Protocol

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Title:

Airflow and Hip Prosthesis Infections: A Register Study Comparing Laminar vs. Turbulent Flow in the Danish Hip Arthroplasty Register.

Brief objectives:

The aim of this study is to evaluate the association of laminar airflow versus turbulent airflow ventilation on prosthetic joint infection and on any revision.

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Study registration number in Pactius Region Hovedstaden:

P-2019-796.

Potential conflict of interests:

None reported.

Abstract

Background: During surgery, bacteria in the air in the operating room (OR) is considered a cause of periprosthetic joint infection (PJI). Previously, turbulent airflow (TAF) has been used in ORs. Later, laminar airflow (LAF) has been developed, which minimize the number of colony forming units in the air. However, most studies show no benefit of LAF regarding PJI incidence.

Aim: To evaluate the association of LAF versus TAF ventilation on primary PJIs in 90 and 365 days in total hip arthroplasties (THAs) using the Danish hip arthroplasty register (DHR) and the Danish microbiology register (MiBa)

Methods: All THAs performed in Denmark in 2010-2020 are identified in DHR. Through DHR, revisions and type of ventilation system is identified. PJI is defined using a validated method combining MiBa with DHR, where infection is defined as two or more positive identical bacteria cultures or is registered by the surgeon as PJI. The risk of PJI s in THAs performed in TAF are compared with THAs performed in LAF using Cox regression models adjusting for confounders.

Use and relevance: PJIs are extremely costly and cause a significant morbidity and mortality for the patient. When constructing or renovating a hospital, it is crucial to choose a ventilation system that minimizes PJIs, while being cost-efficient. Previous studies on LAF vs TAF are based on data from national registers. Since registration of PJI is reported immediately to DHR and other arthroplasty registers after surgery, the microbiology results are not taken into consideration when the revision cause is reported. This study is novel, because it gives a more accurate picture of the PJI incidence and can be part in guiding the decisions when renovating or designing new hospitals, in order to decrease the risk of PJI.

Rationale and background

Prosthetic joint infection (PJI) is one of the most feared complication after total hip arthroplasty (THA), with increased mortality and morbidity, as well as a significant cost for society (1–4). Since the 1960s, in addition to systemic prophylactic antibiotics and antibiotic-laden bone cement, efforts have been made to make the air in the operating rooms (OR) as clean as possible with filtering and replacement of the air (5).

This has led to the current official PJI incidence of 0.57-0.80 % in the first year after surgery according to the Danish Hip Arthroplasty Register (DHR) and the Swedish Hip Arthroplasty

Register (SHAR), even though the true incidence of PJI probably is about 40 % higher, due to under-registration in the registers following revision surgery (6,7).

The risk of PJI is potentially affected by contamination in the OR (5,8–10), patient related risk factors (11,12) and prosthesis factors. The prosthesis factors include type of implant and implant fixation method. Cemented implants have a lower overall revision rate, although the results are not unanimous when it comes to revision due to PJI (13–16).

The risk of contamination in the OR is affected by the cleanliness of the air (5,17–21). There are two different types of ventilation systems used to achieve a clean environment in an OR. The first is turbulent airflow (TAF), where the air is continuously replaced with filtered ultra-clean air that trickles down from the ventilation shaft. The second is laminar airflow (LAF) where the ultra-clean air flows in a single direction, with the goal to prevent particles carrying bacteria, that are floating in the air, to land on the patient or sterile equipment (17,22).

LAF decreases the bacterial load significantly in the OR, measured in CFUs (17–21). However, the number of CFUs has not been found to correlate with the incidence of PJI in real world data, where most studies show no advantage of LAF compared to TAF. Only one major observational study shows that LAF decreases the risk of infection in a subgroup of LAF (23). All other register studies show no difference between LAF and TAF or a higher risk for PJI with LAF (24–28). There are no randomized, controlled trials (RCTs) comparing modern-day ventilation systems when it comes to the PJI incidence in THAs.

