OPTIMIZING QUALITY AND SAFETY OF BREAST IMPLANT SURGERY

Babette Elisabeth Becherer

OPTIMIZING QUALITY AND SAFETY OF BREAST IMPLANT SURGERY

Babette Elisabeth Becherer

Optimizing quality and safety of breast implant surgery

ISBN: 978-94-6423-414-5
Cover design: Fenna Schaap
Printed by: ProefschriftMaken || Proefschriftmaken.nl

Printing of this thesis has been financially supported by the Erasmus University Rotterdam; Nederlandse Vereniging voor Plastische Chirurgie; Dutch Institute for Clinical Auditing; SOLV Advocaten; BlooMEDical Benelux B.V.; Emdaplast B.V.; Aleamed Benelux.
The sponsors had no role in the design, execution, analyses, data interpretation and the decision to submit the results of the studies included in this thesis.

OPTIMIZING QUALITY AND SAFETY OF BREAST IMPLANT SURGERY

Optimalisatie van de kwaliteit en veiligheid van borstimplantaatchirurgie

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam

op gezag van de rector magnificus
Prof. dr. A.L. Bredenoord
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 17 november 2021 om 13:00 uur

door

Babette Elisabeth Becherer
geboren te Drouwen

Erasmus University Rotterdam

PROMOTIECOMMISSIE

PROMOTOREN
Prof. dr. M.A.M. Mureau
Prof. dr. R.R.W.J. van der Hulst

COPROMOTOR
Dr. H.A. Rakhorst

OVERIGE LEDEN
Prof. dr. M.B. Bouman
Prof. dr. H.M. Verkooijen
Dr. ir. P.R. Rijnbeek

Contents

1

CHAPTER 1

GENERAL INTRODUCTION AND THESIS OUTLINE

GENERAL INTRODUCTION

Parts derived from DBIR annual report 2015-2017 and DBIR annual report 2018.(1, 2)

The female breasts play an essential role in physical and mental well-being throughout different stages of a woman's life. Not surprisingly, problems related to the breasts can have a significant impact on women's quality of life. To (re)create the shape and look of a breast or to enlarge a breast, breast implants are routinely used. After breast reconstruction or augmentation, women generally experience a significant improvement in health-related quality of life, body image, and sexual well-being.(3-5)

BREAST IMPLANTS

Just like there is natural variation in female breasts, breast implants come in different sizes and shapes as well. First, an implant may be round or anatomically shaped, and the choice is mainly based on patient- and surgeon preferences. Second, the implant surface can be divided into smooth and textured. The level of texturing can be further classified, ranging from minimal to high surface roughness, including a polyurethane-coated surface. Although different classification systems have been introduced, no international "texturing" consensus has yet been reached.(6) Textured implants enhance adhesion of the surrounding breast tissue to the implant to prevent rotation and displacement. Therefore, anatomically shaped implants are always textured; round implants may be either smooth or textured. Third, an implant may be filled with silicone, saline, or a hydrogel. Silicone and hydrogel filling provide a more natural feeling of the breast and adapt better to the body temperature than saline. Saline filling is preferred by patients who do not want the possibility of leaking silicone particles into the implant pocket if an implant should rupture.

ADVERSE EVENTS

Breast implants have been used since the early 1960s. Although they are amongst the most used medical devices in the world, the safety of breast implants has been questioned since their invention. Surgery-related and implant-related complications may occur, such as hematoma, seroma, infection, implant loss, implant deflation or rupture, capsular contracture, or breast pain. The most recently emerged rare but serious adverse event is the increased risk of a specific type of T-cell lymphoma: breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). The relative risk of BIA-ALCL in women with breast implants is as high as 420. However, the absolute cumulative risk is 1 per 35,000 at the age of 50 and 1 per 7,000 at the age of 75.(7, 8) Different etiologies have been suggested, but the exact etiology is still unknown. If diagnosed and treated early, the prognosis of BIA-ALCL is generally good, and patients can be cured.

Another controversial and longer debated side effect is Breast Implant-Associated Illness (BII), also known as connective tissue disease or ASIA syndrome (autoimmune syndrome

induced by adjuvants), which is a collective term for the supposed association between silicone-exposure and systemic complaints such as fatigue, myalgia, arthralgia, and concentration problems.(9) However, no causal relationship between breast implants and BII has yet been found.(10-12) In some cases, removing the breast implant(s) improves systemic symptoms, whereas no differences are noticed in other cases.(13, 14)

In addition, different manufacturing problems (e.g., illegal use of industrial silicones, pollution of implant components) have negatively impacted patient safety, which has led to the suspension of certain breast implant types and the urge to be able to trace patients with these particular devices.

In conclusion, it is still unknown exactly how many women carry a breast implant and how many develop adverse events. Although pre-and post-marketing approval studies have been performed by manufacturers, most suffered from small patient groups and lost to follow-up. Together, this has created the urge for well-functioning, breast-implant registries to generate independent and epidemiologically sound data to support evidence-based decision-making, better monitor breast implants, and optimize patient safety.

BREAST IMPLANT REGISTRIES WORLDWIDE

In the past, some breast implant registries did exist.(15) However, most are no longer operational due to low capture rates and insufficient funding.(16-19) In 2010, the Poly Implant Prothèses (PIP) crisis was the driver for a new generation of independent breast implant registries.(20) During the PIP crisis, implants appeared to be manufactured with non-medical-grade silicones. There were problems with tracing patients, and epidemiologically sound data to evaluate the health effects and the risk of implant rupture were lacking. As a result, several countries developed a (new) national breast implant registry, among which Australia, France, Germany, Italy, the Netherlands, Sweden, the United Kingdom, and the United States.(21-30) These registries implemented different strategies, among which opt-out patient consent and different sustainable funding structures, inspired by more mature registries, such as the orthopedic or cardiovascular device registries.(31-34)

Additionally, the new breast implant registries united in the International Collaboration of Breast Registry Activities (ICOBRA), founded by the Australasian Foundation for plastic surgery in 2012.(21, 35) The goals of ICOBRA are to enhance collaboration between breast implant registries worldwide, improve breast device monitoring, and optimize patient safety. Among others, ICOBRA tries to achieve this by developing a harmonized dataset containing standardized data points used by the registries involved.(36) The use of a harmonized dataset across different registries facilitates collaborative international projects, specifically for rare events like BIA-ALCL.(37)

DUTCH BREAST IMPLANT REGISTRY

The Dutch Breast Implant Registry (DBIR) was initiated by the Netherlands Society of Plastic Surgery and registers patient, implant, and surgery characteristics since April 2015. It is an opt-out registry, including implanted and explanted temporary tissue expanders and "permanent" breast implants. DBIR has three primary purposes:

1. To monitor and evaluate the quality of care using clinical auditing based on the fundamental thoughts of nurse Florence Nightingale (1820) and surgeon Ernest Codman (1869).(38-40) Healthcare institutions are continuously provided with information on their performance on explicitly predefined quality indicators in relation to their benchmark.(41) These quality indicators are collaboratively defined by the DBIR scientific committee, patient representatives, healthcare insurers, and healthcare institutions.
2. To monitor and evaluate the quality of inserted implants by analyzing the performance of different breast implant types and identifying implants associated with higher rates of adverse events. Depending on the underlying question, performance can be analyzed per manufacturer, implant texture, insertion technique, or other aspects.
3. To serve as a track-and-trace system in case of a recall. The benefit of using DBIR for recall purposes is that patients can also be traced if their healthcare institution goes bankrupt or closes down.

Registration in DBIR is mandatory for all board-certified plastic surgeons in the Netherlands. In contrast to other countries, only board-certified plastic surgeons are allowed to perform breast implant surgery in either a hospital or private clinic.

The dataset of DBIR is based on the ICOBRA harmonized dataset.(36) Data is securely managed by a certified Trusted Third Party in compliance with the General Data Protection Regulation. Daily coordination of DBIR is facilitated by the Dutch Institute for Clinical Auditing (DICA). A delegation of the NVPC – the DBIR scientific committee – manages the registry's content and safeguards the interpretation of the data. DBIR is financially covered by the National Health Insurers for patients receiving reconstructive breast implant surgery and by a fixed fee paid by the private clinics in case of breast augmentation.

OTHER STAKEHOLDERS

Patients can check whether their breast implant(s) have been registered in DBIR via the website www.implantaatcheck.nl by entering the unique combination of manufacturer name and serial number. No patient details are included. Additionally, the website provides patients with information during an implant recall, stating whether their breast implant is involved in the recall or not.

Another unique feature of DBIR is the industrial registry: DBIR SUPPLIERS (DBIR-S). In DBIR-S, vendors of breast implants in the Netherlands register how many breast implants have been delivered per healthcare institution per year. Additionally, the suppliers are asked to register the implant characteristics and device identification information, such as the Unique Device Identifier and serial number. Currently, four of the seven suppliers (five of the eight brands) participate in DBIR-S. Once DBIR-S contains sufficient and valid data, a combined system between DBIR and DBIR-S can be used to validate the implants registered in DBIR. Additionally, the registration burden can be decreased for clinicians by pre-filling implant characteristics in DBIR, and suppliers can be provided with information on the performance of their devices.

OPTIMIZING QUALITY AND SAFETY USING DBIR

Evaluating and optimizing the quality and safety of breast implant surgery is a complex process. For example, different patient profiles for breast reconstruction and breast augmentation, together with differences in surgical techniques and implant handling, might influence the performance of breast implants and need to be taken into account.

The first step in optimizing quality and safety of breast implant surgery is to unravel how many women carry breast implants, what their patient profiles are, and which implant types are used. Second, insight into surgical practices and nationwide variation between healthcare institutions can identify points for quality improvement. Third, methods to monitor implant performance and identify outliers need to be investigated. Finally, DBIR could (inter)nationally be combined with other registries to further expand its value and impact.

THESIS OUTLINE

Against this background, the present thesis aimed to provide insight into breast implant surgery practice in the Netherlands (part I), to investigate nationwide variation in surgical practice and outcomes (part II), and to assess the potential of combining DBIR data with other registries on a national and international level (part III).

PART 1 – BREAST IMPLANT SURGERY IN PERSPECTIVE

In ***chapter 2***, different implant registries are placed in a worldwide perspective. By comparing relatively younger breast implant registries to more mature orthopedic and cardiac device registries, the registries' costs and value, governance and stakeholders, and funding and sustainability were evaluated. ***Chapter 3*** gives an overview of the information registered in DBIR since April 2015. The minimum incidence rate of breast implants, together with patient-, implant-, and surgery characteristics were analyzed.

PART 2 – VARIATION IN SURGICAL PRACTICE AND OUTCOMES

The use and effect of most infection control measures in breast implant surgery are still debated, which results in variation in current practices. ***Chapter 4*** evaluates the use of different infection control measures in the Netherlands for both breast reconstruction and breast augmentation. In ***chapter 5***, the outcomes of two most commonly used techniques for immediate implant-based breast reconstruction were analyzed. The direct-to-implant and two-stage techniques were compared, focussing on revision incidence, revision indications, and the additional number of operations.

PART 3 – JOINING FORCES WITH OTHER REGISTRIES

To conduct proper research into BIA-ALCL, information on patient-, implant-, and surgery characteristics needs to be combined with pathology information. Therefore, in ***chapter 6***, a proof of concept of combining DBIR data with pathology data from the Dutch Pathology Registry PALGA was examined. The results of another initiative to combine breast implant data can be found in ***chapter 7***. In this chapter, data from four currently active breast implant registries were combined and compared using the ICOBRA harmonized dataset. Similarities and variations in patient profiles, surgical preferences, implants used, and revision rates of the registries from Australia, the Netherlands, Sweden, and the United States were evaluated.

Finally, in ***chapter 8*** the main findings and conclusions of this thesis are discussed and recommendations for future research initiatives are provided.

REFERENCES

1. 1. Becherer BE, Rakhorst HA, Mureau MAM, Hommes JE, Hoornweg MJ, Keuter XHA, et al. Dutch Breast Implant Registry (DBIR)–Annual Report (2015-2017). Dutch Institute for Clinical Auditing (DICA);November 2018.
2. Becherer BE, Rakhorst HA, Mureau MAM, Hommes JE, van Bommel ACM, Hoornweg MJ, et al. Dutch Breast Implant Registry (DBIR)–Annual Report 2018. Dutch Institute for Clinical Auditing (DICA); November 2019.
3. Kouwenberg CAE, de Ligt KM, Kranenburg LW, Rakhorst H, de Leeuw D, Siesling S, et al. Long-Term Health-Related Quality of Life after Four Common Surgical Treatment Options for Breast Cancer and the Effect of Complications: A Retrospective Patient-Reported Survey among 1871 Patients. Plast Reconstr Surg. 2020;146(1):1-13.
4. Alderman AK, Bauer J, Fardo D, Abrahamse P, Pusic A. Understanding the effect of breast augmentation on quality of life: prospective analysis using the BREAST-Q. Plast Reconstr Surg. 2014;133(4):787-95.
5. Cordeiro PG. Breast reconstruction after surgery for breast cancer. N Engl J Med. 2008;359(15):1590-601.
6. Munhoz AM, Clemens MW, Nahabedian MY. Breast Implant Surfaces and Their Impact on Current Practices: Where We Are Now and Where Are We Going? Plast Reconstr Surg Glob Open. 2019;7(10):e2466.
7. de Boer M, van Leeuwen FE, Hauptmann M, Overbeek LIH, de Boer JP, Hijmering NJ, et al. Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast. JAMA Oncol. 2018;4(3):335-41.
8. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.
9. Hennekens CH, Lee IM, Cook NR, Hebert PR, Karlson EW, LaMotte F, et al. Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. JAMA. 1996;275(8):616–21.
10. Janowsky EC, Kupper LL, Hulka BS. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med. 2000;342(11):781-90.
11. Balk EM, Earley A, Avendano EA, Raman G. Long-Term Health Outcomes in Women With Silicone Gel Breast Implants: A Systematic Review. Ann Intern Med. 2016;164(3):164-75.
12. Barbosa MR, Makris UE, Mansi IA. Association of Breast Implants with Nonspecific Symptoms, Connective Tissue Diseases, and Allergic Reactions: A Retrospective Cohort Analysis. Plast Reconstr Surg. 2021;147(1):42e-9e.
13. de Boer M, Colaris M, van der Hulst R, Cohen Tervaert JW. Is explantation of silicone breast implants useful in patients with complaints? Immunol Res. 2017;65(1):25-36.
14. Misere RML, van der Hulst R. Self-Reported Health Complaints In Women Undergoing Explantation of Breast Implants. Aesthet Surg J. 2020;sjaa337.

