Prosthetic Joint Infection following Total Hip Arthroplasty

- Incidence, Mortality and Validation of the Diagnosis in the Danish Hip Arthroplasty Register

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THIS THESIS IS BASED ON THE FOLLOWING FOUR PAPERS:

Study I: 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 Summary prospective cohort study. Acta Orthop. 2015 Jun;86(3):326-34

Study II: Gundtoft PH, Pedersen AB, Schønheyder HC, Overgaard S. Validation of the diagnosis 'prosthetic joint infection' in the Danish Hip Arthroplasty Register. Bone Joint J. 2016 Mar;98-B(3):320-5

Study III: Gundtoft PH, Pedersen AB, Møller JK, Schønheyder HC, Overgaard S. Incidence of one-year prosthetic joint infection in total hip arthroplasties: a cohort study with linkage of the Danish Hip Arthroplasty Register and Danish Microbiology Databases. Osteoarthritis Cartilage. 2017 May;25(5):685-693

Study IV: Gundtoft PH, Pedersen AB, Varnum C, Overgaard S. Increased mortality following prosthetic joint infection in total hip arthroplasty. Clin Orthop Relat Res. 2017 Feb 24. doi: 10.1007/s11999-017-5289-6.

1. INTRODUCTION

1.1 PRIMARY TOTAL HIP ARTHROPLASTY SURGERY

Experiments aiming to replace a painful hip joint have been carried out since the early 1920s [56], but it was not until Sir John Charnley developed the low-friction, ball-and-socket total hip arthroplasty (THA) during in the 1950-60s that THA gained a foothold as the widespread and successful treatment it is today [25, 87].

The initial procedure during which a severely impaired hip joint is replaced with implantation of a prosthesis is often referred to as a primary THA, whereas any subsequent surgery, including removal or exchange of the primary prosthesis, is referred to as a revision. Primary THA is most commonly performed on patients suffering from primary hip osteoarthritis. This group accounts for approximately 75-80% of all THAs [5, 99]. The remaining 20-25% of the operations are performed for other reasons such as inflammatory, traumatic or congenital hip disorder and avascular necrosis of the femoral head. As THA is considered a safe and very successful treatment [87], the indication for surgery has been expanding. This, together with an ageing population, has resulted in an increasing incidence of primary THA in the Western countries during the past decades [76, 119, 127, 173] with approximately 9,000 primary THA being performed in Denmark annually and an incidence of 170 primary THA per 100,000 inhabitants [5].

Indication	Nr.	%
Aseptic loosening	8,311	52
Dislocation	2,745	17
Prosthetic joint infection	1,409	9
Periprosthetic fracture	1,209	8
Component failure	869	5
Other	577	4
Pain	459	3
Osteolysis without loosening	251	2
Wear of polyethylene	227	1
Total	16,057	100

Table 1: Indication for first-time revisions according to the Annual Report from the Danish Hip Arthroplasty Register, 2015.

The first prosthesis developed by Sir John Charnley consisted of femur monoblock prostheses in which the stem and head are produced as one piece of metal, fixated to the bone with cement and interacted with a polyethylene acetabulum cup [26]. Subsequently, a number of different designs have been introduced, e.g. modular prostheses (in which the head and stem can be separated), cementless fixation, and also various different bearings, types of cement and brands have been used [7]. This growing diversity of products of which some have been shown to have a high risk of failure [172] called for surveillance, which triggered the establishment of the Danish Hip Arthroplasty Register (DHR). The DHR was modelled on the Swedish Hip Arthroplasty Register [102] and has been monitoring the epidemiology and outcome of THA surgery since 1995 [99].

Author	Year	Time	Reported incidence	Trend estimated by the study	Reference
Charnley	1960	Percentage	7-9%	-	[27]
Charnley	1970	Percentage	<1%	-	[27]
Poss et al	1970-80	Percentage	0.89%	-	[132]
SHAR	1985	Cumulatice revision rate, 5-year	0.4%	-	[2]
Kurtz et al.	1990-2004	Percentage*	1.23%	↑	[77]
Ridgeway	1997-2003	Percentage	0.18	-	[143]
Ong et al.	1997-2006	Incidence, 2-year	1.63%	-	[115]
Wolf et al.	1991-2008	90 day incidence	0.7%	↓	[177]
Dale et al.	1995-2009	Cumulative revision rate, 5-year	0.6%	↑	[31]
Pedersen et al.	1995-2005	Percentage	0.7%	↑	[128]
Pulido et al.	2001-2006	Percentage*	0.7%	-	[134]
Kurtz et al.	2001-2009	Percentage*	1.99%	↑	[78]
Lindgren et al.	2005-2008	Cumulative Incidence rate, 2 years	0,9%	↑	[95]

*Percentage of number of total hip arthroplasties performed yearly

SHAR: Swedish Hip Arthroplasty Register

Table 2: Reported incidence of prosthetic joint infection since 1960.

Like any other operation, THA carries a risk of complications. The annual report published by the DHR as well as the reports published by other arthroplasty registers have made it possible to estimate the risk of various complications following primary THA which shows that although declining, aseptic loosening continues to be the most common indication for revisions [5], followed by dislocation and prosthetic joint infection (PJI) (Table 1). However, the distribution of complications varies over time, as aseptic loosening is rarely seen in the first few years following primary THA where PJI and dislocation are more common indications for revision [65, 131]. PJI is generally perceived as the most devastating complication due to the impact on the patients' lives [110] and the poor prognosis associated with a revision for PJI [5, 149], which led Sir John Charnley to state that: "*Postoperative infection after total hip replacement is the saddest of all complication…" [23]*.

1.2 INCIDENCE OF PROSTHETIC JOINT INFECTION

In the beginning of the modern era of THA, the risk of PJI was as high as 7-9% [27]. Subsequently, a number of initiatives, such as closed clean air operating rooms [27, 89], stricter pre- and postoperative routines [88] along with the addition of antibiotics to the cement [66], reduced the infection rate to 3-5% [88], and later even lower incidences of PJI have been reported (Table 2). The risk of PJI is often reported as an incidence, which is a measure of the probability that a disease will occur within a specified time period, but not all studies report the length of the follow-up or use a very short follow-up period [55, 109]. This, together with other factors such as different definitions of PJI and national differences between patients, surgeons, different standards for reporting of PJI to registers and databases, and loss to follow-up makes comparison of the various reported incidences difficult [175].

As PJI is a rare event, large cohorts and long follow-up periods are needed to obtain precise estimates of PJI [19]. National arthroplasty registers offer such large cohorts and long follow-up periods. Moreover, data in these registers are easily available for researches at a low cost, as they consist of prospectively collected information. The prospective collection of data also reduces selection and information bias as the data are collected independently of the research question. Furthermore, studies based on national registers lend themselves more readily to generalisation as various patients and surgeons are included.

Beginning with the Swedish Hip Arthroplasty Register in the 1990s [2], the national arthroplasty registers have been used ever more frequently to study trends in PJI incidence (Table 2). However, the national arthroplasty registers were not designed for registration of PJI, and several problems with the registration of revisions for PJI have been reported. In 2006, Espehaug et al. showed that only 76% of removal revisions (in which only part of the prosthesis is removed) were reported to the Norwegian Arthroplasty Register [41]. This greatly affects the estimation of revisions for PJI, as PJI is often treated with removal of only part of the prosthesis. Combining data from several registers, Jämsen et al. [62] and Huotari et al.[59] later showed that the incidence of revision for PJI was probably underestimated in the Finnish Arthroplasty Registers as well. Thus, the previously reported incidence rates from the DHR and other national registers may be underestimated, and the true incidence therefore remains – to some degree – unknown.

Showing how arthroplasty registers probably underestimate the incidence of PJI, these studies highlight the importance of validating the data in these registers. Before the present thesis was conducted, the Swedish Hip Arthroplasty Register was the only arthroplasty registers with a validated PJI diagnosis. Validation of this register was performed by Lindgren et al. in 2014, who showed a sensitivity of the PJI diagnosis of only 60% [93]. However, this should not cause us to disregard national registers as a tool for PJI research as other infection registers are, indeed, facing the same problem of underestimation [41, 59, 62]. Moreover, in most countries, arthroplasty registers are the only available tool for national-level surveillance [182]. Rather than discarding the use of the registers due to the lacking validation, we should carefully consider when data from these registers can be used and how the registers may be improved.

1.2.1 Increasing Incidence of Prosthetic Joint Infection and Risk Factors

Several studies have reported an increasing risk of PJI from the 1990s to the beginning of the 21th century (Table 2). However, only one of these studies has used validated PJI data [95]. Whether this reported increase continues into the next decade remains unclear as none of the studies have used data collected after 2009. A number of variables have been established as risk factors for PJI, i.e. variables that are associated with an increased risk of PJI (Figure 1). If the incidence of PJI rises, this will most likely be a result of a change in one or more of these risk factors (Figure 1). However, none of the studies have been able to explain the increasing incidence by reference to a corresponding increase in risk factors [31, 32, 77, 95, 128]. It has been suggested that the increase could be the result of changes in factors not frequently recorded in national registers, e.g. increasing patient comorbidity and increasing antimicrobial resistance in the bacteria causing PJI [69, 95].

1.3 DEFINITION OF PROSTHETIC JOINT INFECTION

Defining PJI has proven to be surprisingly difficult [125]. Sir John Charnley stated that: "*If one waits long enough for an infection to manifest itself, infection can never be overlooked*" [27]. This holds true in the case of a sinus tract from the skin to the prosthesis, which is recognised as a pathognomonic sign of PJI [121, 187]. However, these cases are rare; and unless the prosthesis is visible from the outside, it can be difficult to distinguish clinically a suppurating wound from a sinus tract [45]. Another subjective sign of PJI, which has previously been regarded as a definitive sign of PJI, is purulence surrounding the prosthesis [125, 187]. In recent years, purulence has been abandoned as a pathognomonic sign of PJI due to its subjective nature and the absence of a standard definition of "purulence"; low sensitivity (as a high number of THA with PJI have no signs of purulence); and due to findings of purulence in revisions without any evidence of infection [20, 108].
In order to address the difficulties in diagnosing PJI, a number of tests have been developed and most of these tests have been incorporated into the definitions of PJI.

1.3.1 Intraoperative Cultures

In 1981, Carl Kamme and Lars Lindberg introduced a method for collecting intraoperative biopsies during revisions surgery. According to this method, five samples of approximately 5 mm were taken with separate sterile forceps *from the same area, adjacent to the cement or prosthesis where an infectious lesion was suspected or bone resorption was seen* [67]. The authors concluded that growth in one to two out of five biopsies was a strong indica-

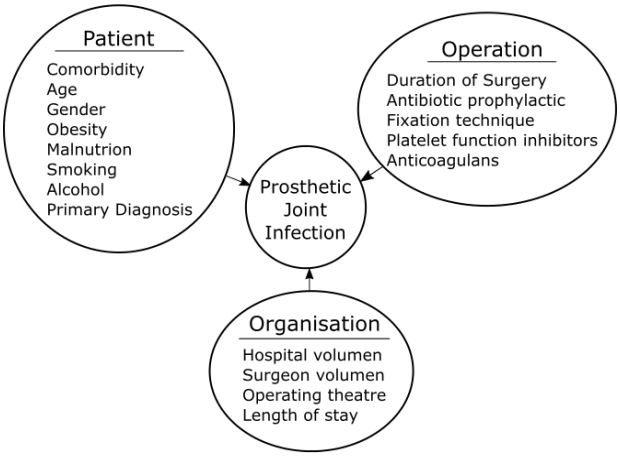

Figure 1: Potential risk factors for prosthetic joint infection.

Author	Year	No. of positive cultures	Total Nr. of cultures	Positive cultures alone is definitive for PJI	Reference
Brandt et al.	1997	≥2	-	yes	[21]
Berbari et al.	1998	≥2	-	yes	[17]
Tattevin et al.	1999	≥2	-	yes	[163]
Spangehl et al.	1999	>1/3	≥3	no	[158]
Meehan et al.	2003	≥2	-	yes	[104]
Parvizi et al	2006	≥1	-	no	[123]
Schinsky et al	2008	≥1	-	no	[150]
Parvizi et al	2008	≥2	-	no	[124]
MSIS: New definition	2011	≥2	-	yes	[178]
International Consensus Group	2013	≥2	>3 and <6	yes	[122]
Zimmerli	2014	≥2		yes	[185]

PJI: Prosthetic Joint Infection

Table 3: Definition of prosthetic joint infection which incorporates intraoperative cultures.

tion for contamination, while growth in five out of five strongly indicated PJI [67]. This method has subsequently been tested in other studies, which confirmed that growth in three out of five biopsies was a strong indication for PJI [13, 37, 105] as this criterion is associated with a high specificity. Subsequently, the method has gained foothold throughout the Western World, including Denmark, where it is generally performed for most revision procedures in a standardised uniform manner in accordance with the originally described method [97]. Intraoperative cultures have thus become a key element in most definitions of PJI (Table 3) [17, 21, 104, 121, 123, 124, 150, 158, 163, 178].