There are no randomized, controlled trials (RCTs) comparing modern-day ventilation systems when it comes to the PJI incidence in THAs. However, in 1982, an RCT was conducted by Lidwell et al., comparing different ultraclean air flow systems, including LAF, with standard operating room ventilation at the time. In this study, there was a significant difference in PJI incidence with 2.2 % PJIs in the standard OR group and 1.0 % in the ultraclean group. However, these standard ORs had much higher bacterial contamination, with a median of 164 CFUs/m3 (29), compared to modern-day TAF ORs, that have a median ranging from 4,5-22 CFU/m3 (18,19,22). The ultraclean group had a median of 2-10 CFUs/m3, thus it resembles modern-day TAF ORs, both in bacterial load and PJI rate (29).

Due to additional costs in building and maintaining LAF systems, a public analysis was conducted in Denmark in 2011 to compare the cost-effectiveness of LAF and TAF. When considering the estimated annual costs, which included operational expenses, depreciation, and interests, LAF ORs were estimated to cost 508,732 DKK per year, whereas TAF ORs were projected to cost 304,530 DKK per year. As a result, there was an annual cost difference of 204,202 DKK (€27,000) per unit, with LAF being 67 % more expensive than TAF. A PJI was estimated to cost the society around 204,000 DKK in the same year (4).

An issue in the previous studies on PJI in LAF and TAF are that they are epidemiological and rely solely on the PJI diagnosis reported to the different registers. However, diagnosing a PJI is not always evident in a clinical setting. It has been shown that the DHR is lacking both registration of revisions and later confirmed PJI (30), and a lack of registered PJI revisions has also been observed in the Swedish hip arthroplasty register (SHAR) (7).

The PJI diagnosis in the DHR can be greatly improved, if combined with the Danish Microbiology Database (MiBa) (31). When validating the diagnosis PJI in DHR, the sensitivity was found to be only 67 %. When using an algorithm including data from MiBa, sensitivity increased to 90 %, without providing more false positives. A simplified algorithm utilizing MiBa data exhibited no statistically significant difference when compared to the more extensive algorithm employed in the validation study by Gundtoft et al. (30,31). This simplified algorithm, which doesn't require access to medical records, will be applied in the criteria for the primary outcome.
Additionally, previous studies show that one positive bacterial sample at a clinically aseptic revision increases the risk of an occult infection, diagnosed later at a re-revision (32). This will be investigated as well.

Thus, using these new and well validated methods, the investigators aim to estimate the risk of PJI with LAF versus TAF ventilation better than has been done in previous studies.

Data sources

The Danish Civil Registration System (Centrale Person Register, CPR) contains information including vital status and time of emigration on all Danish residents (33). All Danish residents and citizens are assigned a unique and permanent individual identification number (CPR number) at birth or upon immigration. It enables an unambiguous linkage between different registers and allows an individual follow-up over time (34).

The Danish National Patient Register (NPR) collects data of all Danish residents contact to a public hospital, including date, performed examinations or surgical procedures and diagnosis, classified by International Classification of Diseases (ICD) (35). The data includes both outpatient and inpatient contacts and is linked with the patient's CPR number (36).

The Danish Hip Arthroplasty Register (DHR) collects data including type of OR ventilation from all THAs performed in Denmark, including primary THAs as well as revisions (37). It is mandatory for all surgeons performing THAs to report to the register, which results in high completeness. The data is previously validated (38). In the case of a revision, the surgeon reports the indication immediately after surgery (39). The revisions performed within 90 and 365 days are located in the DHR, which also contains information from the NPR about revisions.

The Danish Microbiology Database (MiBa) automatically collects all microbiology results from all departments of clinical microbiology in Denmark since 2010, which are then stored electronically using the patient's CPR number as patient identifier (40). The register completeness is previously validated (41). The data will more specifically be extracted from the Healthcare-Associated Infections Database – HAIBA, a part of MiBa.