15. Hume KM, Crotty CA, Simmons CJ, Neumeister MW, Chung KC. Medical specialty society-sponsored data registries: opportunities in plastic surgery. Plast Reconstr Surg. 2013;132(1):159e-67e.
16. Henriksen TF, Holmich LR, Friis S, McLaughlin JK, Fryzek JP, Pernille Hoyer A, et al. The Danish Registry for Plastic Surgery of the Breast: establishment of a nationwide registry for prospective follow-up, quality assessment, and investigation of breast surgery. Plast Reconstr Surg. 2003;111(7):2182-9; discussion 90-1.
17. Renner C, Neuhann-Lorenz C. International Breast Implant Registry: a user report. Aesthetic Plast Surg. 2006;30(5):616-21.
18. Shakespeare PG, Bazire N, Whitworth IH. The UK breast implant registry-ten years on. Br J Plast Surg. 2005;58(3):283-5.
19. American Society of Plastic Surgeons. Tracking Operations and Outcomes for Plastic Surgeons (TOPS): American Society of Plastic Surgeons; 2017 [updated 2017. Available from: https://www.plasticsurgery.org/for-medical-professionals/quality-and-registries/tracking-operations-and-outcomes-for-plastic-surgeons.
20. SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks). Scientific opinion on the safety of Poly Implant Prothèse (PIP) Silicone Breast Implants (2013 update);12 May 2014.
21. Cooter RD, Barker S, Carroll SM, Evans GR, von Fritschen U, Hoflehner H, et al. International importance of robust breast device registries. Plast Reconstr Surg. 2015;135(2):330-6.
22. James S, Daubert JC, Van de Werf F. Commentary: Use of registries to investigate the past and develop the future. BMJ. 2011;342:d2826.
23. Nahabedian MY. Discussion: International importance of robust breast device registries. Plast Reconstr Surg. 2015;135(2):337-8.
24. Hopper I, Ahern S, Nguyen TQ, Mulvany C, McNeil JJ, Deva AK, et al. Breast Implant Registries: A Call to Action. Aesthet Surg J. 2018;38(7):807-10.
25. Hopper I, Ahern S, Best RL, McNeil J, Cooter RD. Australian Breast Device Registry: breast device safety transformed. ANZ J Surg. 2017;87(1-2):9-10.
26. Rakhorst HA, Mureau MAM, Cooter RD, McNeil J, van Hooff M, van der Hulst R, et al. The new opt-out Dutch National Breast Implant Registry–Lessons learnt from the road to implementation. J Plast Reconstr Aesthet Surg. 2017;70(10):1354-60.
27. Registercentrum Västa Götaland. BRIMP Bröstimplantatregistret 2014 [updated 2020]. Available from: https://brimp.registercentrum.se/om-brimp/om-broestimplantatregistret/p/BkuO2oSQS.
28. NHS Digital. Breast and Cosmetic Implant Registry 2016 [updated 29 September 2020]. Available from: https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/breast-and-cosmetic-implant-registry#top.
29. Prantl L, von Fritschen U, Liebau J, von Hassel J, Baur EM, Vogt PM, et al. [Concept for a National Implant Registry to Improve Patient Safety]. Handchir Mikrochir Plast Chir. 2016;48(6):320-9.

30. The Plastic Surgery Foundation. The National Breast Implant Registry (NBIR) 2018 [updated 2020]. Available from: https://www.thepsf.org/research/registries/nbir.
31. Van Leersum NJ, Snijders HS, Henneman D, Kolfschoten NE, Gooiker GA, ten Berge MG, et al. The Dutch surgical colorectal audit. Eur J Surg Oncol. 2013;39(10):1063-70.
32. Weintraub WS, McKay CR, Riner RN, Ellis SG, Frommer PL, Carmichael DB, et al. The American College of Cardiology National Database: Progress and Challenges. Journal of the American College of Cardiology. 1997;29(2):459-65.
33. Kolling C, Simmen BR, Labek G, Goldhahn J. Key factors for a successful National Arthroplasty Register. J Bone Joint Surg Br. 2007;89(12):1567-73.
34. Porter ME. What is value in health care? N Engl J Med. 2010;363(26):2477-81.
35. Cooter R, Barnett R, Deva A, Magnusson MR, McNeil J, Perks G, et al. In Defense of the International Collaboration of Breast Registry Activities (ICOBRA). Aesthet Surg J. 2016;36(7):NP225-7.
36. Spronk PE, Begum H, Vishwanath S, Crosby A, Earnest A, Elder E, et al. Toward International Harmonization of Breast Implant Registries: ICOBRA global common dataset. Plastic and Reconstructive Surgery. 2020;146(2):255-67.
37. Kamali P, van Bommel A, Becherer B, Cooter R, Mureau MAM, Pusic A, et al. Immediate Breast Reconstruction in The Netherlands and the United States. Plastic and Reconstructive Surgery. 2019;144(4):565e-74e.
38. National Institute for Clinical Excellence N. Principles for best practice in clinical audit. United Kingdom; 2002.
39. Nightingale F. Notes on hospitals. London: John W. Parker and Son; 1859.
40. Neuhauser D. Ernest Amory Codman MD. Qual Saf Health Care. 2002;11(1):104-5.
41. Donabedian A. Evaluating the quality of medical care. 1966. Milbank Q. 2005;83(4):691-729.

PART I

BREAST IMPLANT SURGERY IN PERSPECTIVE

2

CHAPTER 2

HIGH RISK DEVICE REGISTRIES; GLOBAL VALUE, COSTS, AND SUSTAINABLE FUNDING

B.E. Becherer
P.E.R. Spronk
M.A.M. Mureau
S. Mulgrew
A.G.B. Perks
B. Stark
A.L. Pusic
D.B. Lumenta
I. Hopper
R.D. Cooter
H.A. Rakhorst.

J Plast Reconstr Aesthet Surg. 2018 Sep;71(9):1362-80.

ABSTRACT

Background: Well-designed implant registries have been shown to be a worthwhile investment, from both a health and economic perspective. However, many registries do not attain desirable capture rates or lack sufficient funding, potentially leading to premature termination. This study aims to provide information about rarely discussed, yet pivotal topics regarding the long-term survival of implant registries, focusing on costs, funding models, and the role of stakeholders.

Methods: Worldwide, relatively recently developed breast device (BD) registries were compared to long-standing, orthopaedic (OD) and cardiovascular device (CD) registries. A standardised questionnaire was sent to the registries' designated representatives with key positions, discussing start-up costs, costs of maintenance, value of investment, governance, stakeholders, funding, and sustainability.

Results: Thirteen registries were included, originating from nine countries (seven BD registries, five OD registries, one CD registry). In general, start-up costs were comparable, and younger registries were more expensive to maintain. Numerous stakeholders showed interest in registry outcomes. However, only 50% of the registries reported a sustainable funding structure.

Conclusion: This study provides a global perspective on implantable device registries. All registries provided important information, serving three unique purposes by evaluating the quality of healthcare provided, the quality of all registered devices, and processing recall information. Yet, only half of the registries were certain of sustainable funding, and thus their future existence. It is of utmost importance to bring this to the attention of all parties involved.

Dear sir, madam,

Globally, clinical registries are progressively being recognised as drivers to improve safety and quality in healthcare.[1,2] Medical device registries however, serve an additional purpose, by evaluating the performance of registered devices in vivo. Orthopaedic (OD) and cardiac device (CD) registries have been successful for many years. Additionally, the importance of the second generation breast device (BD) registries (developed after the Poly Implant Prothèse (PIP) crisis in 2010)[3] has been highlighted once more by the recent SILIMED affair and Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL).[4,5] Nowadays, information on how to set up an implant registry is widely available. However, information regarding the sustainability of these registries is scarce. Therefore, we aimed to provide transparency on pivotal issues for the long-term survival of registries, focusing on costs, funding models, and the role of stakeholders.

A standardised, online questionnaire was designed (*Supplementary file 1*) and sent to designated representatives from OD, CD and BD registries worldwide. Answers were analysed and grouped into three categories: 1) general characteristics, 2) costs & value of investment and 3) funding structures & sustainability. Costs were reported in Euros, using a set currency of €1.00 = $1.14 USD / $1.49 AUD / £0.80 GBP (currency on April 12, 2016; launch of the survey). Uncertainties or discrepancies in provided answers were verified with the participants afterwards.

General characteristics *(Table 1)*

A multinational cohort including thirteen registries originating from nine countries (all seven BD registries, five OD registries, one CD registry) was created. During the study period, ten registries were operational. Two BD were in their start-up phase, and one BD was restructuring an older, paper-based registry. Most registries (10/13) were based on an opt-out system, which means that enrolment is standard unless the physician/patient actively requests not to register. The average number of registered BDs per year (1-4 per 1,000 female inhabitants) was surprisingly close to the number of registered ODs (1-7 per 1,000 inhabitants per year). Beside plastic surgeons, multidisciplinary BD registries included breast surgeons, cosmetic surgeons, gynaecologists, and general surgeons. Multidisciplinary OD registries included orthopaedic surgeons and trauma surgeons.

Costs & value of investment

In general, start-up costs of all registries were comparable, ranging from €100,000–€350,000. In the Australian and American BD registries however, start-up costs were estimated at €450,000 and €1,500,000, respectively, most likely due to substantially bigger country size and multiple state governments in a federal nation. Annual maintenance costs varied by the type of registry and country, regardless of the type or number of outcome measurements

Table 1. General characteristics of included registries (n=13).

Country (establishment[a])	**Development**	**Current status**	**Registered implant** (per year)	**Registered implants per 1,000 inhabitants** (per year[b])	**Method of enrollment**	**Capture rate**	**Mono vs. Multi disciplinary[c]**
Breast device registries							
AUT (1998)	Association of physicians	Restructuring old registry	< 5,000	< 1.3	Opt-in	*Not yet known*	Multi
SWE (2014)	Association of physicians	Operational	5,000 – 10,000	1.2 – 2.5	Opt-out	61% -70%	Multi
AUS (2015)	University	Operational	10,000 – 25,000	1.0 – 2.6	Opt-out	91%–100%	Multi
NLD (2015)	Board of registry, Association of physicians, Non-profit organization	Operational	10,000 – 25,000	1.4 – 3.5	Opt-out	*Not yet known*	Mono
GBR (2016)	Government agency	Operational	25,000 – 50,000	0.9 – 1.8	Opt-in	*Not yet known*	Multi
USA (-)	Board of registry, Association of physicians	Start-up	175,000 – 225,000	1.3 – 1.7	Opt-out	*Not yet known*	Mono
NZL (-)	Association of physicians	Start-up	< 5,000	< 2.6	Opt-out	*Not yet known*	Mono
Orthopaedic device registries							
SWE (1975)	Orthopaedic Association	Operational	10,000 – 25,000	1.2 – 3.1	Opt-out	91–100%	Mono
FIN (1993)	Association of physicians	Operational	10,000 – 25,000	2.2 – 5.4	Opt-out	91–100%	Mono
NZL (1998)	Few physicians	Operational	10,000 – 25,000	2.7 – 6.8	Opt-in	91-100%	Mono
ROU (2001)	Association of physicians, Board of registry, Non-profit organization	Operational	10,000 – 25,000	0.6 – 1.5	Opt-out	91–100%	Multi
NLD (2007)	Board of registry, University	Operational	50,000 – 100,000	3.6 – 7.1	Opt-out	91–100%	Multi
Cardiac device registry							
GBR (1980)	Association of physicians, Government agency	Operational	50,000 – 100,000	0.9 – 1.9	Opt-out	91–100%	Mono

AUS indicates Australia; AUT, Austria; FIN, Finland; GBR, United Kingdom; NLD, The Netherlands; NZL, New Zealand; ROU, Romania; SWE, Sweden; USA, United States of America.
[a] Year of establishment was defined as the first year of actual device registration.
[b] Breast device ratios were defined using the female population, whereas orthopaedic and cardiac device ratios were calculated using the general population. (The World Bank, population 2015, ³15 years of age)
[b] Multi indicates multidisciplinary; Mono, monodisciplinary.

or the comprehensive nature of a registry. With average prices between €5 and €85 per registered device per year, the younger (BD) registries were most expensive to maintain at this point in time. OD and CD registries reported costs of €5-20 per registered device per year. Value of investment was determined by the extent of registry outcomes. Data for post-marketing surveillance of implants were collected by all registries. Benchmark data, quality audit reports, and outcomes per hospital were provided by 12 registries. Outcomes and results per physician, as well as recall information, were present in eight registries. Both participating stakeholders (hospitals, physicians, patients), as well as external stakeholders (government, manufacturers of devices, research institutions, healthcare inspectorates, insurance companies), showed a considerable amount of interest in these data.