However, the sensitivity associated with the use of intraoperative cultures is notably lower than the corresponding specificity, especially when using growth in three out five biopsies as the criterion for PJI [105]. Furthermore, some intraoperative cultures may be false-negatives due to treatment with antibiotics prior to the revision [29, 166]. This may explain why most definitions of PJI employ the criterion that two out of five biopsies need to be positives (as opposed to three out of five) and combine intraoperative cultures with other diagnostic tests (Table 3). However, the lowering of the threshold to only two positive intraoperative cultures instead of three has been decided without any studies to underpin such change.

1.3.2 Laboratory test

Laboratory tests may be used to define PJI. Most definitions include the erythrocyte sedimentation rate and C-reactive protein level – together with white blood cell count [3, 125]. However, many different conditions produce an inflammatory response. These tests therefore have a rather low specificity and they are primarily used in the screening for PJI as they have a high sensitivity [16, 158].

1.3.3 Synovial fluid

Analysis of synovial fluid from the hip joint has been included in most definitions of PJI [125, 187]. Different analyses can be performed on the aspirated synovial fluid of which the most used are:

Direct visualisation of purulence: This test is always performed following aspiration, but is – naturally – a very subjective measurement.

Culture of synovial fluid: This test has been shown to have moderate sensitivity, but a high specificity [135].

Leukocyte esterase colorimetric strip test: This test functions by applying synovial fluid on a strip, with a detergent that lysis any neutrophils causing them to release the leukocyte esterase, which catalyses a reaction that leads to the formation of a dye. This test has a moderate sensitivity and a high specificity [179].

Synovial white blood-cell count: In this test, the number of white blood cells per µL of synovial fluid is counted. The test has a high sensitivity, but a low specificity [15, 189]. This test has the same limitations as histologic analysis (see below).

1.3.4 Histologic analysis

Histologic analysis, most often performed as an intraoperative histologic analysis of frozen sections of prosthetic tissue biopsies, has traditionally been used to determine whether a PJI was present or not [16, 21, 122, 124, 150, 158, 163, 166, 185]. The appropriate diagnostic thresholds for the number of polymorphonuclear leukocytes per high-power field for definition of a PJI are controversial [111], but the most thoroughly studied threshold is 5 to 10 in each of 5 or more high-power fields [168]. However, as is also the case with synovial white blood-cell count, the most crucial part of this test is the sampling of tissue or fluid and the examining pathologist's technique, experience and microscope.

1.3.5 Consensus on Prosthetic Joint Infection Diagnosis

A working group from the Musculoskeletal Infection Society developed a definition of PJI in 2011 [178], which was later modified and adapted by the International Consensus Meeting on PJI in 2013 [121] (Figure 2). However, this definition remains much debated [73, 118] and is not feasible for use in Denmark as four out of the five minor criteria require results from tests that are not routinely used in Denmark.

Although a considerable amount work has been done and conferences [122], consensus documents [121, 178] and guidelines [3] have been drafted, the orthopaedic community along with co-operating medical specialties still have a long way before an international consensus on the PJI diagnosis is achieved. Furthermore, though most of the principles from the previously mentioned definitions of a PJI can be applied, diagnosing a PJI in the clinic is something entirely different from studying PJI by exploring register data - and no PJI definition based on register data has yet been proposed.

PJI Is Present When One of the Major Criteria Exists or Three Out of Five Minor Criteria Exist

Major Criteria	Two positive periprosthetic cultures with phenotypically identical organisms, **OR** A sinus tract communicating with the joint, **OR**
Minor Criteria	1) Elevated serum C-reactive protein (CRP) **AND** erythrocyte sedimentation rate (ESR) 2) Elevated synovial fluid white blood cell (WBC) count **OR** ++change on leukocyte esterase test strip 3) Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) 4) Positive histological analysis of periprosthetic tissue 5) A single positive culture

Declaration: The consensus group wishes to state that PJI may be present without meeting these criteria, specifically in the case of less virulent organisms (e.g. *Propionibacterium acnes*). Thus, the clinicians are urged to exercise their judgment and clinical acumen in reaching the diagnosis of PJI.

Figure 2: Definition of prosthetic joint infection according to the International Consensus Group.

1.3.6 Classification of Prosthesis Joint Infection

Different classifications of PJI have been proposed based on the time that passes after primary THA during which PJI occurs, or based on symptom duration. The majority of PJIs occur within the initial postoperative months [95] and they are often the result of the introduction of bacteria during the prosthesis implantation procedure. These infections are often characterised as 'early' as opposed to 'delayed' and 'chronic', but a wide range of time intervals from surgery to onset of symptoms and symptom durations have been proposed (Table 4). As is the case for the definition of PJI, international consensus on the classification of PJI has yet to be reached.

1.4 SURGICALLY & NON-SURGICALLY TREATED PROSTHETIC JOINT INFECTION

PJI can be treated in a various ways, of which the most common are:

Debridement with exchange of liner and cup – or with retention of the entire implant (in case of a monoblock prosthesis) - is performed mainly in patients who acquire a PJI within the first months following their primary THA or in patients who acquire an infection at a later point time if the prosthesis is still fixed, as is occasionally the case in an acute haematogenous infection [74, 117].

The two-stage exchange is a procedure in which the prosthesis is removed and a new prosthesis is implanted after an interim period of weeks to months. This procedure has been considered the standard; although neither the revision procedures nor the interim period are complication free [49].

The one-stage procedure in which a new prosthesis is implanted immediately following removal and thorough debridement of the infected prosthesis and surroundings. The one-stage procedure has gained popularity in recent years as the risk of subsequent revisions may be similar to that of a two-stage revision [75, 83] and the process is less agonizing for the patient than the two-stage exchange with the long interim period [110].

A permanent resection can be performed if the patient is expected to have no or only limited mobility as the removal of the foreign body may improve the chances of curing the disease [186].

Life-long antibiotics can be used as a life-saving treatment. However, it has been proposed that antibiotics treatment without surgery will ultimately fail in most cases [38]. Therefore, suppressive antibiotic therapy is mainly used for patients who cannot accept any further operation or who have a high risk of mortality, and even then some might eventually be treated with some degree of surgery as the risk of failure is high [133].

1.5 TREATMENT OUTCOME FOLLOWING PJI

While the primary THA is a very successful and safe operation, this is not the case for the revision for PJI. Whether a one- or two-stage procedure is performed, the re-infection rate is approximately 8-10% [75, 83], and the risk of a secondary revision is considerable higher than for other indications such as aseptic loosening and dislocation (Figure 3). Moreover, revision for PJI is associated with a high risk of complications such as adverse effects following long-term treatment with antibiotics, i.e. diarrhoea, tendinitis, myelosuppression [154, 167], more unplanned readmissions to hospital [149], and a longer hospital stay following the revision [68].

1.6 MORTALITY OF PROSTHETIC JOINT INFECTION

The most feared complication following any operation is death. One previous study has shown that revision for PJI of THA and total knee arthroplasty is associated with a five-fold higher mortality than aseptic revisions [188]. Nevertheless, not all studies have found that revisions for PJI are associated with a higher mortality risk when compared with aseptic revisions [28, 171]. All three previously performed studies included both first-time and multiple revisions, and none of the studies had a maximum defined time interval of follow-up from implantation of primary THA. Including all these different types of revisions and different types of prosthesis may pose a problem as they differ on important parameters, e.g. acute and chronic PJI have different disease courses [116], THA and TKA are characterised by different incidences of PJI and length of stay [77, 134], and first-time and multiple revisions carry a different risk of subsequent revisions [5, 132].

Moreover, whereas it is difficult to alter the risk factors associated with a late haematogenous PJI prior to implantation of a primary THA, the risk of an early PJI can more easily be altered. A high mortality following an early PJI might motivate clinicians to pay extra attention to the risk factors of PJI in the discussion with the patient before the primary THA is performed.

Fitzgerald 1995	
Stage I: Acute postoperative infection	
Stage II: Delayed deep infection	6-24 months postopoerative
Stage III: Late hematogenous infection	
Tsukayama et al. 1996	
Early deep infection	<4 weeks postoperative
Late chronic infection	>4 weeks duration
Mcperhson et al. 2002	
Early postoperative infection	<4 weeks postoperative
Haematogenous infection	<4 weeks duration
Late chronic infection	>4 weeks duration
Zimmerli & Trampuz 2004	
Early	0-3 months postoperative
Delayed	3-24 months postoperative
Late chronic infection	>24 months postoperative
Senneville et al. 2011	
Acute	<1 months of symptoms
Chronic	>1 months of symptoms
Zimmerli 2014	
Acute haematogenous	<3 weeks of symptoms
Early postinterventional	<1 months postoperative
Chronic	>3 weeks of symptoms

Table 4: Classification of Prosthetic Joint Infection.

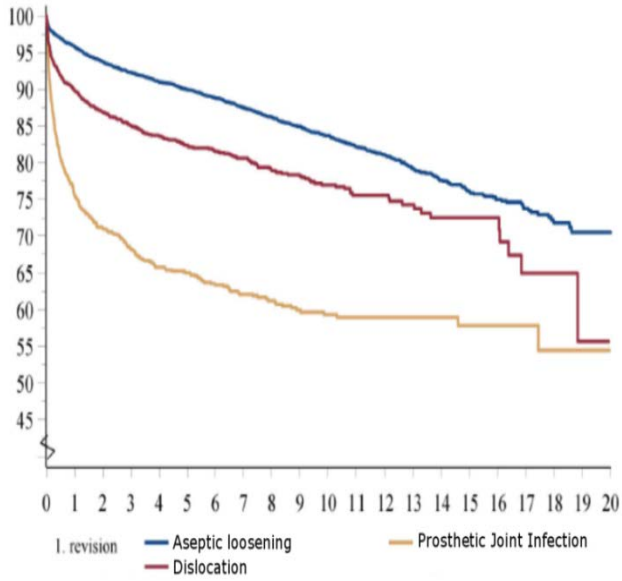

Figure 3: Risk of subsequent revisions following 1. revision. From the Danish Hip Arthroplasty Register, annual report 2014.

1.7 MOTIVATION FOR PHD THESIS

An ageing population and expanding indications for surgery have resulted in an increasing incidence of primary THA during the past decades in the Western World [76, 114, 155, 177]. However, as the incidence of primary THA has increased, so has the burden of complications [76, 78]. The most feared and devastating complication following primary THA is PJI and it is therefore essential that doctors and patients know how prevalent this complication is and if the risk of acquiring the infection is increasing [80], which is why this PhD study was initiated. Like for other infections, the conditions leading to PIJ and the incidence of PJI are constantly evolving, wherefore there is a need for a validated surveillance system. To this day, the only feasible manner in which PJI incidence may be studied on a national level in Denmark is through the use of the national registers. However, studies from other arthroplasty registers have shown that national arthroplasty registers such as the DHR often underestimate the incidence of PJI [41, 59, 62, 93], and no validation of the PJI data in the DHR has so far been performed. Therefore, a secondary aim of this thesis was to validate the PJI diagnosis in the DHR and to promote further development of the register, possibly in the form of linkage with some of the other Danish registers. Once validated, data from the register can be used to explore important research questions about trends in PJI incidence and mortality following revisions for PJI.

2. AIM OF THESIS

The overall aim of this thesis is to examine the incidence of PJI following primary THA and the mortality following a revision for PJI. Specifically, the aims of the four studies included in this thesis were:

Study I:

- To estimate the true incidence of first-time revisions for PJI following primary THA by using several data sources.

Study II:

- To validate the diagnosis of PJI reported to the DHR for first-time revisions by testing it against a reference standard.
- To investigate whether the accuracy of the diagnosis 'PJI' in the DHR could be further improved by linking the diagnosis to data from other databases.

Study III:

- To evaluate the trend in PJI incidence within one year of implantation of a primary THA during the 10-year period from 2005 to 2014, and to assess whether an increase in antimicrobial resistance may be observed that corresponds to the preoperative prophylactic antibiotics used in Denmark.

Study IV:

- To study whether revision for PJI within one year of the primary THA operation is associated with an increasing risk of one-year mortality.

3. METHODOLOGICAL CONSIDERATIONS

3.1 SETTING

All studies in this thesis use prospectively collected data from departmental, regional and national databases and registers. All healthcare contacts are free-of-charge for Danish residents (5.7 million), as the system is tax-supported and provided by the Danish National Health Service [91]. Therefore, all patients should have the same access and possibility of undergoing a primary THA operation for a painful hip joint and any subsequent revisions, which reduces the selection bias in our studies.