The Danish National Prescription Register (DNPR) collects detailed information on redeemed prescriptions in Denmark since 1995. It is previously validated and has a high degree of completeness and is frequently used in epidemiological research (42).

Income Statistics Register – The register contains income data on more than 160 variables including salaries and savings of people with a Danish income and is widely used in research. Each individual is identified with an unambiguous CPR number (43).

Danish Education Register – The register has a high coverage on education level, both among people born in Denmark and immigrants and is widely used in research. Each individual is identified with an unambiguous CPR number (44).

Variables

The investigators will look at several variables and adjust for these where needed. The variables obtained from DHR is body mass index (BMI), age, gender, time of surgery, diagnosis, type of prosthesis and fixation method, whether cement is used and if it contains antibiotics, previous operations on the same hip and ASA score. ASA score and BMI are only available from 2017 and onwards in DHR.

From NPR, concomitant diagnoses will be obtained to produce an Elixhauser comorbidity score, and socioeconomic factors, such as income and education will be obtained from the Danish Income Statistics Register and Education Register.

Methods

The data is reported according to the RECORD guidelines (45) and is stored in the servers of Statistics Denmark, where the data will be analyzed.

Study population:

All people ≥18 years receiving a primary total hip arthroplasty in Denmark between 01.01.2010-31.12.2020 registered in DHR are included. Patients receiving a THA due to a hip tumor or metastasis are excluded, as well as patients with erroneous registration in DHR.

Exposure:

Surgery performed in an OR with LAF compared with surgery in an OR with TAF.

Follow-up:

Follow-up starts on the operation day and ends 365 days postoperatively. Follow-up is also ended at time of any revision, death or emigration.

Null hypothesis:

There is no difference in the risk of PJIs after a THA performed in a LAF OR as opposed to in a TAF OR.

Alternative hypothesis:

There is a lower or higher risk of PJIs after a THA performed in a LAF OR as opposed to in a TAF OR.

Endpoints:

Primary endpoint:

Revision due to infection, measured at t=90 days and t=365 days. Revision is defined as the first surgical intervention in the same hip after a primary THA with debridement, replacement, or removal of prosthetic parts.

A follow-up time of 90 and 365 days respectively is chosen, since 90 days is the recommended surveillance period in the United States and is traditionally the limit between early and late infections, whereas it is important to have a follow up of a year not to miss up to 20 % of the infections (46,47). At 1 year, 80-90 % of the surgically requiring infections that will occur in the lifetime of the hip prosthesis have taken place. After 1 year, the infection rate drastically decreases and is less likely to be due to contamination during surgery (30,47).

PJI is considered present when at least one of the following two criteria exists.

1. Two or more intraoperative deep-tissue samples of the same bacteria, isolated from at least three deep-tissue samples.
2. Deep infection is reported to DHR by the surgeon upon revision surgery.

The definition of PJI is based on the studies by Gundtoft et al. (30,31), where it has been concluded, that the validity of the PJI diagnosis is greatly improved when using these criteria, which are validated specifically for DHR. The original study by Gundtoft et al. used an extensive algorithm to determine if a PJI was present. However, there was no statistically significant difference between the extensive algorithm and a simplified algorithm, that defines a PJI as two or more positive identical bacterial samples (30).

The investigators definition is in line with international consensus (48) and does not differ greatly from the definition made by the European Bone and Joint Infection Society (EBJIS) (49), although erythrocyte sedimentation rate, aspiration of joint fluid, white blood cell count in joint fluid and histological examination of intraoperative tissue biopsies are not routinely used in Denmark. Thus, these criteria are not used. Sinus tract communication with the hip joint or an opening to the hip joint is expected to cause the surgeon to register the diagnosis “infection” in DHR upon revision. Data for this analysis will be extracted from DHR and

HAIBA. For the revision surgery to be registered in HAIBA, at least three biopsies at the revision surgery are required, hence this is a part of the criteria (50).

Secondary endpoints:

1) Revision registered as aseptic loosening in DHR.
2) Any revision registered in DHR.