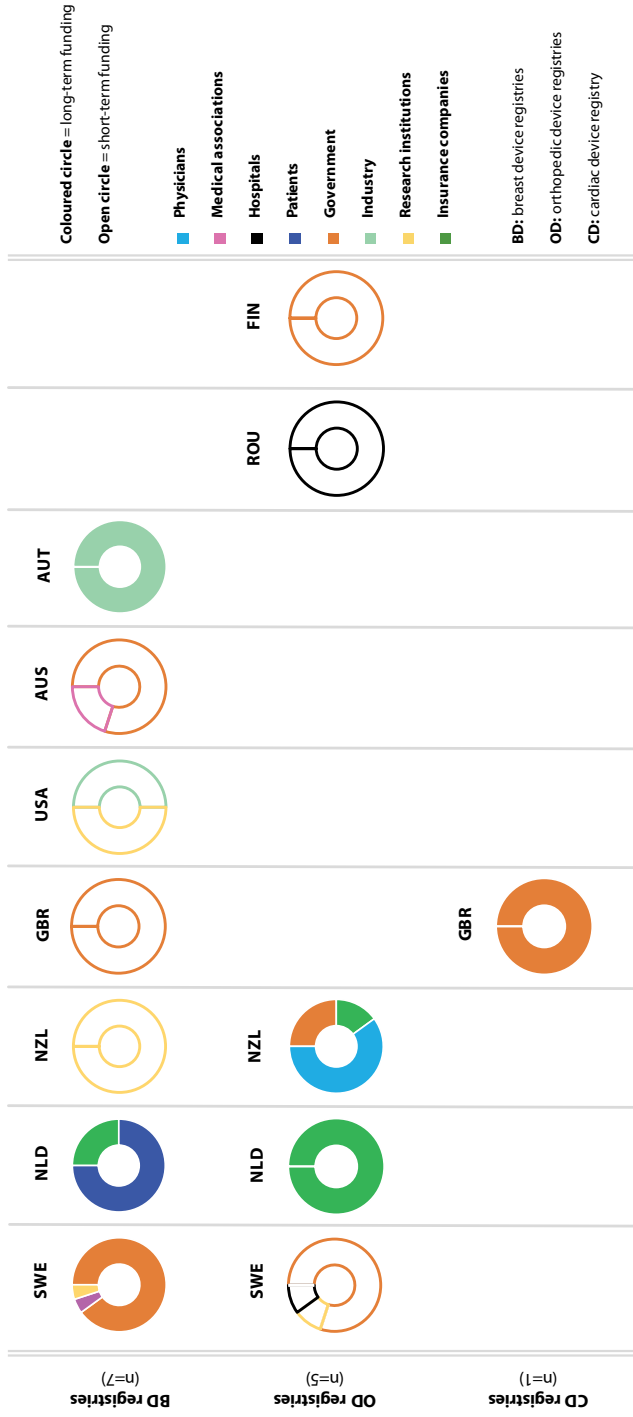
Funding structures & sustainability

Whereas over half of the registries were approached by stakeholders for their data, substantially fewer registries received any financial contribution from these parties. Only six registries reported a sustainable funding structure, for a minimum period of two years (*Figure 1*). No standard, long-term funding model was reported, but there appeared to be two essential elements for financial sustainability. First, funding for core elements such as ICT (information and communications technology), legal issues, governance, recall purposes, and outcome research should be ensured. Preferably, this is achieved through a financial contribution from several large stakeholders, aiming for independence, such as a combination of the government and insurance companies. Furthermore, it is important to attain appropriate funding for innovation, professionalisation, and international collaboration, which might be best accomplished using grants and levies from smaller parties.

Conclusion

Implantable device registries are unique in the sense that they evaluate the performance of healthcare providers, institutions, and registered devices. If these implant registries are to realise their full potential, a steady governance structure and autonomous, sustainable funding models are essential. All involved registries in this study provided important information, of value for multiple stakeholders. Yet, only half of the registries received sustainable funding and thus were certain of their future existence. If implant registries are not sustained, our society loses highly important information, including the traceability of all former registered and implanted devices, leading to decreased patient safety. Therefore, we feel it is important to bring this to the attention of all parties involved.

Figure 1. Funding models

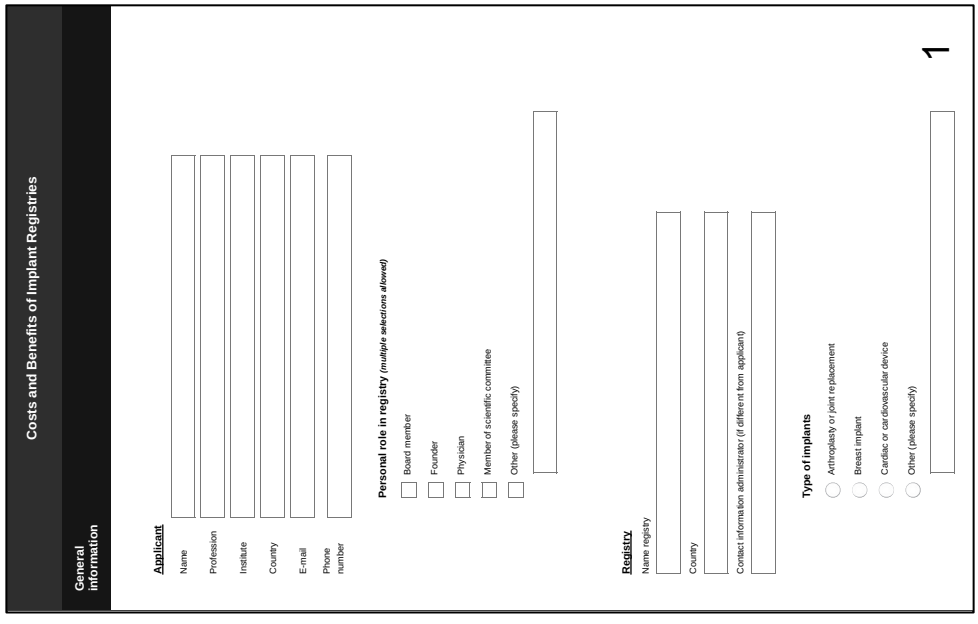


REFERENCES

1. Cooter RD, Barker S, Carroll SM, Evans GR, von Fritschen U, Hoflehner H, et al. International importance of robust breast device registries. Plast Reconstr Surg. 2015;135(2):330-6.
2. Porter ME. What is value in health care? N Engl J Med. 2010;363(26):2477-81
3. SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks). Scientific opinion on the safety of Poly Implant Prothèse (PIP) Silicone Breast Implants (2013 update);12 May 2014.
4. Silimed medical devices (all–including breast implants). Australian Government, Department of Health, Therapeutic Goods Administration. Published 24 September 2015. Updated 26 September 2017. Accessed November 2017. Available from: https://www.tga.gov.au/node/709665.
5. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.

SUPPLEMENTARY DATA

Supplementary file 1. Online questionnaire.



Costs and Benefits of Implant Registries

General information

Applicant

Name

Profession

Institute

Country

E-mail

Phone number

Personal role in registry *(multiple selections allowed)*

- ☐ Board member
- ☐ Founder
- ☐ Physician
- ☐ Member of scientific committee
- ☐ Other (please specify)

Registry

Name registry

Country

Contact information administrator (if different from applicant)

Type of implants

- ◯ Arthroplasty or joint replacement
- ◯ Breast implant
- ◯ Cardiac or cardiovascular device
- ◯ Other (please specify)

1

Current status registry

- ◯ Start up phase *(developmental phase before actual 'going live')*
- ◯ Operational
- ◯ Not operational anymore
- ◯ Restructuring existing or old registry
- ◯ Other (please specify)

NOTIFICATION:
Registry in start up phase: Please answer all the questions from this complete questionnaire according to what the registry is expected to provide once fully operational
Registry not operational anymore: Please answer all questions according to the last years being functional.

Year of first received funding

Year of establishment (i.e. year of first implant registration)

If applicable: Year of shut down

Approximate no. of registrations per year

Estimated capture rate

Method of enrollment

- ◯ Opt-in *(implant will not be registered, unless health care provider & patient actively request to do so.)*
- ◯ Opt-out *(implant will be registered, unless health care provider & patient actively request not to do so.)*

It concerns a multidisciplinary registry

- ◯ No
- ◯ Yes, the involved disciplines are:

2

Costs and Benefits of Implant Registries

Topic 1/3 Funding & Value of investment

START UP FUNDING

Did your registry replace an existing registry, audit or system?

- ◯ No
- ◯ Yes (please specify)

Who developed the current registry? ***(multiple selections allowed)***

- ☐ Board of the registry
- ☐ Medical association of physicians
- ☐ Outsourced to government agency or public authority
- ☐ Outsourced to independent non-profit organization
- ☐ Outsourced to independent for-profit organization
- ☐ Outsourced to university
- ☐ Other (please specify)

3

What were the initial start up costs?

(i.e. amount of money spent from day one until going live)

- ◯ < € 100.000
- ◯ € 100.000 - 200.000
- ◯ € 200.000 - 300.000
- ◯ € 300.000 - 400.000
- ◯ € 400.000 - 500.000
- ◯ € 500.000 - 750.000
- ◯ € 750.000 - 1.000.000
- ◯ € 1.000.000 - 1.250.000
- ◯ € 1.250.000 - 1.500.000
- ◯ € 1.500.000 - 1.750.000
- ◯ € 1.750.000 - 2.000.000
- ◯ > € 2.000.000, please specify

Currency

€ 1 = $ 1,14 (USD)
€ 1 = $ 1,49 (AUD)
€ 1 = £ 0,80 (GBP)

What were the calculated costs for registering 1 implant during the developmental phase?

- ◯ € 0 - 5
- ◯ € 5 - 10
- ◯ € 10 - 15
- ◯ € 15 - 20
- ◯ € 20 - 25
- ◯ € 25 - 30
- ◯ € 30 - 35
- ◯ € 35 - 40
- ◯ € 40 - 45
- ◯ € 45 - 50
- ◯ > € 50

4

Please estimate the proportion of each item that contributed to the start up costs

	0%	1 - 20%	20 - 40%	40 - 60%	60 - 80%	80 - 100%
Medical ethical approval	☐	☐	☐	☐	☐	☐
Pilot study	☐	☐	☐	☐	☐	☐
Restructure an old, existing registry or system	☐	☐	☐	☐	☐	☐
Security data storage	☐	☐	☐	☐	☐	☐
Software development	☐	☐	☐	☐	☐	☐

Other (please specify)

CURRENT FUNDING

Information about sustainable funding is hardly available. Please answer the following questions to provide an impression of how your registry is currently funded.

What are the current costs for registering 1 implant?

- ◯ Not yet known
- ◯ € 0 - 5
- ◯ € 5 - 10
- ◯ € 10 - 15
- ◯ € 15 - 20
- ◯ € 20 - 25
- ◯ € 25 - 30
- ◯ € 30 - 35
- ◯ € 35 - 40
- ◯ € 40 - 45
- ◯ € 45 - 50
- ◯ > € 50

Currency
€ 1 = $ 1,14 (USD)
€ 1 = $ 1,49 (AUD)
€ 1 = £ 0,80 (GBP)

What are the annual costs for maintaining the registry?

- ◯ Not yet known
- ◯ < € 100.000
- ◯ € 100.000 - 200.000
- ◯ € 200.000 - 300.000
- ◯ € 300.000 - 400.000
- ◯ € 400.000 - 500.000
- ◯ € 500.000 - 600.000
- ◯ € 600.000 - 700.000
- ◯ € 700.000 - 800.000
- ◯ € 800.000 - 900.000
- ◯ € 900.000 - 1.000.000
- ◯ > € 1.000.000, please specify

Sources of income

	Payment method	Which portion of the total costs is covered by this source of income? (%)
Government		
Hospital		
Insurance company		
Manufacturer of implant/industry		
Medical association of physicians		
Patients		
Research grant		
Physicians (beside donations through their medical association)		
Health Care Inspection		

Other (please specify)

Do your sources of income provide a sustainable way of funding?

- ◯ Yes
- ◯ No (please specify the problem)

Is there a difference in payment between private or public health care?

- ○ No
- ○ Yes (please specify)

In case of a plastic surgery registry: Is there a difference in costs & payment between implants used for aesthetic surgery and reconstructive surgery?

- ○ No
- ○ Yes (please specify)

VALUE OF INVESTMENT

What kind of information originates from your registry? ***(multiple selections allowed)***

- ☐ Benchmark data & quality audit reports
- ☐ Outcome & results per physician
- ☐ Outcome & results per hospital
- ☐ Recall information
- ☐ No outcome tracking
- ☐ Other (please specify)

Do patients have the possibility to check information about their own implant online?

- ○ No
- ○ Not yet, but this will be available in the future
- ○ Yes

7

Costs and Benefits of Implant Registries

Topic 2/3 Data Governance

Who manages the data? ***(multiple selections allowed)***

- ☐ Government
- ☐ Board of the registry
- ☐ Epidemiologists and statisticians
- ☐ Independent scientific committee
- ☐ Medical associations of physicians
- ☐ Other (please specify)

Who shows interest in the data? ***(multiple selections allowed)***

- ☐ Government
- ☐ Hospitals
- ☐ Insurance compagnies
- ☐ Medical associations
- ☐ Health Care Inspection
- ☐ Physicians
- ☐ Research institute
- ☐ Industry/Manufacturer
- ☐ Patients
- ☐ Other (please specify)

Up to which level is the benchmark data arising from your registry, transparent for the following stakeholders?

8

EXTERNAL PARTIES

Government...

- ○ Has no access
- ○ Can see anonymized benchmark data about devices and participants
- ○ Can see non-anonymized benchmark data about devices and participants
- ○ Other (please specify)

Health Care Inspection...

- ○ Has no access
- ○ Can see anonymized benchmark data about devices and participants
- ○ Can see non-anonymized benchmark data about devices and participants
- ○ Other (please specify)

Insurance Companies...

- ○ Have no access
- ○ Have access to anonymized benchmark data
- ○ Have access to non-anonymized benchmark data and can trace participants
- ○ Other (please specify)

Manufacturers of Implants...

- ○ Have no access
- ○ Can trace own devices
- ○ Can trace own devices and compare them to anonymized benchmark data (e.g. in a scatterplot)
- ○ Can trace own devices and compare them to non-anonymized benchmark data (e.g. in a scatterplot)
- ○ Other (please specify)

9

PARTICIPANTS

Hospitals...