3.2 DATA SOURCES

The following presentation of data sources used in this thesis focuses on the quality of data and the limitations of the registers and databases in regards to PJI research. Data in the below-mentioned databases and registers can be linked through the use of the Danish civil registration number (Figure 4) [151].

3.2.1 The Danish Hip Arthroplasty Register (DHR)

The DHR is a clinical quality database that has served to continuously monitor and improve the quality of primary and revision THAs since 1995 [99]. Reporting to the register is compulsory for

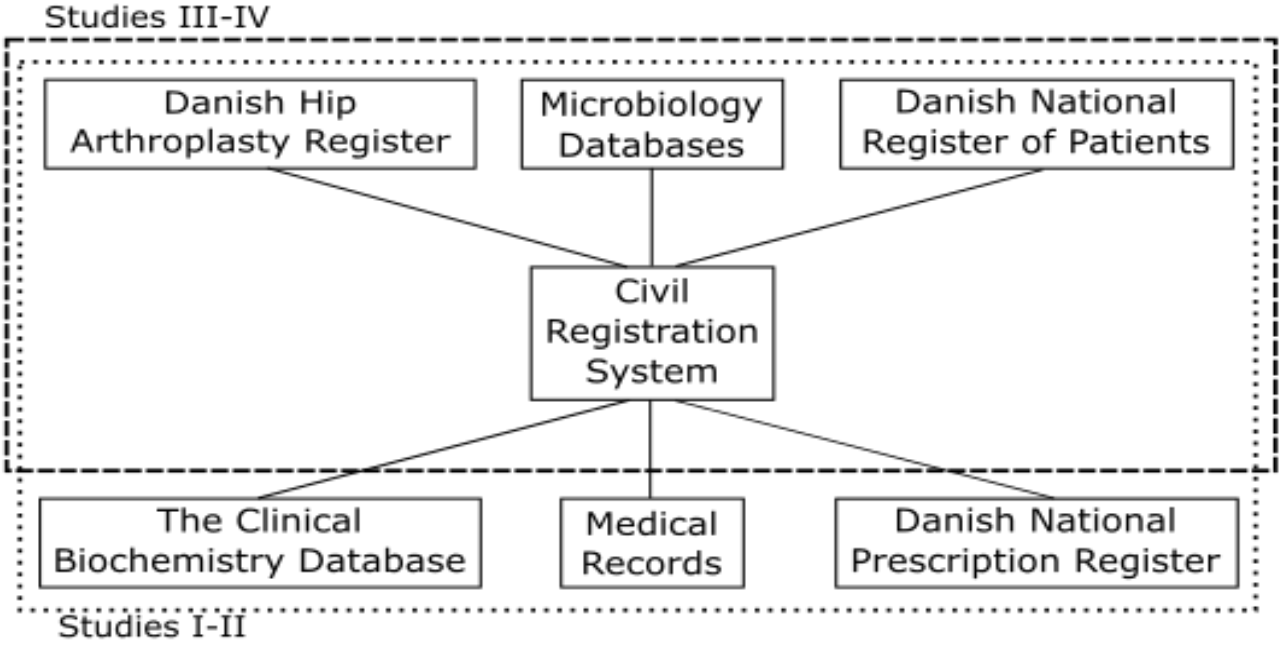

Figure 4: Data sources used in studies I-IV.

all orthopaedic departments in Denmark and is performed by the operating surgeon immediately after surgery. DHR data on primary THA diagnosis and postoperative complications have been validated, showing a PPV of 84% for the registered primary diagnosis [126].
The coverage of the DHR is almost complete as reporting is compulsory and only a very limited number of departments (3 departments in 2014, which performed a total of 58 primary THA [5]) did not report to the register. The completeness of the DHR is measured using the NRP as reference and has been above 90% for primary THA and 80% for revisions while the register has been operational [126]. A high completeness for both primary THA and revisions is essential when studying the absolute values of rare events, e.g. the incidence of PJI. When relative risk is described, a low completeness may not be equally important as long as the completeness does not differ among compared groups or time periods [157]. However, the completeness of both primary operations and revisions has increased in the course of the study period (Table 5).
The ICD-10 codes used in the NRP, to which data in the DHR are compared for calculation of completeness, are either "secondary prosthetic replacement of hip joint" (NOMESCO [4]: KNFC2, KNFC3, KNFC4) or "removal of prosthesis from hip joint" (NOMESCO [4]: KNFU10, KNFU11, KNFU12, KNFU19) [5]. Some procedures that are typical of revisions for PJI – e.g. debridement – are reported to the DHR, but a corresponding NOMESCO code is not used in the calculation of DHR completeness, which may lead to an overestimation of completeness. However, the number of reported debridements to the DHR is very limited and should not have a significant effect on the completeness estimate.

Completeness of Primary THA in the DHR					Completeness of revisions in the DHR				
year	Jutland + Funen Completness	Studies No.	Denmark Completness	Study No.	year	Jutland + Funen Completness	Studies No.	Denmark Completeness	Studies No.
2005	91.3%	Study I-IV	91.3%	-	2005	75,8%	I-IV	75,5%	
2006	91.6%	Study I-IV	90.7%	-	2006	78,3%	I-IV	77,9%	
2007	97.3%	Study I-IV	94.6%	-	2007	87,3%	I-IV	83,2%	
2008	96.9%	Study I-IV	95.5%	-	2008	85,2%	I-IV	85,0%	
2009	97.6%	Study I-IV	96.7%	-	2009	85,7%	I-IV	82,1%	
2010	97.5%	Study I-III	97.2%	Study IV	2010	85,0%	I-III	82,8%	IV
2011	93.1%	Study I-III	96.8%	Study IV	2011	86,8%	I-III	85,6%	IV
2012	97.2%	Study I-III	97.6%	Study IV	2012	90,9%	I-III	92,0%	IV
2013	96.4%	Study III	97.9%	Study IV	2013	90,4%	III	91,3%	IV
2014	98.8%	Study III	97.8%	Study IV	2014	91,1%	III	92,0%	IV
2015			97.5%	Study IV	2015			97,5%	IV

Table 5: Completeness of primary Total Hip Arthroplasty (THA) and revisions, reported in the Annual Report.

3.2.2 The National Register of Patients (NRP)

The NRP was established in 1977 and holds data on non-psychiatric in-hospital admissions and surgical procedures. The diagnoses are assigned by the discharging physician. Diagnoses are recorded in accordance with the International Classification of Diseases (ICD), 8th Edition until 1994, and 10th Edition thereafter [152]. Data from the NRP were used in this thesis to identify patients who had undergone revision for PJI (Study I) and to determine the Charlson Comorbidity Index (Study III-IV), which is a score that predicts the mortality risk based on a weighted range of comorbidities [24]. The score has subsequently been adapted for use with hospital discharge data [136].
The coverage and completeness of the NRP are very high as departments are reimbursed by the national health authorities according to their registrations, but it has, nevertheless, been estimated that 5% of all operations are missing from the registers [101]. The size of this figure is supported by the fact that some primary THA and revisions that are reported to the DHR cannot be found in the NRP. The procedure codes most commonly used for revisions have not been validated individually, but orthopaedic procedures generally have a PPV [86, 152]. The PJI diagnosis code in the NRP has been validated, and if combined with a surgical procedure code – as was the case in this thesis – the PPV was found to be 86% (95% CI: 80; 91) [82]. The diagnosis codes in the NRP used for the Charlson Comorbidity Index score have all been validated and have a high PPV [165].

3.2.3 The Civil Registration System

All Danish citizens are assigned a unique and unchangeable ten-digit identification number at birth or immigration, the Civil Registration Number. The number encodes for sex and date of birth. As registration of the number is compulsory for all healthcare contacts, it is possible to link all Danish registers and databases on an individual level. Foreigners are assigned a temporary civil registration number, but these temporary civil registration numbers were excluded from the studies when compiling the data for this thesis. The civil registration number allows for complete follow-up of all patients, except those who emigrate. The prevalence of disappearing persons is approximately 0.3% [151].

3.2.4 Microbiology Databases

Prior to 2010, all clinical departments of microbiology maintained an electronic laboratory information system. In the Central Denmark Region and in the Region of Southern Denmark, the information system MADS is used [6], while the ADBakt information system is used in the clinical microbiology department in Aalborg [1]. Both systems electronically transmitted the culture results of intraoperative tissue samples and synovial fluid analysis to the re-

questing hospital department and store the information automatically in the databases. Therefore, completeness and coverage should be complete, but no studies have investigated this.
As of 1 January 2010, all Danish departments of microbiology make an electronic copy of the report that is sent to the requesting hospital department. This electronic copy is automatically sent to the national Danish Microbiology Database (MiBa), which is updated continuously throughout the day [170]. Contrary to the local laboratory information systems, which contain results on all analyses performed, the MiBa holds information only on results that have been sent to the requesting hospital department. The implication of this is that only information relevant for the treatment of the specific patient is included and that treatment can be restricted in accordance with the departments' antibiotic policies. One validation study investigating the data in the MiBa database has already been conducted [14].
A limitation of the microbiology databases, including the MiBa, is that a uniform protocol has not been in place for obtaining samples during revision or microbial analysis of intraoperative cultures, synovial fluid or antimicrobial susceptibility testing in all the involved clinical microbiology departments [85]. Although most bacteria would be identified within the first 4-5 days of incubation [153], some bacteria may require longer incubation periods to be identified [22], but there is no consensus on the length of incubation of intraoperative cultures in Denmark. Another limitation is that the different departments used different codes in their laboratory information systems prior to 2010. Moreover, a transition in both the antibiotic susceptibility testing and the categorisation of antimicrobial resistance was implemented independently in each department during the first few years of the study period. Since the completion of the transition, all departments have been following the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [164] and code antimicrobial resistance as "susceptible," "intermediate" or "resistant" (SIR) [145].

3.2.5 Medical Records

Information was primarily extracted from the electronic forms of the medical records. In Denmark, the electronic medical record began as a project initiated by the Danish Health Authorities in 1996 [35], but the project has encountered various problems and not all hospitals had introduced the electronic medical record at the time Study I was conducted. Furthermore, none of the private hospitals had accessible electronic medical records. Therefore, information was extracted from paper medical records where electronic forms of the record were not available. Different procedures could cause selection bias if extracting information from one data source (e.g. paper medical record) was more difficult than extracting data from the other. However, it was possible to identify and extract information from all the medical records that were identified, so this should not be a cause of bias.

3.2.6 The Danish National Health Service Prescription Database

The registers contain information on all prescription drugs redeemed since 2004 [64]. The data in the Danish National Health Service Prescription Database were validated in a recent study, which found a high PPV, but a sensitivity between 64.6% and 91.8% [139]. It should be noted that the proportion of non-electronic prescriptions has been decreasing during the study period, which may cause the validity to change with calendar time [139]. A limitation of the prescription register is that only redeemed prescriptions are registered. If a patient does not fill a prescription, this is not recorded; likewise, drugs dispensed at hospitals for outpatient treatment are not registered. Therefore, information on antibiotics treatment was also extracted from the medical record for those patients whose medical record we reviewed. Another limitation is that we have no measurement of the patients' compliance, i.e. whether they took the prescribed medicine and whether they took it in the recommended doses and at the recommended points in time.

3.2.7 The Clinical Biochemistry Database

Results of analysed blood samples were either extracted from the local databases maintained by the departments of clinical biochemistry at the hospital in the region of Southern Denmark or from the Clinical Laboratory Information System database at Aarhus University, Denmark (LABKA), which holds results from every blood sample taken in the North Denmark Region and the Central Denmark Region [53]. When a blood sample has been analysed, the results are transmitted electronically and automatically stored in the databases. Therefore, the only C-reactive protein tests not included in this thesis were the point-of-care C-reactive protein tests that provide users with an instant analysis and which are primarily used by general practitioners.

3.3 STUDY DESIGN AND STUDY POPULATION

All four studies were population-based cohort studies in which primary THA reported to the DHR was the exposure, except for the second analysis in Study IV, in which the exposure was first-time revision reported to the DHR (Table 6).
We chose not to include primary THAs that were reported only to the NRP in any of the studies as this would have resulted in different variables being available for analysis. Only patients operated with a primary THA in Jutland or Funen (comprising 3.0 million out of the 5.7 million inhabitants of Denmark) were included in Studies I-III as information from some of the databases used outside these areas was not accessible for data extraction prior to 2010. In Study IV, we included patients with a primary THA performed in Jutland or Funen between 1 January 2005 and 31 December 2009 or in Denmark between 1 January 2010 and 31 December 2014.
If a revision had been performed outside of Jutland and Funen on a THA that was included as an index operation, all necessary information was extracted manually, ensuring that all data regarding tests performed in relation to a revision (e.g. intraoperative cultures, laboratory test, etc.) were equally available for all patients, regardless of where the revision had been performed.