Aseptic loosening is a separate endpoint, since it has been shown that aseptic loosening might in fact turn out to be a PJI and is thus a point of interest (32,51,52).

Sensitivity analyses:

In addition, the following sensitivity analyses will be made:

a) Alternative outcome: Primary revision registered as PJI or with at least one positive biopsy of a bacterium.
b) Alternative outcome: Primary revision reported to DHR with at least one positive biopsy of a bacterium AND the prescription of a relevant antibiotic, specified in appendix A.
c) Analysis for the primary endpoint, but for data collected between 2017-2020, allowing for adjustment for BMI and ASA as possible confounders, as these variables are only registered in this period

A sensitivity analysis is made for a) and b), since Milandt et al. have shown that having one positive intraoperative bacterial culture increases the risk of an occult infection, that is later diagnosed upon re-revision. When there was only one unexpected positive culture (unexpected meaning not registered as PJI in DHR), first-time revisions were associated with an increased relative risk of 2.63 for subsequent re-revision specifically for PJI. However, this association was not observed for the patients with two or more unexpected positive cultures, which were much more likely to receive antibiotics and be treated as PJI, after the microbiology results were obtained. This is most likely, because one positive culture has been interpreted as contamination (32). A sensitivity analysis is made for c), since DHR only have ASA and BMI registered starting in 2017 and thus this cannot be adjusted for prior in the data prior to 2017.

EBJIS have proposed a term called PJI-likely which include 1 positive unexpected positive culture. PJI-likely is based on international consensus (48,49); however, the definition relies on analyses that are not commonly performed in routine practice in Denmark, as stated in the description of the primary endpoint. Since it is not possible to use these criteria in Danish register studies, the investigators have instead decided to do sensitivity analyses based on the validation of infections in the DHR by Gundtoft et al. (30) and the findings of Milandt et al. (32).

Statistical analysis:

Descriptive results for continuous variables will be shown as mean(SD)/median(range) depending on the distribution of the variables. Categorical variables will be presented using frequencies and percentages. Persons operated in LAF and TAF ORs are compared using t-tests/Wilcoxon-tests and chi-square tests, respectively. This is supplemented with cumulative incidence plots showing risk of infection (primary outcome) for LAF and TAF, regarding revision due to other causes and death as competing events. The two groups are compared using Grays test. To fulfill the requirements at Statistics Denmark about data on individual persons, a smooth curve is used to make the plot rather than the statistical correct step-function. Information at time 90 and 365 days after the operation will be presented. This type of plot will be used for all endpoints.

For the primary endpoint, two Cox regression analyses will be performed with the time to PJI as outcome. One model will only cover the first 90 days of follow-up, the other will cover all 365 days of follow-up. Censoring is made at time of revision due to other causes than PJI, death, emigration, and end of follow-up (365 days after operation), whichever comes first. Bilateral THA will be included in the model as two observations with inclusion of a time-dependent variable conditioning on the status of the other hip (53). A robust sandwich covariance matrix estimate is used to account for the intrapersonal dependence.

The model will include the following potential confounders:
Education, age, comorbidities, gender, previous hip surgery, primary diagnosis, type of cement, type of fixation, year of surgery, income and duration of surgery. ASA and BMI will be adjusted for in sensitivity analysis c). A direct acyclic graph is used when determining the variables needed to adjust for.

The linearity assumption for continuous confounders is checked by including these as cubic splines with 3 to 7 knots and using the model with lowest AIC, as suggested by Harrell (54). The proportional hazards assumption for the Cox-regression models is assessed using plots for the cumulative sum of martingale residuals. If the assumption is violated for the exposure (LAF/TAF), the time-axis will be split into smaller parts in which the assumption is fulfilled, and a separate Cox regression is made for each part. If the proportional hazard assumption is violated for confounders, time-dependent covariates is used for these.