- ○ Have no access
- ○ Can trace own performance
- ○ Can trace own performance and compare with anonymized benchmark data (e.g. in a scatterplot)
- ○ Can trace own performance and compare with non-anonymized benchmark data (e.g. in a scatterplot)
- ○ Other (please specify)

Physicians...

- ○ Have no acess
- ○ Can trace individual performance
- ○ Can trace individual performance and compare with anonymized benchmark data (e.g. in a scatterplot)
- ○ Can trace individual performance and compare with non-anonymized benchmark data (e.g. in a scatterplot)
- ○ Other (please specify)

Patients...

- ○ Have no access
- ○ Can trace own device
- ○ Can trace own device and compare with anonymized benchmark data
- ○ Can trace own device and compare with non-anonymized benchmark data
- ○ Other (please specify)

Is the data available for research?

- ○ No
- ○ Yes, after submitting a research proposal to the scientific committee.
- ○ Other (please specify)

Is data being exchanged with other countries or an international society?

- ○ No
- ○ Not yet, but this is a future goal (please specify)
- ○ Yes (please specify)

collaboration with:

10

Costs and Benefits of Implant Registries

Topic 3/3 Medical Ethical Approval & Reinforcement

MEDICAL ETHICAL APPROVAL

Is medical ethical approval required for your registry?

- ◯ No
- ◯ Yes

If yes, how is this organized in your country?

- ◯ Per hospital
- ◯ Per county
- ◯ Per city
- ◯ Per state or province
- ◯ Nationwide
- ◯ Other (please specify)

Does each implant require the patient's consent for registration?

- ◯ No
- ◯ Yes

REINFORCEMENT

Is the registry reinforced by law?

- ◯ No
- ◯ Yes

Is participation in the registry mandatory for members of the involved medical associations?

- ◯ No
- ◯ Not mandatory, but strongly recommended
- ◯ Yes

11

Is enrollment to the registry a national quality indicator used for Health Care Inspection?

- ◯ No
- ◯ Yes

Is enrollment to the registry a requirement for the manufacturer to distribute their implants?

- ◯ No
- ◯ Yes

12


3

CHAPTER 3

HOW TO IMPROVE PATIENT SAFETY AND QUALITY OF CARE IN BREAST IMPLANT SURGERY? FIRST OUTCOMES FROM THE DUTCH BREAST IMPLANT REGISTRY (2015-2017)

B.E. Becherer BE*
P.E.R. Spronk*
J. Hommes
X.H.A. Keuter
D.A. Young-Afat
M.J. Hoornweg
M.W.J.M. Wouters
M.A.M. Mureau
H.A. Rakhorst
*contributed equally as first author

J Plast Reconstr Aesthet Surg. 2019 Oct;72(10):1607-15.

ABSTRACT

Background: Although the use of breast implants is generally considered to be safe, breast implants are associated with short- and long-term complications. To evaluate and improve the quality of breast implant surgery, and increase our knowledge of implant performance, the national Dutch Breast Implant Registry (DBIR) was established in 2015. DBIR is one of the first up-and-running breast implant registries worldwide and follows an opt-out structure.

Objective: This article provides an overview of the first outcomes and experiences of the DBIR.

Methods: The national coverage of DBIR was studied using data from the Dutch Health and Youth Care Inspectorate. The incidence rate of breast implants was calculated for 2016 and 2017, and patient, device, and surgery characteristics were compared between cosmetic breast augmentations or reconstructive indications. Four infection control, measures were selected to demonstrate the variation in the Dutch clinical practice.

Results: In 2016, 95% of the hospitals and 78% of the private clinics participated in DBIR. Between 2015 and 2017, a total of 15,049 patients and 30,541 breast implants were included. A minimum breast implant incidence rate of 1 per 1691 women could be determined for 2017. The majority of devices were inserted for a cosmetic indication (85.2%). In general, patient, device, and surgery characteristics differed per indication group. Substantial variation was seen in the use of infection control measures (range 0-100%).

Conclusion: Preliminary results obtained from DBIR show high national participation rates and support further developments toward the improvement of breast implant surgery and patient safety.

INTRODUCTION

Since the introduction of breast implant surgery approximately six decades ago, numerous studies have evaluated the health effects and safety of breast implants.[1] These studies suggested that breast implants are to be considered safe. Nonetheless, a variety of surgical complications may occur following breast implant surgery, such as infection, implant rupture or deflation, late seroma, and capsular contracture.[2-4]

Recently, an association between Anaplastic Large Cell Lymphoma (ALCL) of the breast has been found.[5-7] Furthermore, the debate on possible associations between silicone exposure and various autoimmune diseases or connective tissue diseases continues (e.g., ASIA, an autoimmune/inflammatory syndrome induced by adjuvants).[8-12] Therefore, the outcomes of 'real world' data are becoming of increasing scientific and clinical importance to assess the effect of various intraoperative techniques and the use of different types of breast implants, while controlling for confounding factors adequately.[13-14]

In response to this, several countries have developed breast devices registries, among which the Dutch Breast Implant Registry (DBIR).[15-20] In April 2015, DBIR started to register all patients undergoing breast implant surgery in the Netherlands (both implantations and explantations).[21] Currently, the audit provides hospitals and private clinics with weekly updated, benchmarked information on their performance. Additionally, the registry can be used as a track-and-trace system in case of an implant recall and identify patients who have the implant(s) of interest. DBIR follows an opt-out construct, which is unique compared to other breast implants registries worldwide.

Recent research has shown that the estimated prevalence of women with breast implants was 3,3% in the Netherlands in 2015.[5] However, incidence rates and further details on surgery techniques used, types of inserted devices, and national trends are not known yet. By using data of DBIR, this study aims to provide more insight into the patient characteristics of women undergoing breast implant surgery in the Netherlands, the different types of inserted devices, and the nationwide variation in surgical techniques used.

METHODS

A: REGISTRY METHODS

Governance

The Dutch Breast Implant Registry (DBIR), founded in 2014, was an initiative of the Netherlands Society for Plastic Surgery (NVPC).[22] It provides an audit system for plastic surgeons on outcomes of breast implant surgery and serves as a track-and-trace system

for breast implants. More information on the establishment, organization, and funding of the registry can be found in the paper of Rakhorst et al. and the annual report.[21,23]

Quality indicators

The primary purpose of DBIR is to provide healthcare providers with reliable, benchmarked information on structure, process and outcome parameters. These quantitative measures cover different aspects of breast implant surgery: patient characteristics, information about intraoperative techniques, and short- and long-term outcomes of implants. A first set of quality indicators was defined by the DBIR steering group and external stakeholders (e.g., Dutch Health and Youth Care Inspectorate (IGJ), healthcare insurance companies, the Federation of hospitals, and patient advocates). For 2018, three quality indicators will be made publically transparent for all hospitals and private clinics performing breast implant surgery in the Netherlands: (1) participation in the registry, (2) percentage of registered breast implants compared to the actual inserted/explanted devices, and (3) percentage of completely registered records.

Data collection

Data is entered in DBIR by plastic surgeons (in training) or under supervision by (research) nurses or physician assistants. Data entry can be done in 2 ways: by electronic exchange between the Electronic Patient Record and the registry or by using an internet-based program. Data are stored at a central server of a Trusted Third Party.[24] The dataset consists of four levels: (1) general patient information (e.g. anonymized patient identification number, age), (2) patient characteristics during surgery (e.g. date of surgery, ASA classification, smoking, body mass index (BMI), (3) surgery techniques at the breast level (e.g. indication, incision site, flap cover, or when applicable, the indication for revision), and (4) implant characteristics (e.g. manufacturer, serial number, lot number, texture, fill, shape).

Data verification & participation rate

The quality of the DBIR database is evaluated at three levels: (1) national coverage: the participation of all Dutch hospitals and private clinics participating in breast implant surgery, (2) completeness: the number of registered implant procedures versus the actual number of implant procedures performed at each centre, and (3) validity: the quality of the data compared to that in the patient electronic medical records in the hospitals.

In this study, the national coverage was assessed by comparing the number of institutions in DBIR to the number of eligible institutions known by the Dutch Health and Youth Care Inspectorate (IGJ).

No gold standard is known for the evaluation of completeness of DBIR yet. By now, data from the industry is far from complete, and national insurance data do not include cosmetic procedures. Therefore, this could not be determined in the current study.

B: STUDY METHODS

Patient selection

Per record (i.e., breast), information on the date of birth, date of surgery, type of surgery (insertion/replacement/explantation only), and device type was minimally required to be eligible for analysis. The minimum breast implantation incidence rate was calculated using the total number of women between 20 and 80 years of age in the Netherlands, in 2016 and 2017.[25]

For further analysis, all patients who had received a breast implant from the start of DBIR on April 1, 2015, until the end of the second complete registration year at December 31, 2017, with a known indication (either reconstructive or cosmetic), were included. Patients who had received a tissue expander were excluded from analysis. The population was divided into two cohorts: cosmetic and reconstructive. The cosmetic group included all patients with a breast augmentation. The reconstructive group included all patients with the following indication: reconstruction post (prophylactic) mastectomy, reconstruction for a benign condition, or reconstruction for a congenital deformity. To identify differences between health care institutions and to identify where improvements can be made, four examples of used infection control measures were selected: glove change before implant handling, antiseptic rinse before insertion, the use of postoperative drains, and the use of prophylactic antibiotics.

Analyses

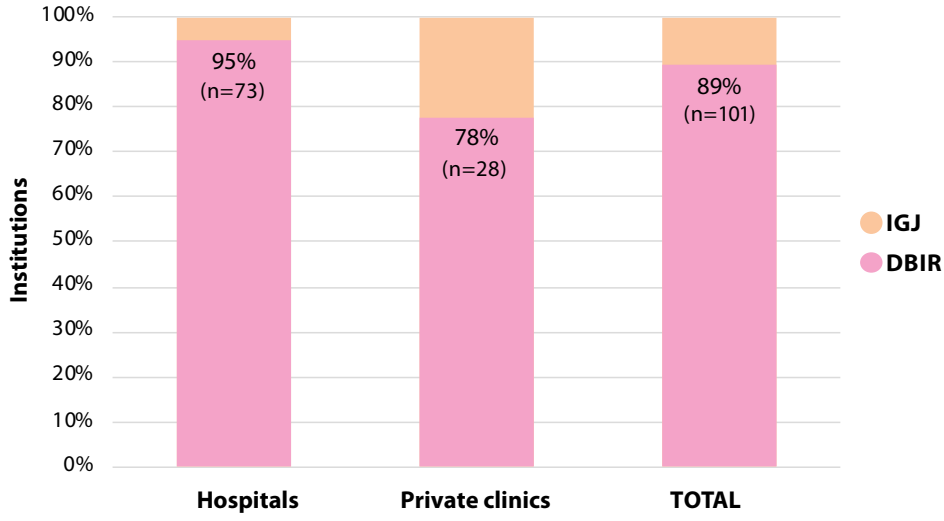
Differences in patient characteristics, device characteristics, and surgical techniques are described using percentages, means, and medians (depending on the distribution). Records with a missing indication (either cosmetic or reconstructive) are presented separately. Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using Student's *t*-test. Nationwide variation in the use of the four selected operative techniques was calculated in percentages per hospital per year and is visualized by scatterplots including the national mean. All analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Nationwide participation rate DBIR

In the first full registration year (2016), 101 institutions were included in DBIR, of which 73 hospitals and 28 private clinics. This means coverage of 95% of the hospitals and 78% of the private clinics when compared with the number of the eligible institutions known by the IGJ (*Figure 1*).

Figure 1. Nationwide participation rate DBIR (2016).
IGJ indicates Dutch Health and Youth Care Inspectorate

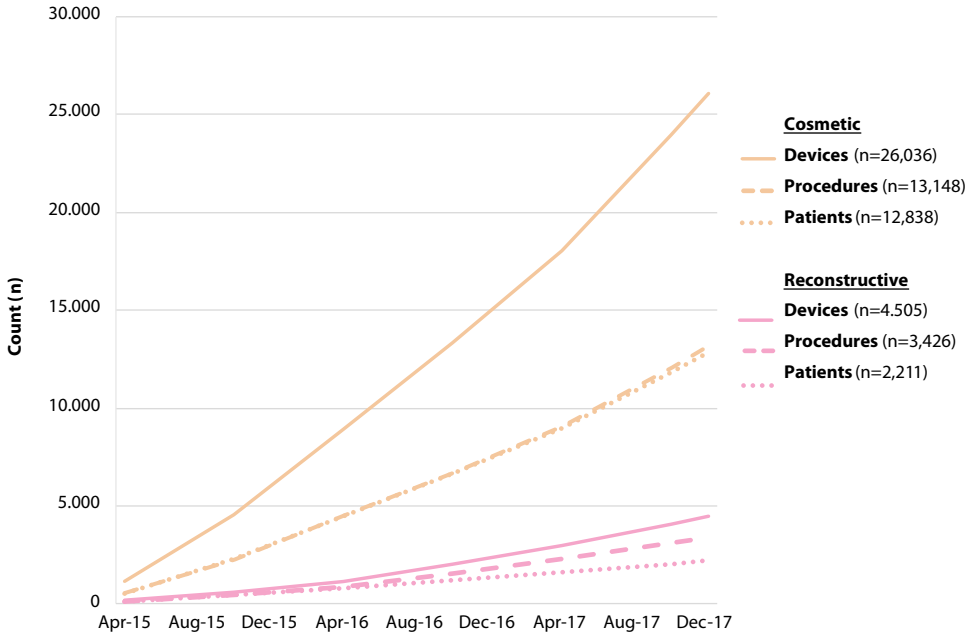


Patients and minimum breast implantation incidence rates

In total, 48,493 records (i.e., breasts) have been registered with an operation date between the start of DBIR on April 1, 2015, and December 31, 2017, of which 48,026 (99.0%) were eligible for analysis (*Supplementary figure 1*). Of these, 41,919 were registered for the insertion of a breast implant. In 2016, 7528 women received one or more permanent breast implant(s), accounting for a minimum incidence rate of one per 1649 women. In 2017, the minimum incidence rate was one per 1691 women (number of insertions: 7391).