3.3.1 Definition of Revision

Only surgically treated PJI were evaluated in this thesis. A recent study from the Swedish Hip Arthroplasty Register found that 91% of the PJI included in that study were treated with a revision [95]. We chose not to include non-surgically treated PJI in this thesis as non-surgically treated PJI is even more difficult to diagnose than surgically treated PJI. Furthermore, the PJI that can be treated without revision is probably less severe that PJI that requires surgical treatment. Although this causes an underestimation of the incidence of PJI, the clinical difference for the patient between a revision for PJI and an antibiotically treated PJI makes this separation of the two treatments meaningful.
A reoperation is generally defined as any subsequent surgery following the primary operation, while a revision has been defined as surgical exchange or removal of a prosthesis or part of it. Arthroplasty registers have generally distinguished clearly between

revisions and re-operation, as one of the more important aims of the registers has been to evaluate the prognosis of different brands and designs, and for that purpose revision surgery only is of interest. In the DHR, it is possible to report debridement without removal of the prosthesis or part of the prosthesis, and these debridement procedures count in the annual estimation of revisions rates, although the number of reported debridements has been very small and is possible also underestimated. In regards to research on the incidence of surgically treated PJI, it makes sense to include debridement as the procedure does not differ in the patient's perspective from a one- or two-stage revision; and the prognosis following debridement versus one- or two-stage revision is comparable if not inferior to the prognosis following revision [72].

3.4 STUDY I: "TRUE" INCIDENCE OF PROSTHETIC JOINT INFECTION

For index surgery, we only included primary THA reported to the DHR (Table 6); but for subsequent first-time revisions, we extracted data from both the DHR and the NRP in order to augment the completeness of our revision data. As previously mentioned, the completeness of the DHR is measured using the NRP as a reference with a pre-defined number of ICD-10 codes used as the definition for a subsequent revision.

Originally, we planned to use these ICD-10 codes for our definition of a first-time revision in the NRP, but during the process we learned that they were not extensive enough as procedures often used in early revision for PJI surgery in particular were not included. Therefore, an extension of the ICD-10 codes defining a first-time revision was used herein (Table 7).

	Study I	Study II	Study III	Study IV	
				Analysis I	Analysis II
Index operation					
- Primary THA	x	x	x	x	
- First-time revision					x
Time Period for index operation	01.01.2005-31.12.2011	01.01.2005-31.12.2012	01.01.2005-31.12.2014	01.01.2005-31.12.2014	01.01.2005-31.12.2015
Exclusion criteria					
>1 report on primary THA*	x	x	x	x	x
Missing/incorrect reporting of:					
- Civil registration number	x	x	x	x	x
- Side of operation	x	x	x	x	x
- Date of surgery	x	x	x	x	x
- Indication for revision	x	x			
End of follow-up					
-First-time revision	x	x	x		
-Death	x	x	x	x	x
-Emigration	x	x	x	x	x
-1 year from index operation			x	x	x
-End of follow-up period	31.12.2012	31.12.2012			

THA: Total Hip Arthroplasty

DHR: Danish Hip Arthroplasty Register

* Per civil registration number and reported side of operation

Table 6: Study population of Study I-IV.

3.3.2 Classifications of PJI

Besides the lack of consensus on the classification of PJI as early, delayed, chronic or acute, etc., another problem with the classification is that the time of onset or the duration of symptoms may be interpreted differently by patients and physicians, respectively, and neither is recorded in the DHR or the NRP. Therefore, none of these classifications were used in this thesis. Only first-time revisions for PJI were included as subsequent revisions have a very different risk and outcome than first-time revisions do [5]. If the revision surgery was conducted in two stages, we included only the first procedure in which the THA is removed.

3.4.1 Diagnosis of Prosthetic Joint Infection

One of the more important aspects to keep in mind before estimating the incidence is to have a clear definition of the disease. In the present study, a new definition of PJI was composed as none of the previous definitions were suitable for use in a register setting. Moreover, consensus is still lacking on any of the previously mentioned definitions (Table 3), and none of the existing definitions are applicable to Danish conditions, as e.g. histological analysis is rarely performed in Denmark.

We developed an algorithm for classification of revisions as either due or not due to PJI (Figure 5). In order to make the algorithm applicable to a register setting in Denmark, we included only tests

ICD-10 code	Diagnosis	Completeness analysis in the DHR	Included in study I-II
KNFC2-4	Revision with secondary insertion of hip prosthesis	x	x
KNFC59	Secondary implantation of interposition prosthesis in hip joint		x
KNFC99	Other secondary prosthetic replacement in hip joint		x
KNFU10	Removal of total prosthesis from hip joint, All parts	x	x
KNFU11	Removal of total prosthesis from hip joint, Single part – proximal	x	x
KNFU12	Removal of total prosthesis from hip joint, Single part – distal	x	x
KNFU13	Removal of total prosthesis from hip joint, Single part – other		x
KNFU14	Removal of total prosthesis from hip joint, More than one, but not all parts		x
KNFU19	Removal of total prosthesis from hip joint, Other or unspecified	x	x
KNFG09	Excision arthroplasty of hip joint		x
KNFG19-29	Other secondary prosthetic replacement in hip joint		x
KNFG39-59	Fusion of hip joint		x
KNFW69	revision because of deep infection		x
KNFS19	Incision and debridement of infection of hip joint		x
KNFS49	Incision and debridement of infection of hip joint with introduction of therapeutic agent		x

Table 7: ICD-10 codes used in our analysis of the completeness analysis of the Danish Hip Arthroplasty (DHR) and to define a revision in

that were routinely or commonly performed in Denmark. This excluded a number of tests which have otherwise often been used in definitions of PJI including: erythrocyte sedimentation rate, leukocyte esterase colorimetric strip test, synovial white blood-cell count and histologic analysis. Similarly, excluded from the algorithm were new methods which were available only in the final years of the study period or used only in some departments, e.g. sonication of prosthesis and test for procalcitonin and alpha-defensin.

3.4.2 Algorithm for Classification of Revisions Due to PJI and Non-PJI

A: Intraoperative Cultures:
We defined a surgically treated PJI as three or more out of five intraoperative cultures showing growth of the same virulent or opportunistic pathogen. The criterion of three instead of two cultures is in contrast to most other definitions (Table 3), but was chosen to achieve a high specificity [13, 67, 105] which we believe is required as this is a register-based definition without any additional information on the patients and as we had no knowledge of pre-test probability. The resulting low sensitivity was addressed by further investigating the revisions that did not fulfil this criterion.
Besides the number of positive intraoperative cultures, on which most definitions of PJI are based, the type of bacteria identified is also of importance. The most commonly identified bacteria are *staphylococcus aureus* and coagulase-negative staphylococcus [92], which are almost always of clinical importance, while other bacteria might be of more questionable relevance as some are more likely to be due to contamination [58, 113, 147]. Clinical relevance of the identified bacteria should be considered when establishing a definition of PJI, but clinical relevance has only rarely been addressed in definitions of the PJI diagnosis. We classified the identified bacteria as virulent, opportunistic and spore-forming or of questionable significance; and we included bacteria only of the virulent and opportunistic groups (Appendix Micro-organisms).

B: Classification of Non-Infected Revisions
For the next step in the algorithm, we wanted to classify those revisions that could be defined as non-infected with a high degree of certainty, i.e. a high specificity. Therefore, we set up a number of criteria that should all be fulfilled for the revisions to be classified as non-infected, including ≥5 intraoperative cultures being without any growth, which could not be a result of antibiotics treatment within 14 days prior to revision. The criteria were based on studies which have established that no positive intraoperative cultures in a sample of five have a high negative likelihood ratio [13, 166], unless the patient was treated with antibiotics prior to revision [103, 166].

C: Sinus Tract
Description of a sinus tract is a subjective measurement, and as previously described it can occasionally be difficult to distinguish a suppurating wound from a sinus tract [45]. Therefore, we conducted a thorough examination of the medical records and included only those with a clear description of a fistula between the skin and the prosthesis.

D: Audit
As the remaining part of the algorithm was based mainly on the number of positive intraoperative cultures, we performed an audit if more than five intraoperative cultures were taken as growth in one or two cultures in a large number of samples has a higher risk of being a result of chance. The classification of these revisions was, of course, subjective in nature. Nevertheless, the risk of misclassification should be minimal as all authors classified the revisions independently based on information on intraoperative culture growth, preoperative antibiotic treatment, results from aspiration of synovial fluid, C-reactive protein level and description of purulence in the joint.

E: C-reactive Protein Level
A C-reactive protein level of 10 mg/L has a very high sensitivity and a low specificity [150, 180], which is why a negative result

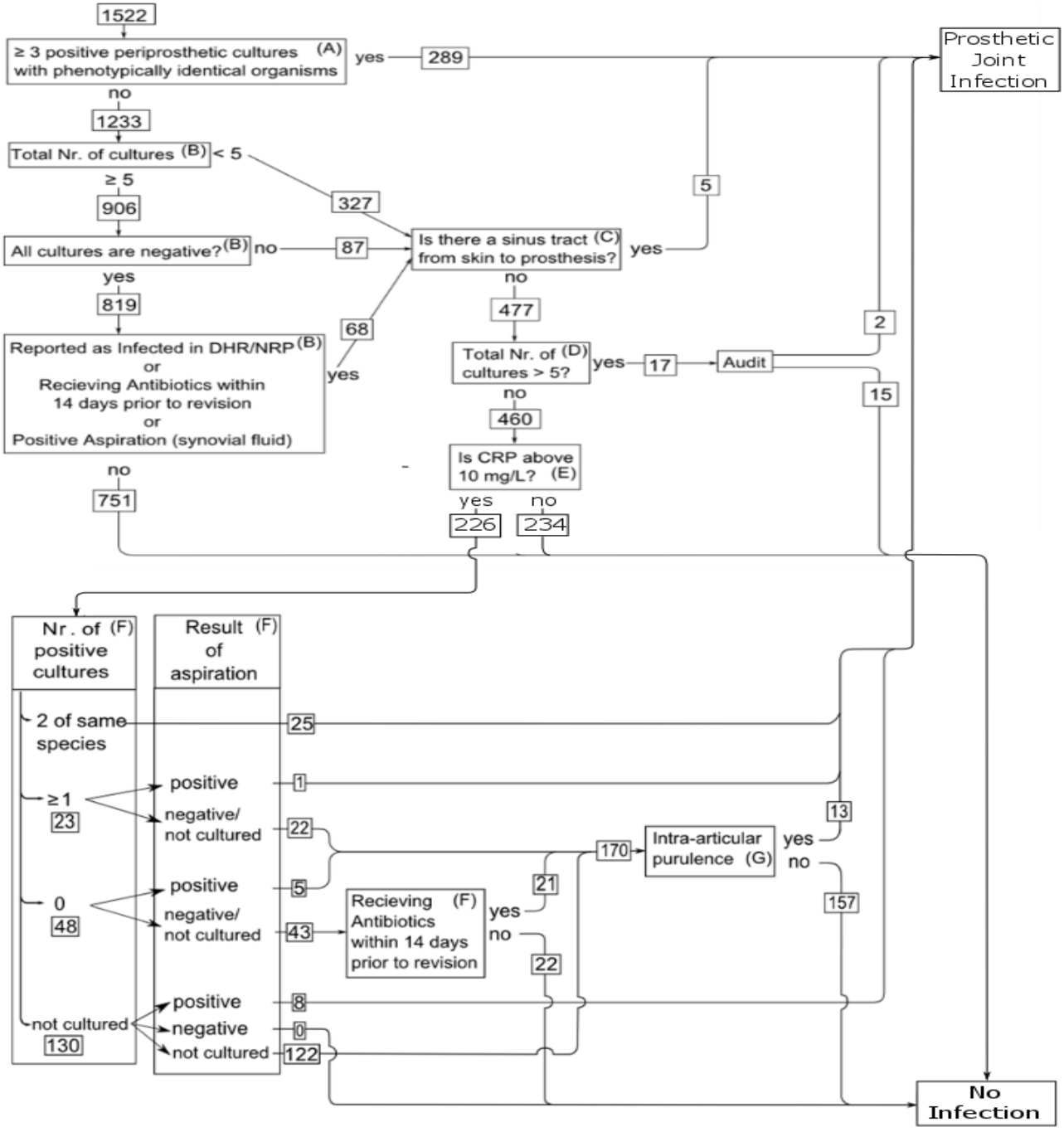

Figure 5: Algorithm for classification of revisions due to prosthetic joint infection and no infection.

was used to rule-out infection. In case of a positive result within 30 days prior to revision, further tests were performed. The revisions, in which a C-reactive protein had not been measured prior to the revision, were also classified as non-infected, although this gives the same status to a negative and a missing test, which might be questionable. However, if there is even a minor risk of a PJI being the indication for revision, most surgeons would perform blood sample analysis.