Similar Cox-regression models will be used to analyze both secondary endpoints, as well as for the sensitivity analysis of the primary endpoint.
The assumptions of proportional hazards for these endpoints are checked as described for the model for the primary endpoint.
All tests will be two-sided and a p-value of <0.05 will be considered statistically significant. Statistical analysis will be conducted using SAS version 9.4 (SAS Institute Inc.).

Missingness

Thanks to the Danish registers, there is no loss to follow-up for the primary and secondary endpoints, nor for the endpoints of the sensitivity analyses. Information for most of the confounders is based om mandatory registration in DHR, thus it is expected a very limited amount of missing data in the confounders (less than 5 % with missing information about one/several confounders). The missingness is not likely to be associated with the exposure, thus the complete case analysis is expected to be valid (55).

If the missingness is found to be more pronounced, multiple imputation will be used to create a full analysis data set. The imputation will use 100 samples. Multiple imputation will be made using R (The R Foundation). Results from analysis on the full analysis data set as well as for the complete case analysis will be presented.

Ethical aspects

The study is registered in Pactius, Region Hovedstaden. The study is approved by the Danish Health Data Authority. Since it is an observational study, an approval by an ethical committee is not needed. An approval from the Danish Society for Patient Safety is not needed since this study solely uses anonymized data from registers and not from medical records. The protocol is uploaded to clinicaltrials.org to maximize transparency of the research process.

Perspectives

When constructing or renovating a hospital, it is crucial to choose a ventilation system that minimizes PJIs, while being cost-efficient. Previous studies on LAF vs TAF are based on data from national registers. Since registration of PJI is reported immediately to DHR and other registers after surgery, the microbiology results are not taken into consideration when the revision cause is reported. This study is novel, because it gives a more accurate picture of the PJI incidence and can be part in guiding the decisions when renovating or designing new hospitals, in order to decrease the risk of PJI.

References

1. Akindolire J, Morcos MW, Marsh JD, Howard JL, Lanting BA, Vasarhelyi EM. The economic impact of periprosthetic infection in total hip arthroplasty. Can J Surg. 2020 Jan 1;63(1):E52–6.
2. Gundtoft PH, Pedersen AB, Varnum C, Overgaard S. Increased Mortality After Prosthetic Joint Infection in Primary THA. Clin Orthop. 2017 Nov;475(11):2623–31.
3. Wildeman P, Rolfson O, Söderquist B, Wretenberg P, Lindgren V. What Are the Long-term Outcomes of Mortality, Quality of Life, and Hip Function after Prosthetic Joint Infection of the Hip? A 10-year Follow-up from Sweden. Clin Orthop. 2021 Oct;479(10):2203–13.
4. Hørder M, Bech M, Ejdrup Andersen S. Sundhedsstyrelsen, Dokumentation af Kvalitet og Standardisering Ventilation på operationsstuer København: Sundhedsstyrelsen, Dokumentation af Kvalitet og Standardisering, 2011 [Internet]. 2011 [cited 2023 May 16]. Available from: http://www.sst.dk/mtv
5. Charnley J, Eftekhar N. Postoperative infection in total prosthetic replacement arthroplasty of the hip-joint with special reference to the bacterial content of the air of the operating room. Br J Surg. 1969 Sep;56(9):641–9.
6. Gundtoft PH, Pedersen AB, Schønheyder HC, Møller JK, Overgaard S. One-year incidence of prosthetic joint infection in total hip arthroplasty: a cohort study with linkage of the Danish Hip Arthroplasty Register and Danish Microbiology Databases. Osteoarthritis Cartilage. 2017 May;25(5):685–93.
7. Lindgren JV, Gordon M, Wretenberg P, Kärrholm J, Garellick G. Validation of reoperations due to infection in the Swedish Hip Arthroplasty Register. BMC Musculoskelet Disord. 2014 Dec;15(1):384.
8. Charnley J, Eftekhar N. Penetration of gown material by organisms from the surgeon's body. Lancet Lond Engl. 1969 Jan 25;1(7587):172–3.
9. Tanner J, Parkinson H. Double gloving to reduce surgical cross-infection. Cochrane Database Syst Rev. 2002;(3):CD003087.
10. Rezapoor M, Alvand A, Jacek E, Paziuk T, Maltenfort MG, Parvizi J. Operating Room Traffic Increases Aerosolized Particles and Compromises the Air Quality: A Simulated Study. J Arthroplasty. 2018 Mar;33(3):851–5.
11. Bozic KJ, Lau E, Kurtz S, Ong K, Rubash H, Vail TP, et al. Patient-Related Risk Factors for Periprosthetic Joint Infection and Postoperative Mortality Following Total Hip Arthroplasty in Medicare Patients. J Bone Jt Surg. 2012 May 2;94(9):794–800.
12. Eka A, Chen AF. Patient-related medical risk factors for periprosthetic joint infection of the hip and knee. Ann Transl Med. 2015 Sep;3(16):233.

