. Charnley prostheses) were used by some hospitals until 2014. They do not contain modular parts, and hence, infections of such THAs treated with debridement, antibiotics, and implant retention (DAIR) were not reported to the NAR until 2011 from when all DAIRs were reported regardless of component exchange or not. This is in contrast to modular THAs, which contain removable components exchanged during a DAIR procedure. Hence, these debridements were defined as revisions throughout the study period, and were subsequently



**Figure 2.** Survival curves for total hip arthroplasties (THAs) performed with different ventilation systems and revised due to infection. Adjusted for sex, age, indication for primary THA, American Association of Anesthesiologists class, modularity of the prosthesis, method of fixation, duration of surgery, and year of primary THA. lvUDVF, small, low-volume, unidirectional vertical flow systems; hvUDVF, large, high-volume, unidirectional vertical flow systems; UDHF, unidirectional horizontal flow systems.

reported to the NAR as such. This will potentially lead to an underreporting of revision due to infection after THA with monoblock prostheses, which was addressed by adjusting for modularity.

Forty of 62 public hospitals were included. Most of the excluded hospitals performed primary THAs throughout the whole study period, as did most of the included ones, and with a completeness of reporting of more than 97% [75]. Time trends of reporting are therefore not thought to affect the findings. The reporting of primary THAs was similar in the two groups (included/excluded) and the distribution of hospital types in the two groups was also similar (rural hospitals, regional/university hospitals, specialized elective hospitals). We therefore believe that the impact of selection bias is minimal.

In conclusion, UDF ventilation assessed as one encompassing entity did not influence the risk of revision due to infection after primary THA compared to CV. When differentiating the UDF systems on technical specifications, however, primary THAs performed in ORs with hvUDVF ventilation systems had a lower risk of revision due to infection compared to ORs with CV. Considering also that UDF systems can create lower particle and microbial load than CV systems, our findings support the use of hvUDVF systems for all ultraclean surgery in the future.

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### Conflict of interest statement

None declared.

### Funding sources

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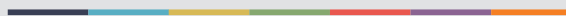
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