F: Growth in Less Than Three Intraoperative Cultures

If the C-reactive protein level was elevated, the revision was classified as due to PJI provided ≥2 intraoperative cultures of the same pathogen tested positive. As aspiration has a high specificity and a moderate sensitivity [135], it was combined with the results of intraoperative cultures and purulence whenever possible to classify the revision. If all cultures were negative, the revision was classified as non-infected, unless the negative results could be due to antibiotic treatment prior to the revision.

G: Purulence

Purulence is a subjective measurement which can be caused by other conditions than PJI [20, 108]. Purulence was therefore regarded as a pathognomonic sign of PJI only if the C-reactive protein level was elevated and the results of intraoperative cultures

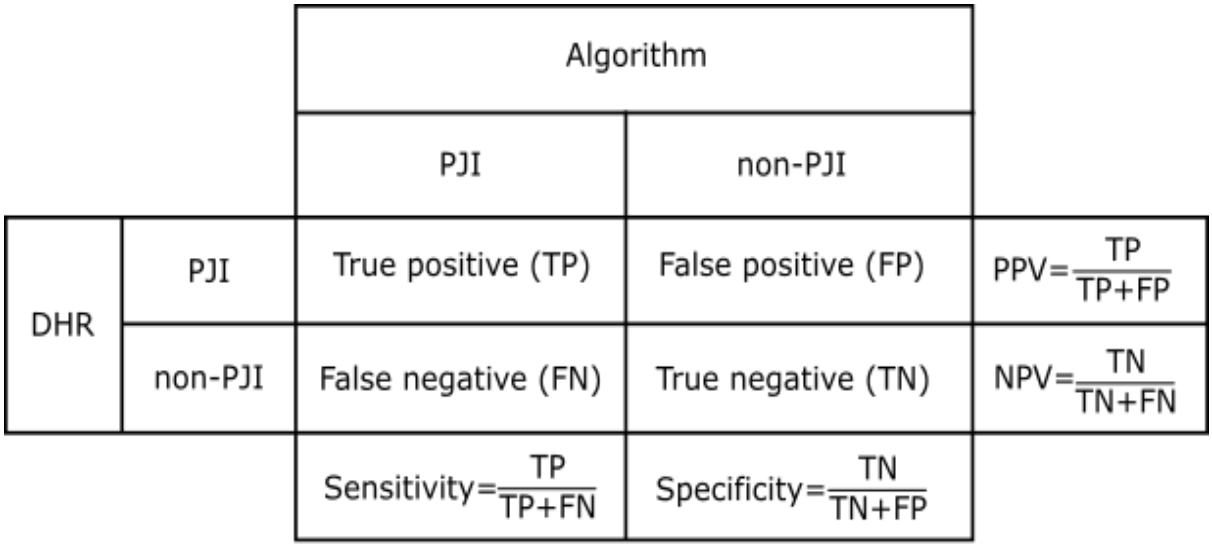

Figure 6: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the prosthetic joint infection (PJI) diagnosis in the Danish Hip Arthroplasty Register (DHR). Revision reported to the National Register of Patients exclusively, would be categorised as either FN or TN.

and aspiration of synovial fluid were inconclusive, e.g. due to preoperative antibiotic treatment. Besides being subjective by nature, the usefulness of the test also depends on the surgeon's description in the medical record. This caused us to define purulence rather strictly, and we did not include description of inflammatory tissue or blurred synovial fluid in our definition.

3.4.3 Outcome of Study I

The outcome of Study I was first-time revision for PJI as defined by the algorithm. We reported the 1- and 5- year incidence of first-time revision for PJI, which were compared with the incidence reported by the DHR and the NRP.

3.5 STUDY II: VALIDATION OF THE DIAGNOSIS PROSTHETIC JOINT INFECTION

When clinical databases are used in research, two issues should be considered when evaluating the quality of the data: validity and completeness [48]. Completeness has previously been addressed in the discussion of the DHR as a data source.
Validity is defined as the percentage of cases in a register with a given characteristic which "truly" has this attribute. Validity can be assessed by various methods [48]:

- The diagnostic criteria method: the number of cases that meet stringent criteria when thoroughly examined (e.g. examination of x-ray showing sequelae of a collum femoris fracture).
- The re-abstracted record method in which the medical record is re-examined and compared with the register record.
- The internal consistency method: Examination of records to check for legitimate codes (e.g. sex can only be male/female).

In the Nordic arthroplasty registers, the validation procedure for primary diagnosis, date of surgery and reoperation was primarily the re-abstracted record method whereby data of the Nordic registers were compared with data in other databases and data from a review of medical records [12, 126, 156]. This method is not applicable for validation of the PJI diagnosis for two reasons. First, diagnosing often requires multiple test results that are not always recorded in the medical record; second, because of lack of consensus, the interobserver variability is of a considerable magnitude.
Preferably, the reference standard of PJI diagnosis should be based on objective measurements and evidence-based tests, i.e. a diagnostic criteria method should be used. In regards to PJI, the diagnostics criteria method is hampered by a lack of consensus on the criteria of the PJI diagnosis, and the diagnostic criteria should therefore be based on the most objective, evidence-based and physician-endorsed test and methods. As reference standard, we used the algorithm developed in Study I.
One major consideration with Study II was whether the revisions reported to the NRP but missing in the DHR should be included in the validation analysis. Inclusion of these revisions would affect the sensitivity estimate and possible also the specificity, while the PPV and most likely also the NPV would remain unaltered as the missing revisions in the DHR would be categorised as false negative and true negative (Figure 6). We decided not to include the revisions that were only reported to the NRP as the sensitivity would then have been dependent on the completeness of the register, which has changed in the course of the study period (Table 5).

3.5.1 Linkage With the Microbiology Databases

Linkage was performed between the DHR and the microbiology databases to investigate whether this combination of data would increase the accuracy of the PJI diagnosis. For this linkage, we defined a revision as due to PJI if three or more intra-operative samples showed growth of the same virulent or opportunistic micro-organism, or if PJI was registered in the DHR as the indication for revision (the micro-organisms that were classified as virulent and opportunistic can be found in the appendix Micro-organisms). If five or more intraoperative cultures were negative on culture, or if PJI was not reported as the indication for revision in the DHR, then the revisions were classified as non-PJI. The revision was also classified as non-PJI if PJI was reported as the indication for revision, but five or more intraoperative-cultures were negative on culture.

We decided to link the DHR with the microbiology databases rather than with the DHR and other databases, because intraoperative culturing was the test that ensured the highest sensitivity and specificity among the tests routinely performed in Denmark. The accuracy of the diagnosis could probably have been enhanced further if additional linkage with the prescription databases and clinical biochemistry databases had been performed. However, as extraction of data from these databases is very labour-intensive and time-consuming, we chose not to include them, given that the aim was to develop a method that was based on easily accessible data of high accuracy and which could be used in further studies of PJI.

3.5.2 Outcome of Study II

The outcome of Study I was first-time revision reported to the DHR due to any reason. The indication reported to the DHR was dichotomised into PJI and non-PJI and was measured against the reference standard defined by the algorithm developed in Study I. To evaluate the quality of the reported PJI diagnosis to the DHR, we calculated the PPV, NPV, sensitivity and specificity.

3.6 STUDY III: CHANGES THE IN INCIDENCE OF PROSTHETIC JOINT INFECTION

In order to study whether the incidence of first-time revision for PJI within the first postoperative year following primary THA increased during the 10-year study period, we estimated the relative risk of undergoing first-time revision for PJI during the last 5 years of the study period (1 January 2010 to 31 December 2014) versus the first 5 years of the study period (1 January 2005 to 31 December 2009). We used the validated definition of PJI developed in Study II. In addition to this, the relative risk between the two time periods was also estimated using data from the DHR exclusively and data from the microbiology databases exclusively.
To describe the development in antimicrobial resistance of bacteria during the study period, we identified the five most common species of bacteria found in intraoperative cultures taken during revision surgery and evaluated their change in antimicrobial resistance pattern. The most likely time period during which an increasing antimicrobial resistance would have an effect on the risk of PJI is at the time of implantation of the primary THA when prophylactic antibiotics are administered. Therefore, we included those PJIs only which were diagnosed within one year of implantation and tested only those antibiotics that were most commonly used as preoperative prophylaxis (i.e. cefuroxime and dicloxacillin) at the implantation of the primary THA, or used in the cement for fixation (i.e. gentamicin). Changes in antimicrobial resistance can, of course, occur in other than the five most commonly isolated bacteria; and previous studies on antimicrobial resistance in bacteria isolated from revisions for PJI have, indeed, included all bacteria [100, 160]. However, changes in the antimicrobial resistance of bacteria that are infrequently identified in revision for PJI are most likely not the cause of an increase in the incidence of PJI.
The susceptibility of bacteria was defined by the EUCAST SIR classification which was dichotomised into susceptible or resistant. Dichotomising of the EUCAST SIR meant that the bacteria, which were classified as “intermediate” would be grouped as either "susceptible" or "resistant”. The “intermediate” category is often defined as including bacteria with an antimicrobial agent minimum inhibitory concentration (generally abbreviated MIC) that approaches the usually attainable blood and tissue levels and for which response rates may be lower than those for susceptible bacteria [174], i.e. the bacteria can be susceptible for the antibiotic if a higher-than-normal dose is used [169]. We choose to group “intermediate” with “resistance”, as a higher-than-normal dose is rarely used in preoperative prophylactics and would unlikely be achieved locally at the implantation site. Previous studies of antimicrobial resistance in PJI research have also combined the “intermediate” and the “resistance” groups [100].

3.6.1 Outcome of Study III

The outcome was first-time revision for PJI within one year following primary THA. For changes in antimicrobial resistance, the outcome was the susceptibility (susceptibility or resistant) of the five most commonly identified bacteria.
We reported the relative risk between the two five-year time periods 2005-2009 and 2010-2014. For changes in antimicrobial resistance, we reported the probability of a change between the two five-year periods.

3.7 STUDY IV: MORTALITY FOLLOWING REVISION FOR PJI

3.7.1 Relative Risk of Mortality Following Revision for PJI Versus Reference Population

In this analysis, a cohort of primary THA was followed from the time of implantation to death. The cohort of primary THA was divided into two groups: 1: Patients who were surgically treated for a PJI within one year of their primary THA, hereafter referred to as the PJI group; and 2: Patients who were not surgically treated for a PJI, hereafter referred to as the reference population. Some of the patients in the latter group did undergo a revision for other causes than PJI. We estimated the relative mortality risk of patients in the PJI group compared with the reference population. One problem with this analysis was that in order to acquire a PJI, patients in the PJI group needed to live long enough to develop the PJI and then be surgically treated for the infection. This could cause so-called immortal bias as patients who acquire a PJI are methodologically immortal from the time of implantation of primary THA until the PJI is surgically treated. Various methods can be used to adjust for this problem [183]; the most simple of these methods is to disregard the first period of follow-up until a point in time when the majority of PJI are likely to have occurred. However, this simple method excludes those patients who have a high risk of mortality, causing the relative risk to be underestimated. We chose a different method called the illness-death model in which a time-dependent variable for the revision of PJI was introduced and the time period from primary THA to revision for PJI was classified as non-PJI time [183]. In our setting, the problem with this model is that we only used one year of follow-up, beginning at time of primary THA. Therefore, patients with a revision for PJI were followed for a shorter period of time which meant that those patients who acquired a PJI at the very end of the first year only had very little time in which there was a probability that death could occur. This could cause the mortality risk to be underestimated for patients who had undergone a revision for PJI. However, as most PJI occur within the first few months, we considered the risk of underestimation to be very limited.

3.7.2 Relative Risk of Mortality Following Revisions for PJI Versus Aseptic Revision

In the second analysis, we compared the mortality risk following a revision for PJI within one year of primary THA with the mortality risk following an aseptic revision within one year from primary THA. In this second analysis, follow-up time was initiated at the

date of revision and patients were followed until death, emigration or a maximum of one year of follow-up. Follow-up was limited to one year from the date of revision because the effect of PJI on mortality was assumed to be highest in the immediate period following surgery, and a 1-year period would therefore be the most clinically relevant result.

Revisions for PJIs were defined using the validated definition developed in Study II.

3.7.3 Outcome of Study IV

The outcome was death within one year of primary THA or within one year of revision surgery.

3.8 CONFOUNDERS

An observational study is the only possible design for the investigation of incidence and trends of incidence (Study III). The ideal method of studying whether revision for PJI was associated with an increased risk of mortality (Study IV) would be to randomise patients to either acquire a PJI or remain uninfected. Evidently, such a design is unethical and therefore impossible. Instead, an observational study can be performed in which patients who sustain a PJI are compared with patients who do not. The weakness of observational studies is the risk of potential confounders which must be thoroughly controlled for. A confounder is a risk factor that can cause the outcome of interest (PJI or death) and which correlates with the exposure, without being affected by the exposure (primary THA or revision surgery) and is unequally distributed between the compared groups thereby causing a mixing of effects [146].