13. Makela KT, Matilainen M, Pulkkinen P, Fenstad AM, Havelin L, Engesaeter L, et al. Failure rate of cemented and uncemented total hip replacements: register study of combined Nordic database of four nations. BMJ. 2014 Jan 13;348(jan13 12):f7592–f7592.
14. McMinn DJW, Snell KIE, Daniel J, Treacy RBC, Pynsent PB, Riley RD. Mortality and implant revision rates of hip arthroplasty in patients with osteoarthritis: registry based cohort study. BMJ. 2012 Jun 14;344(jun14 1):e3319–e3319.
15. Kandala NB, Connock M, Pulikottil-Jacob R, Sutcliffe P, Crowther MJ, Grove A, et al. Setting benchmark revision rates for total hip replacement: analysis of registry evidence. BMJ. 2015 Mar 9;350(mar09 1):h756–h756.
16. Dale H, Fenstad AM, Hallan G, Havelin LI, Furnes O, Overgaard S, et al. Increasing risk of prosthetic joint infection after total hip arthroplasty: 2,778 revisions due to infection after 432,168 primary THAs in the Nordic Arthroplasty Register Association (NARA). Acta Orthop. 2012 Oct;83(5):449–58.
17. Liu Z, Liu H, Yin H, Rong R, Cao G, Deng Q. Prevention of surgical site infection under different ventilation systems in operating room environment. Front Environ Sci Eng. 2021 Jun;15(3):36.
18. Knudsen RJ, Knudsen SMN, Nymark T, Anstensrud T, Jensen ET, La Mia Malekzadeh MJ, et al. Laminar airflow decreases microbial air contamination compared with turbulent ventilated operating theatres during live total joint arthroplasty: a nationwide survey. J Hosp Infect. 2021 Jul;113:65–70.
19. Marsault LV, Ravn C, Overgaard A, Frich LH, Olsen M, Anstensrud T, et al. Laminar airflow versus turbulent airflow in simulated total hip arthroplasty: measurements of colony-forming units, particles, and energy consumption. J Hosp Infect. 2021 Sep;115:117–23.
20. Ahl T, Dalen N, Jörbeck H, Hobom J. Air contamination during hip and knee arthroplasties: Horizontal laminar flow randomized vs. conventional ventilation. Acta Orthop Scand. 1995 Jan;66(1):17–20.
21. Squeri R, Genovese C, Trimarchi G, Antonuccio GM, Alessi V, Squeri A, et al. Nine years of microbiological air monitoring in the operating theatres of a university hospital in Southern Italy. :12.
22. Alsved M, Civilis A, Ekolind P, Tammelin A, Andersson AE, Jakobsson J, et al. Temperature-controlled airflow ventilation in operating rooms compared with laminar airflow and turbulent mixed airflow. J Hosp Infect. 2018 Feb;98(2):181–90.
23. Langvatn H, Schrama JC, Cao G, Hallan G, Furnes O, Lingaas E, 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. J Hosp Infect. 2020 Jun;105(2):216–24.
24. Pedersen AB, Svendsson JE, Johnsen SP, Riis A, Overgaard S. Risk factors for revision due to infection after primary total hip arthroplasty: A population-based study of 80,756 primary procedures in the Danish Hip Arthroplasty Registry. Acta Orthop. 2010 Oct;81(5):542–7.
25. Hooper GJ, Rothwell AG, Frampton C, Wyatt MC. Does the use of laminar flow and space suits reduce early deep infection after total hip and knee replacement?: THE TEN-YEAR RESULTS OF THE NEW ZEALAND JOINT REGISTRY. J Bone Joint Surg Br. 2011 Jan;93-B(1):85–90.
26. Bischoff P, Kubilay NZ, Allegranzi B, Egger M, Gastmeier P. Effect of laminar airflow ventilation on surgical site infections: a systematic review and meta-analysis. Lancet Infect Dis. 2017 May;17(5):553–61.
27. Wang Q, Xu C, Goswami K, Tan TL, Parvizi J. Association of Laminar Airflow During Primary Total Joint Arthroplasty With Periprosthetic Joint Infection. JAMA Netw Open. 2020 Oct 16;3(10):e2021194.
28. Brandt C, Hott U, Sohr D, Daschner F, Gastmeier P, Rüden H. Operating Room