For further analysis, the indication for surgery needed to be known (either reconstructive or cosmetic). Therefore, 11,378 of the 41,919 records (27.1%) were excluded (36.8% in 2015, 32.8% in 2016, and 15.1% in 2017). Eventually, 15,049 unique patients, 16,574 surgical procedures, and 30,541 breasts were included (*Figure 2*).

Figure 2. Cumulative number of registered patients, procedures and inserted breast implants (2015-2017).



Patient characteristics

Patient characteristics per unique surgical procedure are presented in *Table 1*. In general, patients who had undergone a cosmetic breast augmentation were younger and had a lower ASA score than patients who received a breast reconstruction (all *P*-values <0.001). Information on smoking and body mass index (BMI) has been collected since September 2017. However, this information was missing in more than 5% of the records for both indications. *Supplementary table 1a* presents all patient characteristics of the records in which no indication was specified.

Device characteristics

Between April 2015 and December 2017, 26,036 (85.2%) breast implants were inserted for a cosmetic breast augmentation, and 4505 (14.8%) for a breast reconstruction. In both cosmetic and reconstructive indications, most devices had a textured shell (93.1% and 92.5%, respectively) with a silicone coating (96.3% and 91.6%, respectively) and with silicone filling (97.2% and 82.6%, respectively). Implants used in reconstructive indications were more often anatomically shaped instead of round (86.0% versus 30.6%, *P*-value <0.001). The median volume of inserted implants was higher in the reconstructive group (415 cc, IQR 325-520) than in the cosmetic group (350 cc, IQR 300-405; *P*-value <0.001).

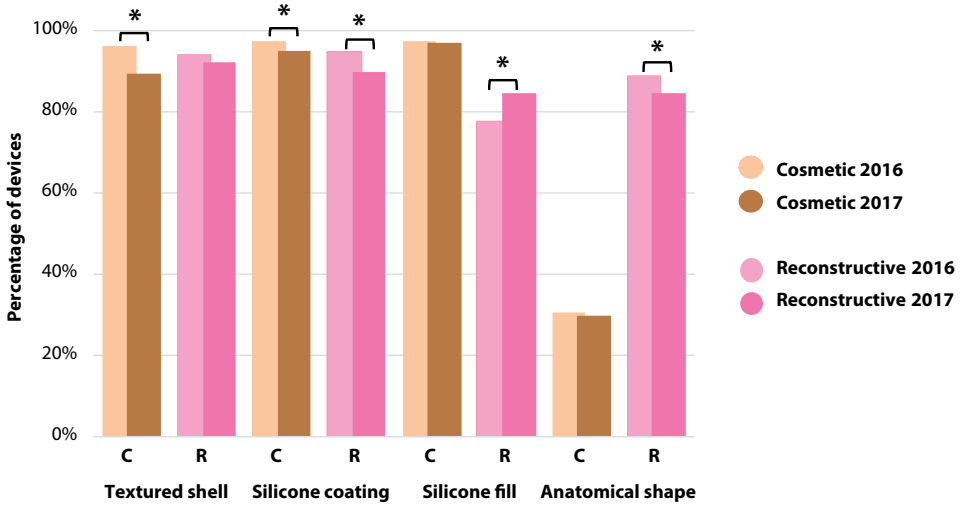
Table 1. Patient characteristics per surgical procedure, presented at the patient level (2015-2017).

	Cosmetic		**Reconstructive**		
	n	%	n	%	*P*-value
Patients[a]	13,148		3426		
Age					<0.001
<30	6227	47.4	205	6.0	
30-39	4140	31.5	488	14.2	
40-49	1794	13.6	876	25.6	
50-59	783	6.0	1112	32.5	
>60	204	1.6	745	21.7	
ASA classification					<0.001
I	12,493	95.0	2235	65.2	
II	532	4.0	1040	30.4	
III-IV	30	0.2	90	2.6	
Unknown	*93*	*0.7*	*61*	*1.8*	
Smoking[b]					<0.001
Yes	218	10.5	61	9.9	
No	1028	49.5	383	62.1	
Unknown	*830*	*40.0*	*173*	*28.0*	
BMI[B] (kg/m^2)					<0.001
<18.5	109	5.3	11	1.8	
18.5-25	1529	73.7	273	44.2	
25-30	218	10.5	148	24.0	
>=30	32	1.5	55	8.9	
Unknown	*188*	*9.1*	*130*	*21.1*	

ASA: American Society of Anesthesiologists. BMI: Body Mass Index.
[a] Patients per unique surgical procedure, no unique patients.
[b] Registered since September 2017. Percentages are calculated for a smaller population: n=2076 (cosmetic), n=617 (reconstructive).

Between 2016 and 2017, a decrease in the use of textured implants was seen for both indication groups (cosmetic: 96% to 89%, *P*-value <0.001; reconstructive: 94-92%, *P*-value = 0.04) (*Figure 3*). A similar trend was observed for the use of silicone coated devices (cosmetic: 98-95%, *P*-value <0.001; reconstructive: 95-90%, *P*-value <0.001). Furthermore, in the reconstructive group, an increase in the use of round implants (11-15%, *P*-value <0.001) and silicone filled implants (78-85%, *P*-value <0.001) was found. Characteristics of the 11,378 devices inserted for no specified indication are listed in *Supplementary table 1b*.

Figure 3. Device characteristics per inserted device (2015-2017).
Textured vs smooth shell, silicone vs polyurethane coating, silicone vs saline fill, anatomical vs round shape. 2015 was not a complete registration year, and is therefore not included in this figure.
*Cosmetic (2016 n=8995; 2017 n=11,253), Reconstructive (2016 n=1546; 2017 n=2175), <5% missing characteristics. *P-value <0.001.*



Surgery characteristics

In the patients with a known indication for surgery, 26,036 (85.2%) breast implants were inserted for a cosmetic breast augmentation. Almost all cosmetic procedures were performed bilaterally (99.0%). Patients in the reconstructive group, however, more frequently underwent a unilateral procedure (52.1%, 2349 of the 4505 devices). As shown in *Table 2*, the incision site for a cosmetic breast augmentation was most frequently the inframammary fold (93.7%), while in reconstructive procedures the mastectomy scar was used in most cases (53.1%). For both cosmetic and reconstructive indications, most devices were placed with full coverage of the pectoral muscle (26.2% and 39.6%, respectively) or dual plane (47.4% and 33.6%, respectively). Autologous flap cover, fat grafting or a MESH or acellular dermal matrix (ADM) were not often used for both indications. See *Supplementary table 1c* for all surgery characteristics of the records in which no indication was specified.

National variation in the use of infection control measures

A wide variation was observed between healthcare institutions in the use of four selected perioperative infection control measures (all ranged 0-100%) (*Figure 4*). From 2016 to 2017, the proportion of procedures (per breast) in which surgeons changed their gloves before the insertion of an implant increased from 88% to 89% in reconstructive indications and from 61% to 80% in cosmetic augmentations. Furthermore, an increase was observed regarding rinsing the breast implant with an antiseptic solution before

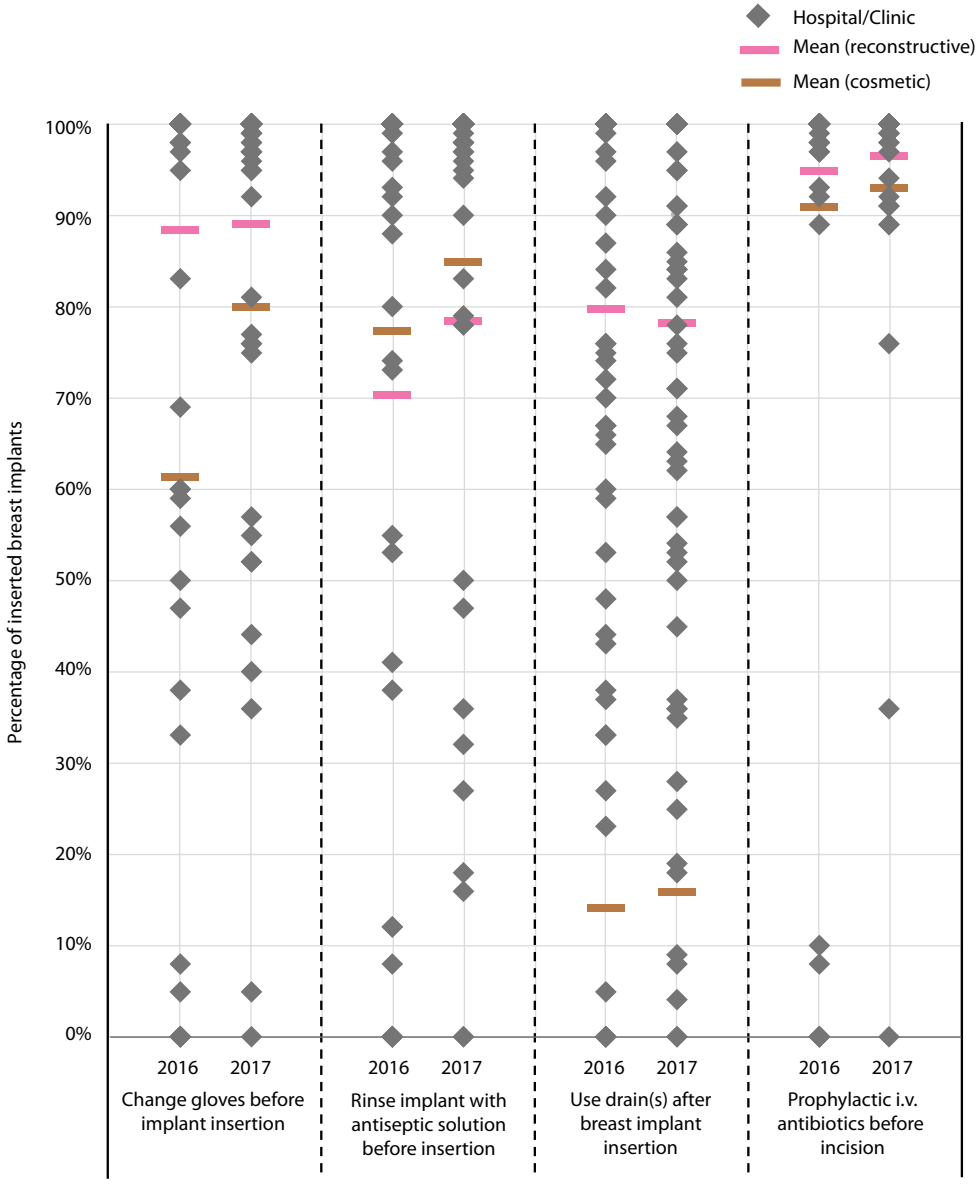
Table 2. Surgery characteristics, presented at the breast level (2015-2017).

	Cosmetic		**Reconstructive**	
	n	%	n	%
Breasts[A]	26,036		4505	
Incision site				
Inframammary	24,404	93.7	854	19.0
Mastectomy scar	194	0.7	2391	53.1
Axillary	55	0.2	1	0.0
Areolar	109	0.4	370	8.2
Latissimus Dorsi	0	0.0	218	4.8
Other	1072	4.1	344	7.6
Unknown	*202*	*0.8*	*327*	*7.3*
Plane				
Subglandular	3584	13.8	173	3.8
Subfascial	1823	7.0	34	0.8
Sub flap	13	0.0	360	8.0
Subcutaneous	20	0.1	52	1.2
Full pectoral muscle	6830	26.2	1783	39.6
Dual plane	12,343	47.4	1512	33.6
Unknown	*1,423*	*5.5*	*591*	*13.1*
Mastopexy				
Yes	935	3.6	212	4.7
No	24,567	94.4	3659	81.2
Unknown	*534*	*2.1*	*634*	*14.1*
Autologous flap cover				
Yes	95	0.4	511	11.4
No	25,386	97.5	3362	74.6
Unknown	*555*	*2.1*	*632*	*14.0*
Fat grafting				
Yes	14	0.1	87	1.9
No	25,486	97.9	3791	84.2
Unknown	*536*	*2.1*	*627*	*13.9*
Mesh/ADM use				
Yes	16	0.1	333	7.4
No	25,487	97.9	3776	83.8
Unknown	*533*	*2.0*	*396*	*8.8*

ADM: Acellular Dermal Matrix.
[a] Breasts per unique surgical procedure, no unique breasts.

insertion (from 70% to 78% (reconstructive), and from 78% to 85% (cosmetic)). Increased use of prophylactic intravenous antibiotics before the incision was noticed too, from 95% to 97% (reconstructive) and from 91% to 93% (cosmetic). The use of drains decreased in reconstructive procedures (80-78%) but increased in cosmetic augmentations (14-16%).

Figure 4. Nationwide variation for a selection of infection control measures (2016-2017), presented on breast level.
2015 was not a complete registration year, and is therefore not included in this figure.



DISCUSSION

This study provides an overview of the first outcomes and experiences of the Dutch Breast Implant Registry (DBIR), one of the first opt-out breast implant registries in the world. Since the national rollout in April 2015, information on 41,919 breast implants has been registered, including details of patients, devices, and procedures. The participation rate of hospitals (95%) and private clinics (78%) is high compared to other breast implant registries in the world with a maximum participation rate of 80% (or unknown capture rates).[15-18] For the first time, we were able to calculate the minimum breast implantation incidence rate in the Netherlands. In 2016 and 2017, at least one woman per 1649 women or one per 1691 women, respectively, received one or more breast implant(s). However, it must be realized that this incidence rate is an underestimation, considering the current nationwide coverage of procedures.