Risk factor	Scale	Study III	Study IV	
			Primary THA versus PJI revision	Aseptic revision versus PJI revision
Comorbidity	Charlson comorbidity index: 0-1, 1-2, ≥3	x	x	x
Age	Continous	x		
Age	<60 years, 60-70, 70-80, >80		x	x
Sex	Female/male	x	x	x
Indication for primary THA	Primary osteoarthritis Traumatic Non-traumatic avascular femoral head necrosis Inflammatory arthritis Congenital hip disease	x		
Duration of primary THA operation	<60, ≥60 minutes	x		
Duration of revision surgery	<60, ≥60 - <90, ≥90 - <120, >120 minutes			x
Fixation technique	Cemented Cementless Hybrid Other	x		
Operating theatre	Conventional Laminar airflow ventilation	x		
Primary THA preoperative antibiotics prophylaxis	Cefuroxime Dicloxacillin Other	x		
Number of secondary revisions	0, 1, ≥2			x

Table 8: Confounders adjusted for in Study III and IV.

A number of risk factors for PJI have been identified. These risk factors can be divided into:

Patient-related risk factors, e.g.**:** comorbidity [115, 128, 140], age [33, 77, 143], male sex [32, 61, 140], indication for primary THA [32, 128, 142], weight/BMI [39, 98], smoking [36, 107] and alcohol consumption [52].

Surgery-related risk factors, e.g.**:** fixation technique [33, 57], duration of surgery [115] and antibiotic prophylaxis [8, 40].

Organisation-related risk factors, e.g.: hospital and surgeon volume [71].

In Studies III and IV, a number of confounders were identified and adjusted for (Table 8).

As some of these risk factors are not reported in all register, the registers need to be merged to perform this analysis. Furthermore, some important risk factors that are not reported in any of the Danish registers cannot be adjusted for, e.g., weight/BMI and smoking.

There is a risk of bias as some risk factors are easily identified and studied because information on these risk factors is readily available in registers, e.g. fixation technique [32, 33, 57, 128], whereas other factors, e.g. malnutrition, are not recorded in most registers and have been studied less exhaustively [9, 54, 181]. Moreover,

the lack of consensus on the PJI diagnosis and the resulting different PJI definitions used in these studies hampers the interpretation of the findings [148]. Furthermore, some studies find an association with a risk factor and PJI that other studies do not, e.g. cementless fixation [33, 57, 128], and some risk factors are time-dependent, e.g. one study found that advanced age is a risk factor within the first year, but not after the first year [31].

3.9 STATISTICS

Time-to-event analysis has traditionally been performed using the Kaplan-Meier method [137]. This method was originally designed to study events that would eventually occur for all patients in a study population [70]. As death is such an event, we used the Kaplan-Meier method to estimate patient survival following primary THA and revisions in Study IV.

In studies of PJI, not all primary THA will eventually experience a first-time revision for PJI because competing events that preclude the revisions for PJI might occur, e.g. death or revisions for other causes. In studies in which competing events are present, the Kaplan-Meier method is inappropriate as it overestimates the probability that the event of interest will occur with time [79], though some argue that the overestimation is not clinically relevant [47], especially not from the patient's view [138]. However, in studies with competing events, a more accurate method of estimating the risk of an event of interest is the cumulative incidence function [50]. As primary THA is most frequently performed in older patients who have a high risk of death, we used the cumulative incidence function in Study I.

The problem with competing risk is also present when estimating the relative risk between two groups. The hazard rate ratio of Cox regression analysis [30] can be interpreted as a measure of relative risk of a rare event [159], such as PJI, but is less appropriate if a competing risk is present. Instead of Cox regression analysis, the proportional hazards model by Fine and Gray can be used as it is based on cumulative incidence functions [44]. This method was used in Study III to estimate the relative risk of PJI in the 2010-2014 period as compared with the 2005-2009 period.

When Cox regression analysis or the proportional hazards model by Fine and Gray is used, the hazards must be proportional throughout the study period, i.e. the proportional hazards assumption must be met. This assumption of proportional hazard can be evaluated by a log-minus-log plot or by Schoenfeld residuals. If the assumptions are violated, several different approached can be used [138]. One approach is to use the pseudo-value method which also takes into account competing risk such as death and revisions for other causes than PJI; and using this method, we may directly estimate the relative risk rather than calculating the relative risk based on hazard rate ratio interpretation.

The pseudo-value method is based on a transformation of data – called pseudo observations – which are calculated at pre-specified time points [11]. Individual pseudo observations are computed using information on other patients and are therefore not independent. The pseudo observations can subsequently be used in a generalised linear model of the relative risk [120], as was done in Study IV.

In Studies I-IV, Stata 12.1-14.0 (Stata crop. College Station, TX) was used and all statistical analyses were performed by the PhD student under the supervision of the supervisor and co-author, Claus Varnum in study IV.

3.9.1 Bilateral Observations

The cumulative incidence function, Cox regression, the Fine and Gray method and the pseudo value method are based on the assumption of independent observations. As a patient can and often will have more than one THA, this assumption of independency is violated. Several methods can be used to remedy this problem: One simple method is to only include all cases of left or right THA and exclude any contralateral THA. However, this approach will cause selection bias that may result in an even more biased estimate than the inclusion of both hips. A second simple method is to include the first primary THA only, but this will result in a violation of the principle that an analysis should not depend on events happening in the future [10]. More advantageous methods of dealing with the dependency associated with bilateral THA exist, but studies have shown than the results are only marginally different from results obtained when observations of bilateral THA are treated as independent observations, especially if the outcome is rare [90, 144]. In this thesis, we chose to regard all bilateral THA as independent observations, but assessed the dependency of bilateral THA by examining the number of bilateral PJI.

Another problem with bilateral observations is that this approach introduces an extra risk of erroneous reporting as a revision in a primary THA may be missed due to incorrect reporting of the side of the operation following either primary or revision surgery. This problem can be controlled for at least in part by going through medical records, which was done to some extent in Studies I, III and IV.

3.9.2 Missing Values

In observational studies, two forms of missing values can occur. One is *loss to follow-up*, which may cause selection bias as patients who for some reason are lost to follow-up may differ from patients with complete follow-up. In all studies, the loss to follow-up was less than 0.5%, and no further actions were taken to address this problem.

The second form of missing values occurs due to incomplete registration of variables for a given event, e.g. reporting of a primary THA to the DHR, but missing registration of the date of surgery. Missing data are generally classified as*: Missing completely at random* when the missing data are independent of both observable and unobservable parameters; *Missing at random* when data are not missing randomly, but a non-missing variable can account for the missing data; *Missing not at random* when missing data are related to the value of the variable that is missing [51]. The missing category can only rarely be determined from the data, but must be resolved by reference to the process, setting and research question. As missing data in the DHR are primarily due to incorrect reporting, we considered that any missing data were *Missing completely at random*.

Different methods have been developed to handle missing data, including complete case analyses, single and multiple imputation [161] and deletion [129]:

For key variables, such as side of operation, date of surgery or incorrect civil registration number, we excluded the patients from the study populations, thereby using list-wise deletion. List-wise deletion is not recommended for all variables because it may lead to a high percentage of excluded cases, with reduces the power of the analysis and introduces a risk of selection bias [129].

For variables that were not needed in order to link the databases, e.g. type of fixation, different methods of imputation was considered in which missing variables are replaced with values [161].

However, the percentage of cases with missing variables was small; and instead of imputation, the pairwise deletion method was used. In pairwise deletion, a case is deleted if a variable used in one analysis is missing, but the case is included in other analyses if the required variable for that analysis is present [129].

4. RESULTS

4.1 STUDY I

A total of 33,353 THA were identified of which 457 were excluded due to missing or incorrect registration of the patient's civil registration number, the operative side or the date of operation or indication. That left a total of 32,896 primary THA in 29,077 patients. Their median age was 69 (range 11-98 years) and 55.0% were females.

In the DHR, we identified 1,332 subsequent first-time revisions, and 1,392 first-time revisions were found in the NRP (Appendix: Frequency of ICD-10 codes), which combined to form a total of 1,522 revisions after exclusion of 25 first-time revisions due to erroneous reporting.

A total of 1,095 first-time revisions were reported to both registers, while 452 (29%) were registered only in one register. The major reason for this discrepancy between the NRP and the DHR was incorrect reporting of the side of operation or registration of a procedure code in the NRP that we had not defined as a revision. For both the one- and the five-year follow-up, the NRP underestimated the incidence of all first-time revisions by approximately 10%, whereas the DHR underestimated the incidence of first-time revisions by 20% (Table 9).

	1-year			5-year		
Register	No. of primary THA	No. of revisions	Cumulative incidence	No. of primary THA	No. of revisions	Cumulative incidence
DHR	32,896	730	2.22 (2.06; 2.38)	13,175	560	4.25 (3.92; 4.60)
NRP	32,896	839	2.55 (2.39; 2.73)	13,175	589	4.54 (4.19; 4.90)
Combined	32,896	930	2.83 (2.65; 3.01)	13,175	662	5.02 (4.66; 5.41)

Table 9: Cumulative incidence of first-time revisions due to any cause following primary total hip arthroplasty (THA).

4.1.1 Algorithm for Classification of Revisions

The results from classification using the algorithm are shown in Figure 5. In the following, the findings are described more detailed where they are not evident from the figure presenting the algorithm.

In 1,210 of the 1,522 first-time revisions, three or more intraoperative cultures had been obtained of which 91% included exactly five samples. Other frequent numbers of samples were four (2%), six (3%) and ten (2%). The last category (ten samples) was probably a result of two sets of five intraoperative cultures. In total, 289 revisions showed growth of the same virulent or opportunistic micro-organism in three or more out of five intraoperative cultures. From the remaining 921 revisions in which intraoperative cultures had been obtained, 89% were without any growth and 8% showed growth in one or two cultures.

Of the 819 revisions that were culture-negative, 68 first-time revisions underwent additional analysis as they were reported as revision for PJI in either the DHR (50 cases) or the NRP (42 cases), had received antibiotics (31 cases) or showed growth of bacteria in culture of synovial fluid from the joint prior to revision (6 cases).

Of the 460 cases in which C-reactive protein was used to classify the revisions as "no infection" or "further tests needed", 226 (49%) were found to have a C-reactive protein level above 10 mg/L, in 88 (19%) the level was below 10 mg/L, and the remaining 146 (32%) were not tested for C-reactive protein.

4.1.2 Incidence of Prosthetic Joint Infection

In the DHR, 227 (17%) of all revisions were reported to be due to PJI; in the NRP, the corresponding number was 207 (16%). The

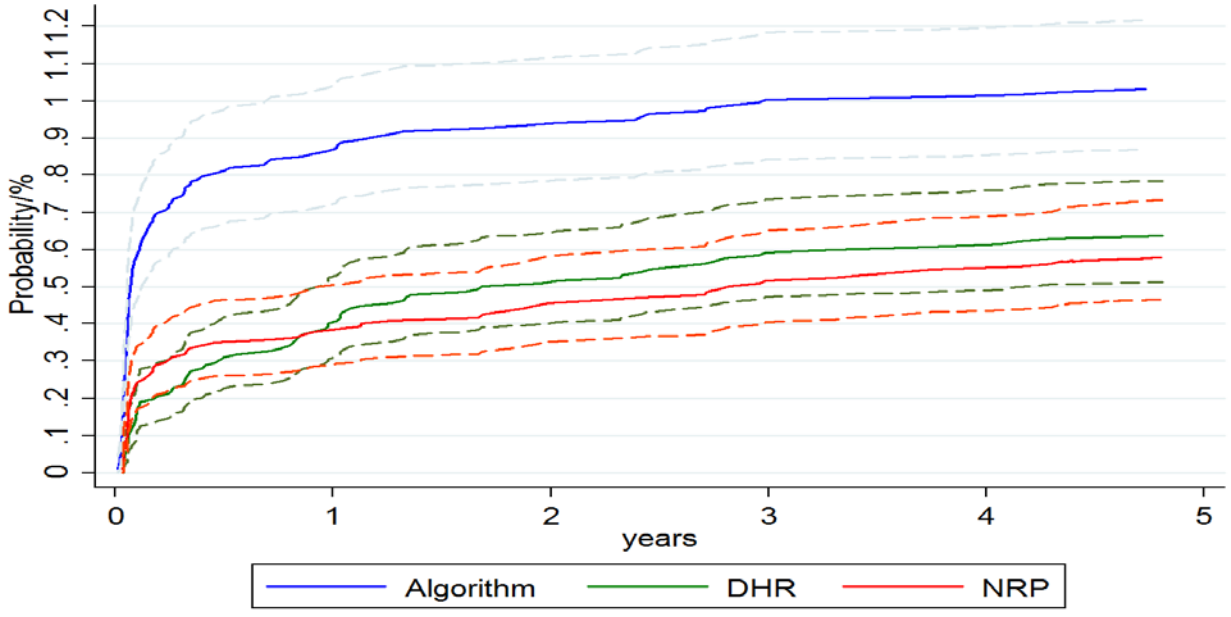

Figure 7: Five-year cumulative incidence of prosthetic joint infection. DHR: Danish Hip Arthroplasty Register. NRP: National Register of Patients.

one-year incidence of PJI was estimated to be approximately 40% higher by our algorithm than reported by the DHR and the NRP for both one- and five-year follow-up (Table 10 & Figure 7).