Ventilation With Laminar Airflow Shows No Protective Effect on the Surgical Site Infection Rate in Orthopedic and Abdominal Surgery. Ann Surg. 2008 Nov;248(5):695–700.
29. Lidwell OM, Lowbury EJ, Whyte W, Blowers R, Stanley SJ, Lowe D. Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement: a randomised study. BMJ. 1982 Jul 3;285(6334):10–4.
30. Gundtoft PH, Overgaard S, Schønheyder HC, Møller JK, Kjærsgaard-Andersen P, Pedersen AB. The "true" incidence of surgically treated deep prosthetic joint infection after 32,896 primary total hip arthroplasties: A prospective cohort study. Acta Orthop. 2015 May 4;86(3):326–34.
31. Gundtoft PH, Pedersen AB, Schønheyder HC, Overgaard S. Validation of the diagnosis 'prosthetic joint infection' in the Danish Hip Arthroplasty Register. Bone Jt J. 2016 Mar;98-B(3):320–5.
32. Milandt NR, Gundtoft PH, Overgaard S. A Single Positive Tissue Culture Increases the Risk of Rerevision of Clinically Aseptic THA: A National Register Study. Clin Orthop. 2019 Jun;477(6):1372–81.
33. Danmarks statistik befolkningstal [Internet]. 2022. Available from: https://www.dst.dk/da/Statistik/emner/borgere/befolkning/befolkningstal
34. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014 Aug;29(8):541–9.
35. WHO International Classification of Diseases. 2022 Jul 9; Available from: https://www.who.int/classifications/classification-of-diseases
36. Landspatientregisteret fra sundhedsdatastyrelsen. 2022 Jul 9; Available from: https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sygdomme-laegemidler-og-behandlinger/landspatientregisteret
37. Gundtoft P, Varnum C, Pedersen AB, Overgaard S. The Danish Hip Arthroplasty Register. Clin Epidemiol. 2016 Oct;Volume 8:509–14.
38. The Danish Hip Arthroplasty Register (DHR), 2021 National Annual Report. Available from: http://www.dhr.dk
39. Pedersen A, Johnsen S, Overgaard S, Søballe K, Sørensen H, Lucht U. Registration in the Danish Hip Arthroplasty RegistryCompleteness of total hip arthroplasties and positive predictive value of registered diagnosis and postoperative complications. Acta Orthop Scand. 2004 Jan;75(4):434–41.
40. Voldstedlund M, Haarh M, Mølbak K, the MiBa Board of Representatives. The Danish Microbiology Database (MiBa) 2010 to 2013. Eurosurveillance [Internet]. 2014 Jan 9 [cited 2022 Jul 9];19(1). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES2014.19.1.20667
41. Chaine M, Gubbels S, Voldstedlund M, Kristensen B, Nielsen J, Andersen LP, et al. Description and validation of a new automated surveillance system for *Clostridium difficile* in Denmark. Epidemiol Infect. 2017 Sep;145(12):2594–602.
42. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol. 2016 Oct 27;dyw213.
43. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. Scand J Public Health. 2011 Jul;39(7_suppl):103–5.
44. Jensen VM, Rasmussen AW. Danish education registers. Scand J Public Health. 2011 Jul;39(7_suppl):91–4.
45. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLOS Med. 2015 Oct 6;12(10):e1001885.
46. Muscatelli S, Zheng H, Muralidharan A, Tollemar V, Hallstrom BR. Limiting the Surveillance Period to 90 Days Misses a Large Portion of Infections in the First Year After