Essentially, there were two different groups of patients undergoing breast implant surgery with significant differences in characteristics: elective patients undergoing augmentation for cosmetic reasons who are generally young, healthy adults versus more complex patients requiring reconstructive surgery (mainly) after breast cancer treatment. Within our population, there was a predominance of textured silicone gel implants used for both indications, which is in line with other European countries but in contrast to the United States.[26-27] However, a significant increase in the use of smooth implants was observed, which appears to coincide with the critical issue of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), a rare cancer of the immune system believed to be causally associated with textured breast implants.[28-29] In recent research of Becherer and de Boer et al., data of DBIR and the Dutch Nationwide Network and Registry of Histo- and Cytopathology (PALGA) were combined, resulting in a dataset with pathological, clinical, and implant-related information. This demonstrates the potential of DBIR as an important tool for health risk assessments of implants.[30]

The main purpose of DBIR is to improve the quality of breast implant surgery in the Netherlands by providing benchmarked information of a set of process and outcome measures (quality indicators). Several other clinical audits have preceded, leading to substantial improvements in quality of care.[31-33] As an example of possible interesting process indicators, the national variation in the use of 4 infection control measures was presented (the use of antibiotics, antiseptic rinse of the implant, glove change before implant handling, and the use of postoperative drains). A wide variation from 0 to 100% between healthcare institutions in the use of these measures was seen. Understanding the nature of this variation and the effect of infection prevention on clinically relevant outcomes, is paramount in decision-making about improvement efforts.

A balance is required between capturing all valuable information, on the one hand, and spending an acceptable amount of time needed for data entry, on the other hand. To reduce the administrative burden and minimize the chance of typing errors, the GS1 barcode system was implemented in the online data form of DBIR. With the help of this barcode, relevant implant characteristics, including the unique device identification (UDI) number, is automatically retrieved and registered. This will also help to decrease the amount of missing information of implant characteristics. Fortunately, an increasing amount of implant manufacturers are using a correct GS1 barcode in the Netherlands.

In general, completeness of the DBIR data has increased during the last three years.[23] It can be deduced from our results that missing data are not random but patient records in certain hospitals. The DBIR online system provides already instant feedback on missing records using a "list of errors". Further, a data verification project to evaluate the validity of the data will be scheduled shortly.

FUTURE PERSPECTIVES

To provide clinicians with outcome information and recommendations for change in practice in the near future, research projects with more mature data are scheduled and other outcome indicators are being evaluated. Potential outcome indicators are the percentage of explanations due to complications within an *x* number of days or implant rupture rates. Additionally, DBIR plans to add patient-reported outcome measures to the registry. For this, the registry awaits the BREAST-Q Implant Surveillance module, which contains 5 questions, particularly developed to measure patient-reported outcomes in women with breast implants.[34]

Internationally, the International Collaboration of Breast Registry Activities (ICOBRA) has defined an internationally agreed minimum core set of data points to be used by all breast device registries globally.[35] This dataset is integrated into the DBIR dataset. A future step is to combine breast implant registries globally to perform implant surveillance and evaluate clinical outcomes at an international level. Long-term data will eventually reveal the actual health effects of breast implants and breast implant surgery.

CONCLUSIONS

The opt-out DBIR is one of the first up-and-running breast implant registries worldwide, which is the result of collaborative and conjoint efforts from clinicians, healthcare providers, and policymakers. First experiences with DBIR and its preliminary results show that DBIR

has the potential to provide answers to clinically relevant questions and to provide quality assurance and outcome research for breast implant surgery.

REFERENCES

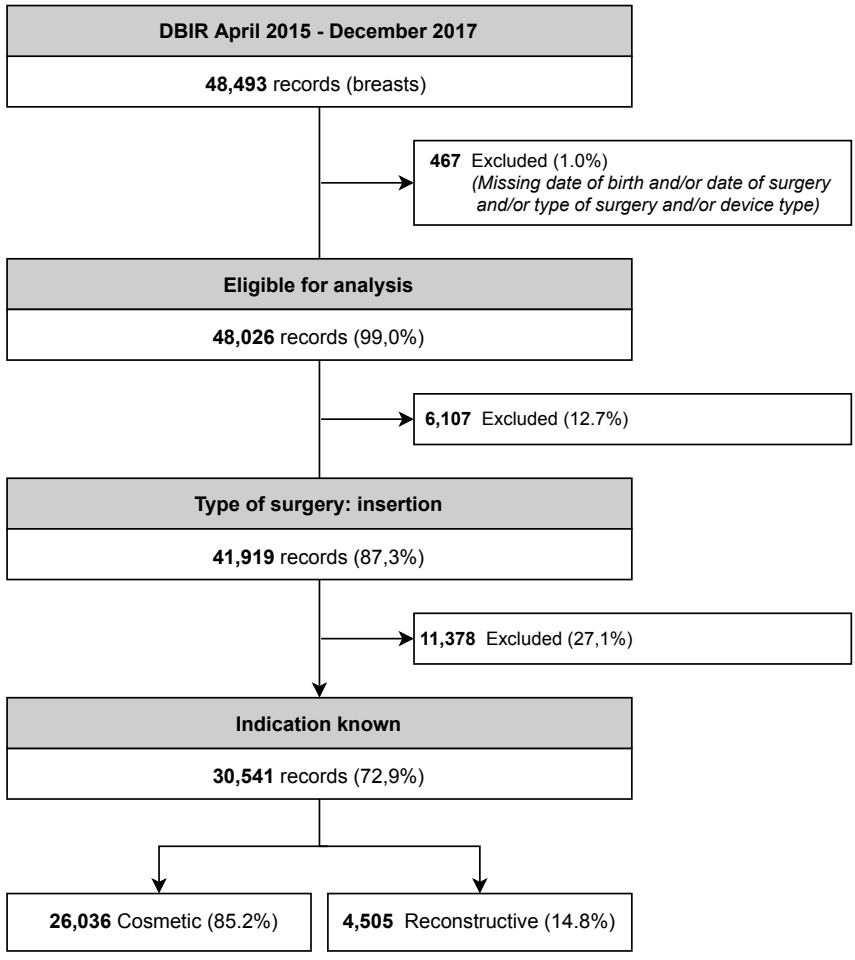
1. Rocco N, Rispoli C, Moja L, Amato B, Lannone L, Testa S, et al. Different types of implants for reconstructive breast surgery. Cochrane Database Syst Rev. 2016;(5):CD010895.
2. Coroneos CJ, Selber JC, Offodile AC, Butler CE, Clemens MW. US FDA Breast Implant Postapproval Studies: Long-term Outcomes in 99,993 Patients. Ann Surg. 2019;269(1):30-6.
3. Cheng NX, Chen B, Li Q, Wu DH, Zhu L, Zhang XM, et al. Late haematoma and seroma in patients with silicone mammary prosthesis: our reports and literature review. J Plast Reconstr Aesthetic Surg. 2011;64(7):185–6.
4. Park BY, Lee DH, Lim SY, Pyon JK, Mun GH, Oh KS, et al. Is late seroma a phenomenon related to textured implants? A report of rare complications and a literature review. Aesthetic Plast Surg. 2014;38(1):139–45.
5. de Boer M, van Leeuwen FE, Hauptmann M, Overbeek LIH, de Boer JP, Hijmering NJ, et al. Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast. JAMA Oncol. 2018;4(3):335-41.
6. Thompson PA, Prince HM. Breast implant-associated anaplastic large cell lymphoma: a systematic review of the literature and mini-meta analysis. Curr Hematol Malig Rep. 2013;8(3):196–210.
7. de Jong D, Vasmel WL, de Boer JP, Verhave G, Barbé E, Casparie MK, et al. Anaplastic large-cell lymphoma in women with breast implants. JAMA. 2008;300(17):2030–5.
8. Hennekens CH, Lee IM, Cook NR, Hebert PR, Karlson EW, LaMotte F, et al. Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. JAMA. 1996;275(8):616–21.
9. Sánchez-Guerrero J, Colditz GA, Karlson EW, Hunter DJ, Speizer FE, Liang MH. Silicone breast implants and the risk of connective-tissue diseases and symptoms. N Engl J Med. 1995;332(25):1666–70.
10. Watad A, Rosenberg V, Tiosano S, Cohen Tervaert JW, Yavne Y, Shoenfeld Y, et al. Silicone breast implants and the risk of autoimmune / rheumatic disorders: a real-world analysis. Int J Epidermiol. 2018;47(6):1846-54.
11. Balk EM, Earley A, Avendano EA, Raman G. Long-Term Health Outcomes in Women With Silicone Gel Breast Implants: A Systematic Review. Ann Intern Med. 2016;164(3):164-75.
12. Coroneos CJ, Selber JC, Offodile AC, Butler CE, Clemens MW. US FDA Breast Implant Postapproval Studies: Long-term Outcomes in 99,993 Patients. Ann Surg. 2019;269(1):30-6.
13. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. PLoS Med. 2008;5(3):e67.
14. Colwell AS, Mehrara B. Editorial: US FDA Breast Implant Postapproval Studies–Long-term Outcomes in 99,993 Patients. Ann Surg. 2019;269(1):39-40.
15. Renner C, Neuhann-Lorenz C. International breast implant registry: A user report. Aesthetic Plast Surg. 2006;30(5):616–21.
16. Henriksen TF, Holmich LR, Friis S, McLaughlin JK, Fryzek JP, Pernille Hoyer A, et al. The Danish Registry for Plastic Surgery of the Breast: establishment of a nationwide registry for prospective

follow-up, quality assessment, and investigation of breast surgery. Plast Reconstr Surg. 2003;111(7):2182-9; discussion 90-1.
17. Shakespeare PG, Bazire N, Whitworth IH. The UK breast implant registry-ten years on. Br J Plast Surg. 2005;58(3):283–5.
18. Wurzer P, Rappl T, Friedl H, Kamolz LP, Spendel S, Hoflehner H, et al. The Austrian Breast Implant Register: Recent Trends in Implant-Based Breast Surgery. Aesthetic Plast Surg. 2014;38(6):1109–15.
19. Rowell KS, Turrentine FE, Hutter MM, Khuri SF, Henderson WG. Use of National Surgical Quality Improvement Program Data as a Catalyst for Quality Improvement. J Am Coll Surg 2007;204(6):1293–300.
20. Heidekrueger PI, Juran S, Patel A, Tanna N, Broer PN. Plastic Surgery Statistics in the US: Evidence and Implications. Aesthetic Plast Surg. 2016;40(2):293–300.
21. Rakhorst HA, Mureau MAM, Cooter RD, McNeil J, van Hooff M, van der Hulst R, et al. The new opt-out Dutch National Breast Implant Registry–Lessons learnt from the road to implementation. J Plast Reconstr Aesthet Surg. 2017;70(10):1354-60.
22. https://nvpc.nl. Accessed September, 4th, 2018.
23. Becherer BE, Rakhorst HA, Mureau MAM, Hommes JE, Hoornweg MJ, Keuter XHA, et al. Dutch Breast Implant Registry (DBIR)–Annual Report (2015-2017). Dutch Institute for Clinical Auditing (DICA);November 2018.
24. https://mrdm.nl. Accessed September, 4th, 2018.
25. https://opendata.cbs.nl/statline. Accessed September 4, 2018.
26. Tandon VJ, DeLong MR, Ballard TN, Clemens MW, Brandt KE, Kenkel JM, et al. Evolving trends in textured implants use for cosmetic augmentation in the United States. Plast Reconstr Surg. 2018;142(6):1456-61.
27. Deva AK. Discussion: evolving trends in textured implants use for cosmetic augmentation in the United States. Plast Reconstr Surg. 2018;142(6):1464-6.
28. Doren EL, Miranda RN, Selber JC, Garvey PB, Liu J, Medeiros LJ, et al. U.S. Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Plast Reconstr Surg. 2017;139(5):1042-50.
29. Loch-Wilkinson A, Beath KJ, Knight RJW, Wessels WLF, Magnusson M, Papadopoulos T, et al. Breast Implant-Associated Anaplastic Large Cell Lymphoma in Australia and New Zealand: High-Surface-Area Textured Implants Are Associated with Increased Risk. Plast Reconstr Surg. 2017;140(4):645-54.
30. Becherer BE, de Boer M, Spronk PER, Bruggink AH, de Boer JP, van Leeuwen FE, et al. The Dutch Breast Implant Registry (DBIR): Registration of Breast Implant–Associated Anaplastic Large Cell Lymphoma (BIA-ALCL), a proof of concept. Plast Reconstr Surg. 2019;143(5):1298-1306.
31. Van Leersum NJ, Kolfschoten NE, Klinkenbijl JHG, Tollenaar RAEM, Wouters MWJM. ['Clinical Auditing', a novel tool for quality assesment in surgical oncology]. Ned Tijdschr Geneesk. 2011;155(45):A4136.

32. Bergqvist D, Troëng T, Elfström J, Hedberg B, Ljungström KG, Norgren L, et al. Auditing Surgical Outcome: Ten years with The Swedish Vascular Registry–Swedvasc. The Steering Committee of Swedvasc. Eur J Surg Suppl. 1998;(581):3–8.
33. Van Bommel ACM, Spronk PER, Vrancken Peeters MTFD, Jager A, Lobbes M, Maduro JH, et al. Clinical Auditing as an Instrument for Quality Improvement in Breast Cancer Care in the Netherlands: The National NABON Breast Cancer Audit. J Surg Oncol. 2017;115(3):243–9.
34. Ng S, Pusic A, Parker E, Vishwanath S, Cooter RD, Elder E, et al. Patient-Reported Outcome Measures for Breast Implant Surgery: A Pilot Study. Aesthet Surg J. 2019;39(8):NP314-NP21.
35. Spronk PE, Begum H, Vishwanath S, Crosby A, Earnest A, Elder E, et al. Toward International Harmonization of Breast Implant Registries: ICOBRA global common dataset. Plastic and Reconstructive Surgery. 2020;146(2):255-67.

SUPPLEMENTARY DATA

Supplementary figure 1. Patient selection process.



Supplementary table 1a. Patient characteristics per surgical procedure in which no indication was specified, presented on patient level (2015-2017).