4.2 STUDY II

A total of 37,826 primary THAs were identified in the DHR of which 1,382 were also reported to the DHR with a subsequent first-time revision. The mean age at the time of revision was 69 (range 22 to 96) years, and 54% of those who underwent revision were females. In the DHR, 232 (17%) of the 1,382 revisions were reported as having been performed due to PJI.

When measured against the reference standard defined by the algorithm in Study I, the PJI diagnosis in the DHR had a sensitivity of 67%, a specificity of 95%, a PPV of 77% and an NPV of 92% (Table 11).

Sensitivity was significantly higher if purulence was present, if the C-reactive protein level was elevated or if the prosthesis had become infected with virulent bacteria.

When data from the DHR were combined with data from the microbiology databases using the previously described definition of PJI, the sensitivity increased to 90%. This pooling of data also produced an increase in the other parameters: the specificity increased to 100%, the PPV to 98% and the NPV to 98% (Table 11).

4.3 STUDY III

In total, 48,867 primary THAs in 42,210 patients were identified. The mean age was 68.85 (95% CI: 68.8; 68.9) at the time of primary THA, and 55.1% were females. Within one year of follow-up, 1,120 patients had a revision performed of which 271 could be classified as having been performed due to PJI by the validated definition.

4.3.1 Trend in the Incidence of Prosthetic Joint Infection

The incidence of PJI was 0.53% (95% CI: 0.44; 0.63) for the 2005-2009 period and 0.57% (95% CI: 0.49; 0.67) for the 2010-2014 period, resulting in a relative risk of PJI of 1.08 (95% CI: 0.82; 1.38) for the 2010-2014 period versus the 2005-2009 period. The adjusted relative risk was 1.05 (95% CI: 0.82; 1.35)).

The relative risk was 1.16 (95% CI: 0.91; 1.49) when data from the DHR were used without linkage to the microbiology databases. When defining PJI as three or more intraoperative cultures of the same pathogen, the relative risk was 1.01 (95% CI: 0.77; 1.32).

4.3.2 Bacteria and Antimicrobial Resistance

The most commonly identified micro-organisms were *Staphylococcus aureus* (31%), coagulase-negative staphylococci (26%), Enterobacteriaceae (11%), *Enterococcus* species (9%) and *Streptococcus* species (8%). For these five bacteria, the antimicrobial resistance to beta-lactams and gentamicin did not change during the study period.

4.4 STUDY IV

A total of 68,504 primary THA were identified in 59,954 patients. The median age at implantation of a primary THA was 69.7 years (interquartile range, 62.3-76.7 years), and the majority were female (55.4%). According to the validated definition, 445 of the 1,795 revisions that were performed within one year of the primary THA were due to PJI. Within one year from the primary THA, 1,907 patients died.

	1-year			5-year		
Register	No. of primary THA	No. of revisions	Cumulative incidence	No. of primary THA	No. of revisions	Cumulative incidence
DHR	32,896	167	0.51 (0.44; 0.59)	13,175	84	0.64 (0.51; 0.79)
NRP	32,896	158	0.48 (0.41; 0.56)	13,175	75	0.57 (0.45; 0.71)
Combined	32,896	285	0.86 (0.77; 0.97)	13,175	136	1.03 (0.87; 1.22)

Table 10: umulative incidence of first-time revisions for prosthetic joint infection following primary total hip arthroplasty (THA)

	DHR	DHR + Microbiology Databases
Sensitivity	67.0 (61.0; 72.6)	90.3 (86.1; 93.5)
Specificity	95.2 (93.8; 96.4)	99.6 (99.1; 99.9)
Positive Predictive Value	77.2 (71.2; 82.4)	98.4 (95.9; 99.6)
Negative Predictive Value	92.3 (90.7; 93.8)	97.7 (96.7; 98.5)

Table 11: Sensitivity, specificity, positive predictive value, negative predictive value of the prosthetic joint infection diagnosis in the Danish Hip Arthroplasty Register (DHR).

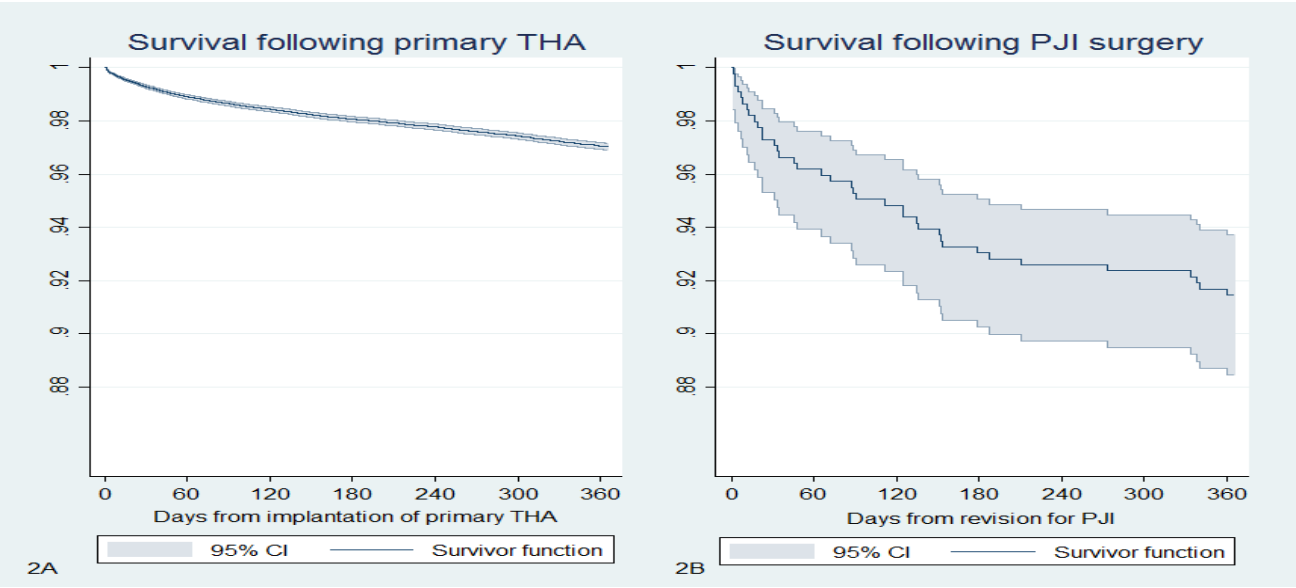

Figure 8: Mortality rate following primary total hip arthroplasty operation (2A) and following revision for prosthetic joint infection (PJI) (2B).

4.4.1 Mortality Risk Following Revisions for PJI versus a Reference Population

The mortality rate following a revision for PJI was notably increased compared with other patients from the study population who were not revised due to PJI, (figure 8).

The crude relative mortality risk was 3.10 (95% CI: 2.33; 4.13). When adjusting for age, gender and comorbidity, the adjusted relative mortality risk was 2.18 (95% CI: 1.54; 3.08).

4.4.2 Mortality Risk Following Revision for PJI versus Aseptic Revision

The crude relative mortality risk within one year following a revision was 1.65 (95% CI: 1.15; 2.40) for revision for PJI versus aseptic revisions. Adjusting for age, gender, comorbidity and duration of revision surgery, the adjusted relative risk was 1.87 (95% CI: 1.11; 3.15).

Patients infected with enterococci had a significantly higher one-year mortality risk than patients infected with other bacteria species (p: 0.01). Patients with an enterococci-infected prosthesis were treated with a beta-lactam exclusively prior to revision in 75% of the cases.

4.5 MAIN FINDINGS:

1. The one- and five-year cumulative incidences of PJI were estimated to be 0.86% (95% CI: 0.77; 0.97) and 1.03% (95% CI: 0.87; 1.22). Both the NRP and the DHR underestimated the incidence by approximately 40%.
2. For the PJI diagnosis reported to the DHR, the sensitivity was 67%, the specificity 95%, the PPV 77% and the NPV 92%. Sensitivity was higher when the PJI resulted in elevated C-reactive protein or purulence in the joint, or if the PJI was caused by virulent bacteria.
   When the data from the DHR were combined with data from the microbiology databases, the sensitivity of the PJI diagnosis increased to 90% which also improved the specificity (100%), the PPV (98%) and the NPV (98%).
3. The relative risk of PJI was 1.05 (95% CI: 0.82; 1.35) in the 2005-2009 period versus the 2010-2014 period. No changes were observed in antimicrobial resistance to cefuroxime, dicloxacillin or gentamicin for the five most commonly isolated bacteria causing PJI during that period.
4. Revision for PJI within one year of the primary THA resulted in a 2.18 (95% CI: 1.54; 3.08) adjusted relative mortality risk compared with patients without a revision for PJI, and a 1.87 (95% CI: 1.11; 3.15) adjusted relative mortality risk compared with patients with an aseptic revision. Patients infected with enterococci had a particularly high mortality risk (p: 0.01).

5. DISCUSSION

5.1 INTERNAL VALIDITY

All studies in this thesis are observational studies and they are therefore limited by factors that affect observational studies, including confounding (as discussed in chapter 3.8), selection and information bias.

5.1.1 Selection Bias

The structure of the Danish National Health Service and the unique and unchangeable civil registration number allow for inclusion of almost all patients of interest in Denmark [91, 151], which should reduce the risk of selection bias. However, selection bias might have been introduced due to the inclusion criteria used in this thesis, of which the limitation of only including patient reported to the DHR that were operated in Jutland-Funen probably have the highest impact on our results.

The DHR: Included were only patients reported to the DHR, which has a completeness of 91-98% (Table 5). However, as the primary THAs that are missing in the DHR are missing due to the surgeon's forgetfulness and misclassification, there is probably very little difference between the characteristics of the patients reported to the register and those of the patients who are missing in the register. It is therefore unlikely that there should be any association between missing registration in the DHR and the outcomes studied in this thesis. Selection bias may be reduced by the fact that

revisions can be performed and reported to the DHR by a different surgeon that the one performing the primary THA.
Jutland-Funen: Only patients operated in Jutland or Funen were included in Studies I-III, and they comprised the majority of the study population in Study IV. This inclusion criterion may cause selection bias in some of our estimates.
Study I: The reported incidence of revision is similar for Jutland and Funen and the remaining parts of Denmark when completeness is incorporated into the estimation [5]. This led us to conclude that the estimation of the "true" incidence of PJI may be generalised to the remaining parts of Denmark and that the risk of selection bias is minimal.
Study II: We believe that it is unlikely that the inclusion of only Jutland and Funen has caused selection bias in the validation of the PJI diagnosis in the DHR, as the DHR-reporting procedure is the same in all of Denmark and for the Norwegian and Finish arthroplasty registers as well [176],
Study III: Changes in the risk of PJI and antimicrobial resistance may differ between Jutland and Funen and the remaining parts of Denmark. With the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA), *staphylococcus aureus* is one of the bacteria species that has been subject to change of antimicrobial resistance [162]. Although MRSA remains a rare infection, the prevalence of this infection is increasing in Denmark [34]. Still, the prevalence seems to be equally distributed throughout Denmark [43, 84], and we expect selection bias to be limited in Study III if this scenario applies generally to other bacteria as well.
Study IV: The treatment of PJI (especially the choice of antibiotic) probably has much influence on the risk of mortality, and our mortality estimate may be affected if treatment differs between Jutland and Funen and the remaining parts of Denmark. However, preoperative prophylactic antibiotics are used uniformly in Denmark [5], which indicates that the treatment is similar in all parts of the country.

5.1.2 Completeness in the Danish Hip Arthroplasty Register

The completeness of both primary THAs and revisions in the DHR changed during the study periods of all four studies. Specifically, it should be mentioned that PIJ revisions are occasionally performed acutely, e.g. if the patient is septic. In these cases, the surgeons performing the acute revision may be more inexperienced and less familiar with the reporting procedures of the DHR than surgeons who regularly perform THA operations, and therefore more prone to forget to report. This could have had an effect on the results of Studies I, III and IV.
Study I: The incidence of PJI may be underestimated if all revisions were not included in the study. As both the DHR and NRP were used, this underestimation is expected to be small, but the percentage of revisions missed by both registers remains unknown.
Study III: The completeness of primary THAs and revisions increased during the study period, but these increases were non-proportional as the completeness of revisions increased more than the completeness of primary THAs (Table 5). This heightens the probability of registration of a PJI in the later years of the study period, which could cause the relative risk of PJI in the later period to be overestimated.
Study IV: The estimation of the higher mortality risk for patients who received surgical treatment for a PJI is probably underestimated because some revisions for PJI are not reported as revisions and are therefore included in the reference population instead.