Total Hip and Knee Arthroplasty. Arthroplasty Today. 2022 Aug;16:90–5.
47. Tande AJ, Patel R. Prosthetic Joint Infection. Clin Microbiol Rev. 2014 Apr;27(2):302–45.
48. Parvizi J, Gehrke T, Chen AF. Proceedings of the International Consensus on Periprosthetic Joint Infection. Bone Jt J. 2013 Nov;95-B(11):1450–2.
49. McNally M, Sousa R, Wouthuyzen-Bakker M, Chen AF, Soriano A, Vogely HC, et al. Infographic: The EBJIS definition of periprosthetic joint infection: a practical guide for clinicians. Bone Jt J. 2021 Jan;103-B(1):16–7.
50. Statens Serum Institut. Hoftealloplastikinfektion [Internet]. 2023 [cited 2023 May 31]. Available from: https://miba.ssi.dk/overvaagningssystemer/haiba/casedefinitioner/hoftealloplastik
51. Hipfl C, Mooij W, Perka C, Hardt S, Wassilew GI. Unexpected low-grade infections in revision hip arthroplasty for aseptic loosening: a single-institution experience of 274 hips. Bone Jt J. 2021 Jun 1;103-B(6):1070–7.
52. Goldman AH, Osmon DR, Hanssen AD, Pagnano MW, Berry DJ, Abdel MP. The Lawrence D. Dorr Surgical Techniques & Technologies Award: Aseptic Reoperations Within One Year of Primary Total Hip Arthroplasty Markedly Increase the Risk of Later Periprosthetic Joint Infection. J Arthroplasty. 2020 Jun;35(6):S10–4.
53. Lie SA, Engesaeter LB, Havelin LI, Gjessing HK, Vollset SE. Dependency issues in survival analyses of 55,782 primary hip replacements from 47,355 patients. Stat Med. 2004 Oct 30;23(20):3227–40.
54. Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis [Internet]. New York, NY: Springer New York; 2001 [cited 2023 Jun 16]. (Springer Series in Statistics). Available from: http://link.springer.com/10.1007/978-1-4757-3462-1
55. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Med Res Methodol. 2017 Dec;17(1):162.
56. Lindgren V, Gordon M, Wretenberg P, Kärrholm J, Garellick G. Deep Infection after Total Hip Replacement: A Method for National Incidence Surveillance. Infect Control Hosp Epidemiol. 2014 Dec;35(12):1491–6.

Appendix A

List of antibiotics screened for 2 weeks after revision, originating from the study by Lidgren et al. from 2014 (56), adapted to Danish conditions

J01CA04 Amoxicillin
J01CR02 Amoxicillin and clavulanic acid
J01CE02 Phenoxymethylpenicillin
J01CF05 Flucloxacillin
J01CF01 Dicloxacillin
J01FA01 Erythromycin
J01FA06 Roxithromycin
J01FA09 Clarithromycin
J01FA10 Azithromycin
J01XC01 Fucidin
J04AB02 Rifampicin
J01FF01 Clindamycin
J01XX08 Linezolid
J01XD01 Metronidazole
J01MA02 Ciprofloxacin
J01MA12 Levofloxacin
J01MA14 Moxifloxacin
J01EE01 Sulfametoxazol and trimetoprim