	Indication not specified	
	n	%
Patients[A]	6,884	
Age		
<30	750	10.9
30-39	1,336	19.4
40-49	1,701	24.7
50-59	1,878	27.3
>60	1,219	17.7
ASA		
I	5,149	74.8
II	1,417	20.6
III-IV	130	1.9
Unknown	*188*	*2.7*
Smoking[B]		
Yes	2	4.8
No	1	2.4
Unknown	*39*	*92.9*
BMI[B] (kg/m^2)		
<18.5	0	0.0
18.5-25	6	14.3
25–30	0	0.0
>=30	0	0.0
Unknown	*36*	*85.7*

ASA: American Society of Anesthesiologists. BMI: Body Mass Index.
[A] Patients per unique surgical procedure, no unique patients.
[B] Registered since September 2017. Percentages are calculated for a smaller population: n=42.

Supplementary table 1b. Device characteristics per inserted device for the records in which no indication was specified (2015-2017).

	Indication not specified	
	n	n
Inserted devices	11,378	
Texture		
Smooth	164	1.4
Textured	9.353	82.2
Unknown	*1,861*	16.4
Coating		
Silicone	9,517	83.6
Polyurethane	1,130	9.9
Unknown	*731*	6.4
Fill		
Silicone	10,080	88.8
Saline	155	1.4
Hydrogel	106	0.9
Unknown	*1,013*	8.9
Shape		
Round	4,989	43.8
Anatomical	5,529	48.6
Unknown	*860*	*7.6*
Volume[A] (median, in cc with IQR)	N/A	

IQR: Interquartile Range. N/A: not applicable.
[A] Registered since September 2017. Percentages are calculated for a smaller population: n=0.

Supplementary table 1c. Surgery characteristics for the records in which no indication was specified, presented on breast level (2015-2017).

	Indication not specified	
	n	%
Breasts[A]	26,036	
Incision site		
Inframammary	6,228	54.7
Mastectomy scar	2,389	21.0
Axillary	10	0.1
Areolar	150	1.3
Latissimus Dorsi	206	1.8
Other	271	2.4
Unknown	*2,124*	*18.7*
Plane		
Subglandular	1,444	12.7
Subfascial	108	0.9
Sub flap	393	3.5
Subcutaneous	53	0.5
Full pectoral muscle	3,035	26.7
Dual plane	1,654	14.5
Unknown	*4,691*	*41.2*
Mastopexy		
Yes	473	4.2
No	8,534	75.0
Unknown	*2,371*	*20.8*
Autologous flap cover		
Yes	252	2.2
No	8,780	77.2
Unknown	*2,346*	*20.6*
Fat grafting		
Yes	157	1.4
No	8,892	78.2
Unknown	*2,329*	*20.5*
Mesh/ADM use		
Yes	62	0.5
No	9,102	80.0
Unknown	*2,214*	*19.5*

ADM: Acellular Dermal Matrix.
[A] Breasts per unique surgical procedure, no unique breasts.

PART II

VARIATION IN SURGICAL PRACTICE AND OUTCOMES


4

CHAPTER 4

VARIATION IN THE USE OF INFECTION CONTROL MEASURES AND INFECTION-RELATED REVISION INCIDENCE AFTER BREAST IMPLANT SURGERY IN THE NETHERLANDS.

B.E. Becherer
P.J. Marang-van de Mheen
D.A. Young-Afat
R.R.W.J. van der Hulst
X.H.A. Keuter
H.A. Rakhorst
M.A.M. Mureau
on behalf of the Dutch Breast Implant Registry (DBIR) group

Submitted.

ABSTRACT

Background: The use and effect of most infection control measures (ICMs) in breast implant surgery are still debated, likely resulting in variation in current practices. This study investigated the relationship between the number and combinations of ICMs used and the infection-related revision incidence after breast implant surgery. Additionally, national variation between Dutch healthcare institutions in ICM-use was evaluated.

Methods: For this multicentre, population-based study, all patients who received a primary breast implant or tissue expander for breast reconstruction or augmentation between 2015 and 2019 were identified in the Dutch Breast Implant Registry. Seven prospectively collected ICMs were investigated: preoperative antibiotics, implant and/or pocket irrigation, glove change, nipple guards, insertion sleeve, postoperative drains, and postoperative antibiotics.

Results: 52415 implants were included (15 percent reconstruction, 85 percent augmentation). For reconstruction, the median (IQR) number of ICMs used was four (4-5), for augmentation, three (3-4). Median follow-up was 34 months (reconstruction) and 30 months (augmentation). Infection-related revision incidence was 2.1 percent (reconstruction) and 0.1 percent (augmentation). Most infection-related revisions occurred within 2.5 months (reconstruction) and 2 months (augmentation). The impact of ICM-use on infection-related revision incidence remained unclear, given the low incidence. Between institutions, most variation was observed for postoperative antibiotics and drains.

Conclusion: Although the use of different ICMs varied considerably between institutions, infection-related revision incidence after breast implant surgery was low. Most surgeons used 4 ICMs for breast reconstruction and 3 ICMs for breast augmentation. Further exploration of the reasons for and impact of the observed variation is needed.

INTRODUCTION

In many countries, breast augmentation is the most performed cosmetic surgical procedure. Breast reconstruction is one of the most performed reconstructive procedures in plastic surgery.[1-3] In the Netherlands, approximately 1 in 30 women have one or two breast implant(s).[4] The majority of these women (85 percent) received breast implants for cosmetic augmentation and 15 percent for breast reconstruction.[5,6]

Unplanned revision of a breast implant or tissue expander is one of the most severe complications following breast implant surgery. Reported incidences are up to 6 percent in patients undergoing breast reconstruction and up to 3 percent after a cosmetic augmentation.[7-10] Several studies have identified potential predictors or risk factors for postoperative complications after breast implant surgery.[7-9,11-16] These predictors or risk factors, however, cannot always be controlled by surgeons or are not always associated with the quality of care delivered (e.g., radiotherapy or smoking). Therefore, to further reduce the unplanned revision incidence, clinicians need information on factors associated with these revisions that can be modified in daily clinical practice.

Many unplanned revisions are related to surgical site infections.[9,12,17] Therefore, perioperative measures that could potentially result in fewer infections are of particular interest. Various guidelines advise administering prophylactic antibiotics before incision.[18-21] However, especially in the current era of evidence-based medicine, the beneficial effects of other measures such as postoperative antibiotics or nipple guards are still under debate.[20,22-26] Therefore, the first aim of the present study was to investigate the association between the number and combinations of infection control measures (ICMs) used per breast implant insertion procedure and the infection-related cumulative revision incidence over time. The second aim was to investigate the national variation between Dutch healthcare institutions in the use of each ICM.

METHODS

Design and Study Population

This observational cohort study included all women who had been prospectively registered in the Dutch Breast Implant Registry (DBIR) after receiving at least one primary breast implant or tissue expander between January 1, 2015, and December 31, 2019. Indications for a breast implant or tissue expander were breast reconstruction or augmentation. Patients who had received any previous breast implant surgery or in whom additional surgical techniques had been used during implant insertion (ADM/Mesh, fat grafting, autologous flap cover, or mastopexy) were excluded from analysis to reduce group heterogeneity.

Patients with missing data about the use of ICMs were excluded as well (*Supplementary figure 1*).

Data Collection: The Dutch Breast Implant Registry

The DBIR is a national, population-based registry, for which data collection started in 2015. Per inserted or explanted implant, information on patient, surgery, and implant characteristics are collected. In the Netherlands, breast implant surgery is performed in both hospitals and private clinics. Currently, 74 hospitals (100 percent) and 37 private clinics (95 percent) where breast implant surgery is being performed actively register breast implants and tissue expanders in DBIR. Data is securely stored at a Dutch Trusted Third Party for medical data (MRDM), according to the General Data Protection Regulation (GDPR). More details about the registry have been described previously.[27-29] For the current study, the last data update was on May 8, 2020.

Definitions

Primary implant insertion was defined as the first operation known in the registry in which a new breast implant or tissue expander was inserted. Breast reconstruction included reconstructions after mastectomy due to breast cancer, after risk-reducing mastectomy, or after benign conditions such as a congenital deformity, tuberous breasts, or gender-affirming surgery. Breast augmentation was defined as a surgical intervention to enlarge breasts for cosmetic reasons. Seven prospectively collected infection control measures (ICMs) were evaluated: preoperative prophylactic antibiotics, implant and/or pocket irrigation with betadine and/or an antibiotic solution, change of gloves before implant handling, nipple guards, use of an insertion sleeve such as the Keller funnel, postoperative drains, and postoperative prophylactic antibiotics. Per implant, the total number of ICMs used at implant insertion was calculated and classified as lower than the median number, equal to, or higher than the median number of ICMs. Infection-related revision surgery was defined as the first reoperation after insertion, in which the implant or expander was repositioned, explanted, or replaced due to an infection. Exact definitions of all variables used for analysis are based on the ICOBRA (International Collaboration of Breast Device Activities) core dataset and can be found in the Data Dictionary (*Supplementary table 1*).[30]

Outcomes

The outcomes were the number and combinations of ICMs used per primary implant insertion, the infection-related cumulative revision incidence over time in relation to the number of ICMs used, and variation between Dutch healthcare institutions in the use of each ICM.

Statistical Analysis

All analyses were performed separately for breast reconstructions and breast augmentations, with the implant as the unit of analysis, because most of the ICMs were applied per implant side, and each implant had a risk of revision surgery.

Missing data patterns were evaluated, resulting in the assumption of data being missing at random. Multiple imputation by chained equations was performed, creating 10 imputed datasets with each 50 iterations, using all variables, including the outcome variable ('mice' package version 3.11.0).[31,32] In the case of highly correlated variables, only one was used as auxiliary variable. The outcome variable itself was not imputed. Statistical models were fitted and results were pooled following Rubin's rules.[33] See *Supplementary table 2* for non-imputed data.

Baseline characteristics were compared between the groups with less than, equal, or more than the median number of ICMs used per primary implant insertion. Student's t-tests were performed for continuous variables and Chi-square tests or Fisher's exact tests for categorical variables. Reported *P*-values were two-sided, and values <0.05 were considered statistically significant.

The crude, infection-related cumulative revision incidence was calculated for both indication groups using the Fine-Gray cumulative incidence function.[34] Scheduled replacements of tissue expanders for breast implants and unplanned revisions due to other indications were included as competing risks. Subsequently, we compared the infection-related cumulative revision incidence between the three ICM groups using a log-rank test. Implants without any revision at closure of the dataset on May 8, 2020, were censored.

The variation between healthcare institutions in the use of each ICM was calculated for the years 2015-2019 and visualized in Sina plots, including nationwide means and 95 percent confidence intervals.

All analyses were performed with R software, version 1.3.959 – © 2009-2020, RStudio, Inc.

RESULTS

From 2015 to 2019, a total of 28653 patients and 52415 implants met the inclusion criteria (*Supplementary figure 1*). Of these, 7941 implants (15.2 percent) were inserted for breast reconstruction and 44474 (84.8 percent) for breast augmentation. The procedures were performed in 114 healthcare institutions, including university or specialized (breast) cancer hospitals, general hospitals, and private clinics.

Number of Infection Control Measures Used

For breast reconstruction, the median number of ICMs used per primary implant insertion was four (IQR 4-5). Of the 7941 primary implant procedures, 20.4 percent (n=1621) were performed with fewer than four ICMs, 36.8 percent (n=2921) with four ICMs, and 42.8

percent (n=3399) with more than four ICMs (*Figure 1A)*. Among these three ICM groups, statistically significant differences were seen in most baseline characteristics (*Table 1*).

For breast augmentation, the median number of ICMs used per primary implant insertion was three (IQR 3-4). Of the 44474 primary augmentation procedures, 17.8 percent (n=7904) were performed with fewer than three ICMs, 46.7 percent (n=20771) with three ICMs, and 35.5 percent (n=15799) with more than three ICMs (*Figure 1B*). These three ICM groups showed statistically significant differences in all baseline characteristics (*Table 1*).

Figure 1. Number of infection control measures used per primary implant insertion. *(ICMs, infection control measures.)*

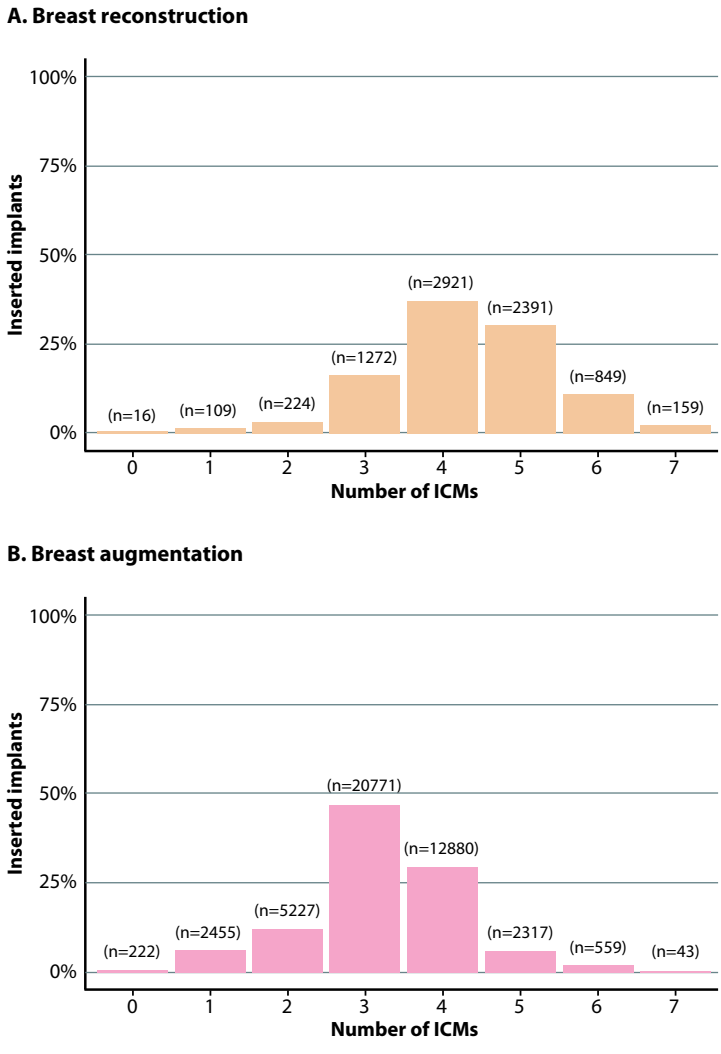


Table 1. Patient, surgery, and implant characteristics per number of infection control measures used, per primary implant insertion.