5.1.3 Information bias

In this thesis, information bias occurs when the exposure (predominantly primary THA) or outcome (revision for PJI or death) is misclassified [146]. As the risk of misclassification of the exposure 'primary THA' is limited, the following presentation will focus on the consequences when misclassification of the outcome occurs, e.g. when a revision for PJI is classified as an aseptic revision.
Study I: Some revisions may have been misclassified. This occurred primarily when the tests included in the algorithm failed to diagnose a PJI. Inclusion of more tests would probably have identified a higher number of revisions for PJI; however, such tests were unavailable or not commonly used during the 2005-2011 period [166]. We therefore expect the sensitivity of the algorithm to be lower than the specificity. Thus, if the estimated incidence of revisions for PJI is biased, the result is probably underestimated.
Study II: As the outcome in Study II is the reported PJI diagnosis in the DHR, the risk of information bias is limited.
Study III: In Study II, the developed linkage of the DHR and the microbiology databases ensured a sensitivity of 90%. Using the same approach in Study III, we expect an underestimation of 10%, which is most likely non-differential. Therefore, the relative risk of PJI in the later part of the study period will be biased towards an underestimation. In contrast, the increasing trend towards obtaining intraoperative cultures in the later part of the study period produces differential misclassification and biases the relative risk towards overestimation. As only surgically treated PJI were included in the analysis, a change towards a more or less aggressive surgical policy would also bias our result. However, we have no knowledge of any studies describing such a change and can therefore not take into account how such a change would affect our result.
Study IV: The outcome in Study IV was death and revision for PJI. Death – as reported by the civil registration system – is almost never misclassified [151]. In contrast hereto, the revision for PJI diagnosis as defined by Study II, with the above mentioned 90% sensitivity, leads to a non-differential misclassification and a resulting underestimation of the relative mortality risk.

5.2 COMPARISON WITH EXISTING LITERATURE

5.2.1 Incidence of Prosthetic Joint Infection

A considerable number of studies and reports from the national arthroplasty registers have been published on the incidence of PJI following primary THA (Table 2). Dale et al. included 432,168 primary THAs [31] and showed a five-year cumulative incidence of surgically treated PJI was estimated to 0.62% (95% CI: 0.60; 0.65), which is very similar to the five-year cumulative incidence of 0.64% (95% CI: 0.54; 0.79) found in Study I when using only data from the DHR. We therefore believe that our result of the "true" incidence of PJI may be generalised to the other Nordic countries. Whether our results can be generalised to other countries is more questionable because of differences between these countries' patient populations [42], health service organisations and antimicrobial resistance patterns [34].
Dale et al. also reported that the incidence of PJI was increasing during the 1995-2009 study period [31], which is in line with the results of many other studies from that study period (Table 2). However, only the study from the Swedish Hip Arthroplasty Register used validated data in their analysis of the trend in PJI incidence [95]. If data from the DHR are used exclusively in our analysis, the relative risk of 1.16 (95% CI: 0.91; 1.49) indicates that an

increase might be present if register data are used exclusively during the study period 2005-2014, although the confidence interval is too wide to determine this. Application of the validated definition of PJI decreases the relative risk to 1.05 (95% CI: 0.82; 1.35), indicating that the incidence has actually not been increasing, even though there was a higher probability of identifying PJI in the later study period as the completeness of revisions in DHR increased during the study period, and intraoperative cultures were obtained from a higher percentage of revisions in the later study period. It should be noted, though, that Dale et al. reported small increases in relative risk of 1.1 (95% CI: 1.0; 1.2) and 1.6 (95% CI: 1.4; 1.7). This underlines that large study populations are needed to study the incidence of PJI, and our study population might be too small to detect minor changes in the incidence of PJI [19].

Various risk factors can influence the trend of PJI. In the studies, which describe an increasing incidence of PJI a number of risk factors have been assessed [31, 32, 128], but in the studies it has not been possible to explain the increasing incidence of PJI by a corresponding increase in risk factors. However, studies of micro-organisms from PJI have identified an increasing antimicrobial resistance of coagulase-negative staphylococci from the 1980s to the beginning of the 21st century [100, 160], which could explain the increasing incidence of PJI. In the analysis of trends of PJI estimated from register studies, it is of importance to remember that on top of changes in completeness various confounders exist, which can be difficult to adjust for. The increasing number of revisions in which intraoperative cultures were obtained during the study period in study III could be a result of an increasing awareness of PJI that would also affect the reporting to the registers. Moreover, a change in the threshold of revision for PJI and a shift towards treating a higher or lower percentage of PJI with antibiotics exclusively would also affect the results.

5.2.2 Validation of the Prosthetic Joint Infection Diagnosis

The only validation of the PJI diagnosis in a national arthroplasty register undertaken before the present thesis was conducted was performed by Lindgren et al [93] who validated the PJI diagnosis in the Swedish Hip Arthroplasty Register through linkage with the Swedish Prescribed Drug Register and subsequently reviewed the medical records of possible PJI cases [93]. Even though Lindgren et al. used a different method and reference definition of PJI than us, our results are remarkably similar. Thus, they reported a sensitivity of 60%, a specificity of 99%, a PPV of 76% and a NPV of 99%, whereas our result from Study II showed a sensitivity of 67%, a specificity of 95%, a PPV of 77% and a NPV of 92%. Zhu et al. have later demonstrated that with a sensitivity of 63% for the PJI diagnosis, the incidence of PJI was underestimated in the New Zealand Joint Registry [184].

The reporting procedure differs between the DHR, the New Zealand Joint Registry and the Swedish Hip Arthroplasty Register, but all the reporting procedures are based on a subjective estimation which does not always include an assessment of all tests performed, including intraoperative cultures. That the reporting of PJI is based on a subjective estimation might explain why the sensitivity was higher if C-reactive protein was elevated or purulence was present, which made the PJI more easily recognisable at the time of revision.

5.2.3 Mortality

PJI has been associated with a high mortality [18, 60], but few studies have studied the risk of mortality compared with other revisions, and no previous studies have followed a cohort of primary THA to date of death and described the impact of PJI on mortality.

Choi et al. and Webb et al. found that the mortality risk after PJI revision was not significantly higher than the mortality risk after aseptic revision [28, 171]. However, both studies did report a higher mortality rate following revision for PJI, and both studies may be subject to type II error. Zmistowski et al., on the other hand, found that the relative mortality risk was 5.9 (95% CI: 3.5; 10.2) for revision for PJI compared with aseptic revision [188]. This is notably more than the 1.87 (95% CI: 1.11; 3.15) relative mortality risk found in the present study. This difference in relative mortality risk is probably due to differences in study population as Zmistowski et al. included both THA and total knee arthroplasties, which have a different incidence of PJI [77] and different length of stay following revision for PJI, which could indicate that the PJI in THA has a different course than the PJI in total knee arthroplasties. Furthermore, we only included first-time revisions, and as the risk of failure increases by each revision performed [5], this might also be an explanation of the different relative mortality risk estimates. Moreover, only early revisions performed within the first year were included in our study, and chronic PJI – which were included in the study by Zmistowski et al. - might have a higher mortality risk than early PJI [81].

Enterococci infected PJI had a higher mortality risk than PJI caused by other bacteria. This is in accordance with several studies which have shown that THA infected with enterococci have a high risk of failure, high risk of subsequent revisions, and longer length of stay [96, 106, 141]. A possible explanation of the higher mortality rate in enterococci infected PJI could be that most revisions were treated with a beta-lactam as preoperative prophylactic antibiotic prior to revision, which enterococci are intrinsic resistant to [112].

6. CONCLUSION

This thesis demonstrates that the difficulties associated with PJI diagnostics which often rely on results from multiple tests cause the incidence of PJI to be underestimated in the national registers and also cause the PJI diagnosis to be inaccurately recorded in the Danish Hip Arthroplasty Register, especially when the PJI is not manifest or evident at the time of surgery. This thesis also demonstrates that one method of circumventing this inaccuracy is by merging the DHR with data from microbiology databases.

By linkage of data from the DHR with microbiology data, we show that the risk of PJI, which has been reported to be increasing from the 1990s to the beginning of the 21st century, seems not to follow an increasing trend in the 2005-2014 period. Nor is there any change in the antimicrobial resistance to the most commonly used prophylactic antibiotics used in primary THA surgery.

PJI is a devastating complication that needs to be closely monitored. This is underlined by the fact that a PJI following primary THA caused an approximately two-fold increase in the relative mortality risk, even after adjusting for multiple risk factors. Patients infected with enterococci that are resistant to the most commonly used preoperative prophylactic antibiotic administered prior to revision surgery have a particularly high mortality risk.

7. PERSPECTIVES & FUTURE RESEARCH

It is of pivotal importance that continuous research is conducted to establish how PJI may be prevented and to optimise treatment for those unfortunate patients who acquire this condition as they have a high risk of treatment failure and – as shown in this thesis - death. Moreover, the severity of this complication means that a method of surveillance of its incidence is called for. Most national registers are characterised by underestimation and inaccuracy of the PJI diagnosis [59, 82, 93]. This is deplorable as such registers are often the only available research tool for studying the incidence of PJI and other important issues regarding PJI. It is therefore essential to improve the reporting to these registers, and new methods of surveillance are required. Various methods have been tested, e.g. in the Swedish Arthroplasty Registers the medical records are submitted along with the report, but the effect of this approach currently remains unclear. As shown in this thesis and in Victor Lindgren's thesis [94], another applicable method is linkage of various databases and registers. However, linkage may not be applicable in countries where the processing of non-depersonalised data is not an option [130]. This underlines the unique possibility of merging the exceptionally many and large databases in Denmark, which will hopefully continue to be available for valuable research, even if it has been suggested that access to data should be limited [46, 63].

7. SUMMRAY IN ENGLISH

Prosthetic joint infection (PJI) is a rare, but devastating complication following primary total hip arthroplasty (THA). As PJI is a rare event, large cohorts of patients are required in order to study this complication. National arthroplasty registers offer such large and unselected cohorts, but studies have shown that these registers – used alone – underestimate the incidence of PJI.

The aim of this thesis was to estimate the incidence of PJI and the mortality risk following a PJI by combining data from the Danish Hip Arthroplasty Register (DHR), the National Register of Patients (NRP), the Microbiology Databases, the Civil Registration System, the medical records, the Danish National Prescription Registry and the Clinical Biochemistry Databases.

The thesis comprises the following four studies:

Study I: The aim of this study was to estimate the "true" incidence of surgically treated PJI following primary THA. To estimate the true incidence, we developed an algorithm that classified the revisions as due to PJI or due to other causes. The algorithm incorporated data from the DHR, the NRP, medical records, the microbiological databases, the prescription database and the clinical biochemistry databases. The one- and five-year cumulative incidences were estimated to be 0.86% (95% confidence interval (CI): 0.77; 0.97) and 1.03% (95% CI: 0.87; 1.22), respectively. These figures are approximately 40% higher than the equivalent figures reported by the DHR and the NRP.

Study II: The aim of the second study was to validate the PJI diagnosis in the DHR. We did this by comparing the PJI diagnosis in the DHR with the PJI diagnosis derived from the algorithm developed in Study I. We found a sensitivity of 67%, a specificity of 95%, a positive predictive value (PPV) of 77%, and a negative predictive value (NPV) of 92%. When the data from the DHR were linked with data from the microbiology databases, the sensitivity increased to 90% and the specificity also increased (to 100%) along with the PPV (98%) and the NPV (98%).

Study III: The aim of the third study was to examine whether the incidence of PJI observed within the first year of primary THA increased in the course of the ten-year study period from 2005 to 2014. We used the validated PJI diagnosis described in Study II and found that the incidence of PJI did not appear to be increasing as the relative risk of PJI was 1.05 (95% CI: 0.82; 1.34) for the 2010-2014 period compared with the 2005-2010 period. Nor did we find any changes in the antimicrobial resistance pattern.

Study IV: The aim of the fourth study was to estimate the mortality risk following a revision for PJI within one year following a primary THA. When combining data from the DHR with data from the microbiology databases, we found that the mortality risk of patients with a revision for PJI was 2.18 (95% CI: 1.54; 3.08) compared with the reference population, and 1.87 (95% CI: 1.11; 3.15) when compared with patients who had an aseptic revision.

In conclusion, the incidence of PJI is approximately 40% higher than that reported by the NRP and the DHR. By linkage of the DHR and the microbiology databases, the validity of the PJI diagnosis can be improved notably. By such a combination of data from the DHR and the microbiology databases, we show that the incidence of PJI does not seem to be increasing and that revision for PJI is associated with a high mortality.

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