	Breast Reconstruction				Breast Augmentation			
	<4 ICMs (<median, *n* = 1621)	**4 ICMs** (median, *n* = 2921)	**>4 ICMs** (>median, *n* = 3399)	***P***	**<3 ICMs** (<median, *n* = 7904)	**3 ICMs** (median, *n* = 20771)	**>3 ICMs** (>median, *n* = 15799)	***P***
Patient Characteristics								
Age in years*	47.6 (12.2)	47.6 (12.0)	48.5 (11.6)	0.003	31.0 (9.0)	30.8 (8.9)	32.3 (9.9)	<0.001
ASA classification								
I	1191 (73.4)	1934 (66.2)	2100 (61.8)	<0.001	7435 (94.1)	20118 (96.9)	14378 (91.0)	<0.001
II	385 (23.8)	907 (31.1)	1185 (34.8)		464 (5.9)	640 (3.1)	1368 (8.7)	
III+	45 (2.8)	80 (2.7)	114 (3.4)		5 (0.1)	13 (0.1)	53 (0.3)	
Body mass index in kg/m²†	23.5 (21.3-26.4)	23.8 (21.2-26.9)	24.1 (21.6-27.0)	<0.001	21.6 (19.4-24.1)	21.6 (19.7-23.9)	21.4 (19.6-23.5)	<0.001
Smoking status								
Not smoking	1427 (88.0)	2566 (87.8)	3003 (88.3)	0.820	6672 (84.4)	16758 (80.7)	12591 (79.7)	<0.001
Smoking	194 (12.0)	355 (12.2)	396 (11.7)		1232 (15.6)	4013 (19.3)	3208 (20.3)	
Previous radiotherapy								
No	1509 (93.1)	2774 (95.0)	3225 (94.9)	0.007	7864 (99.5)	20739 (99.8)	15757 (99.7)	<0.001
Yes	112 (6.9)	147 (5.0)	174 (5.1)		40 (0.5)	32 (0.2)	42 (0.3)	
Surgery Characteristics								
Year of surgery								
2015	298 (18.4)	547 (18.7)	435 (12.8)	<0.001	1780 (22.5)	2204 (10.6)	1429 (9.1)	<0.001
2016	312 (19.2)	716 (24.5)	728 (21.4)		2576 (32.6)	3563 (17.2)	2437 (15.4)	
2017	283 (17.5)	687 (23.5)	738 (21.7)		1784 (22.6)	5053 (24.3)	3182 (20.1)	
2018	295 (18.2)	511 (17.5)	749 (22.0)		915 (11.6)	4926 (23.7)	4329 (27.4)	
2019	433 (26.7)	460 (15.7)	749 (22.0)		849 (10.7)	5025 (24.2)	4422 (28.0)	
Healthcare institution volume per year								
<100 implant surgeries	430 (26.5)	891 (30.5)	1156 (34.0)	<0.001	509 (6.5)	594 (2.9)	1401 (8.9)	<0.001
100-249 implant surgeries	626 (38.6)	1536 (52.6)	1774 (52.2)		1147 (14.5)	2298 (11.1)	3263 (20.6)	
250-500 implant surgeries	297 (18.3)	456 (15.6)	437 (12.9)		2130 (26.9)	4250 (20.5)	5230 (33.1)	
>500 implant surgeries	268 (16.5)	38 (1.3)	32 (0.9)		4118 (52.1)	13629 (65.5)	5905 (37.4)	

	Breast Reconstruction				Breast Augmentation			
	<4 ICMs (<median, *n* = 1621)	**4 ICMs** (median, *n* = 2921)	**>4 ICMs** (>median, *n* = 3399)	***P***	**<3 ICMs** (<median, *n* = 7904)	**3 ICMs** (median, *n* = 20771)	**>3 ICMs** (>median, *n* = 15799)	***P***
Laterality								
Unilateral	996 (61.4)	1606 (55.0)	2030 (59.7)	<0.001	34 (0.4)	53 (0.3)	175 (1.1)	<0.001
Bilateral	625 (38.6)	1315 (45.0)	1369 (40.3)		7870 (99.6)	20718 (99.7)	15624 (98.9)	
Incision site								
Inframammary	298 (18.4)	377 (12.9)	488 (14.4)		7726 (97.7)	20503 (98.7)	15562 (98.5)	
Mastectomy scar	1109 (68.4)	2112 (72.3)	2517 (74.1)	<0.001	94 (1.2)	106 (0.5)	91 (0.6)	<0.001
Areolar	129 (8.0)	278 (9.5)	278 (8.2)		23 (0.3)	33 (0.2)	56 (0.4)	
Other	85 (5.2)	154 (5.3)	116 (3.4)		61 (0.8)	129 (0.6)	90 (0.5)	
Plane								
Subglandular	0 (0)	0 (0)	0 (0)		1150 (14.5)	2604 (12.5)	2813 (17.8)	
Subcutaneous or subfascial	154 (9.5)	145 (5.0)	211 (6.2)	<0.001	241 (3.0)	2828 (13.6)	539 (3.4)	<0.001
Completely covered with PM	874 (53.9)	1809 (61.9)	2176 (64.0)		2229 (28.2)	2807 (13.5)	2011 (12.7)	
Partially covered with PM	593 (36.6)	967 (33.1)	1012 (29.8)		4284 (60.3)	12532 (60.4)	10436 (66.1)	
Implant Characteristics								
Inserted implant type								
Breast implant	847 (52.3)	904 (30.9)	815 (24.0)	<0.001	7883 (99.7)	20737 (99.8)	15738 (99.6)	<0.001
Tissue expander	774 (47.7)	2017 (69.1)	2584 (76.0)		21 (0.3)	34 (0.2)	61 (0.4)	
Texture								
Textured	1523 (94.0)	2838 (97.2)	3249 (95.6)	<0.001	6830 (86.4)	19769 (95.2)	13768 (87.1)	<0.001
Smooth	57 (3.5)	21 (0.7)	32 (0.9)		179 (2.3)	770 (3.7)	1812 (11.5)	
Polyurethane	41 (2.5)	62 (2.1)	118 (3.5)		895 (11.3)	232 (1.1)	219 (1.4)	

*Values in parentheses are percentages unless indicated otherwise; values are *mean (SD) and †median (IQR). ICMs, infection control measures; ASA, American society of anesthesiologists; PM, pectoralis major.*

Combinations of Infection Control Measures

Most surgeons who only used one ICM during breast reconstruction used only postoperative drains (64.2 percent). If more than one ICM was used, postoperative drains were most frequently combined with preoperative antibiotics, followed by the change of gloves, implant and/or pocket irrigation, postoperative antibiotics, nipple guards, and an insertion sleeve (in this exact order).

Most surgeons who only used one ICM during breast augmentation used only preoperative antibiotics (73.1 percent). If more than one ICM was used, preoperative antibiotics were usually combined with implant and/or pocket irrigation, followed by the change of gloves, nipple guards, drains, postoperative antibiotics, and an insertion sleeve (in this exact order).

Cumulative Incidence of Infection-Related Revisions

For the total breast reconstruction group, the median follow-up was 33.7 (IQR 18.6-47.1) months. The crude cumulative incidence of infection-related revisions was 2.1 percent (95 percent CI 1.8-2.4) within three years (*Figure 2A*). Most infection-related revisions occurred within 2.5 months. The cumulative incidence of infection-related revisions differed between the three ICM groups, with 2.1 percent (95 percent CI 1.3-2.8) for less than four ICMs, 1.8 percent (95 percent CI 1.3-2.3) for four ICMs, and 2.8 percent (95 percent CI 2.2-3.4) for more than four ICMs (*P*-value = 0.020) (*Figure 2B*).

For the total breast augmentation group, the median follow-up was 30.1 (IQR 17.2-44.4) months. The crude cumulative incidence of infection-related revisions was 0.1 percent within three years (95 percent CI 0.1-0.1) (*Figure 2C*). Most infection-related revisions occurred within 2 months. The cumulative incidence of infection-related revisions between the three ICM groups was comparable, with <0.1 percent (95 percent CI 0-0.1) for less than three ICMs, 0.1 percent (95 percent CI 0.1-0.1) for three ICMs, and 0.1 percent (95 percent CI 0.1-0.2) for more than three ICMs (*P*-value = 0.500) (*Figure 2D*).

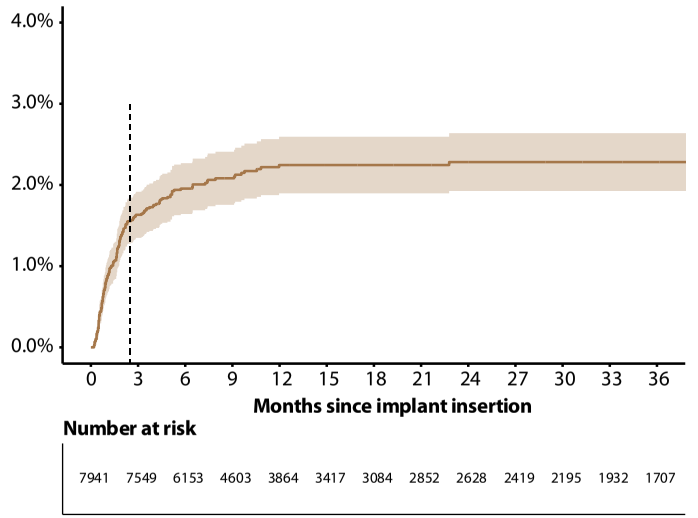
The association between the number of ICMs used and the infection-related revision incidence could not be studied further for both indication groups. Neither could the association between different combinations of ICMs and the infection-related revision incidence. Event rates were too low to appropriately adjust for confounding factors and to limit confounding by indication.

Nationwide Variation

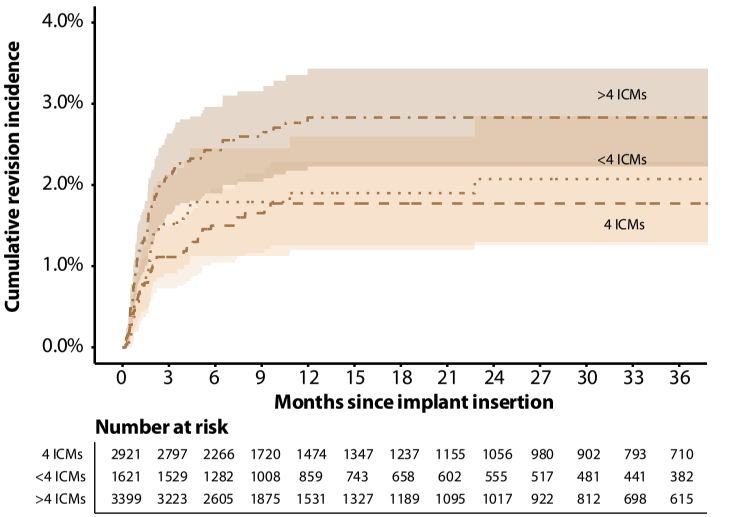
For reconstructive indications, the four most frequently used ICMs were preoperative antibiotics (nationwide mean 96.8 percent, 95 percent CI 83.1-100), drains (95.2 percent, 80.4-100), implant and/or pocket irrigation (93.0 percent, 64.4-100), and glove change (92.4 percent, 68.2-100) (*Figure 3A*). Between the institutions, most variation was seen in the use

Figure 2. Crude cumulative revision incidence of infection-related revisions since primary implant insertion.
*(Different scales on y-axis. The dotted line in 2A and 2C represents the time in which most infection-related revisions occurred (reconstruction: 2.5 months, augmentation: 2 months). ICM, infection control measure. Log-rank test: *P-value = 0.020 and †P-value = 0.500.)*

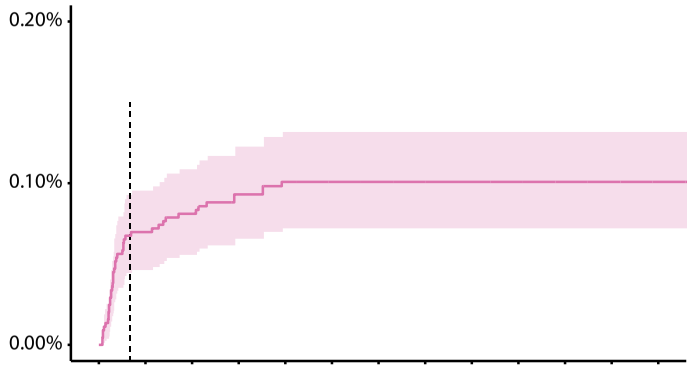
Breast reconstruction (total group)



B. Breast reconstruction (per ICM group)*



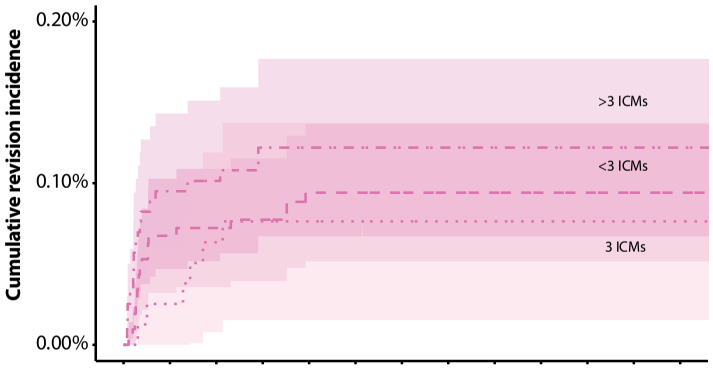
Breast augmentation (total group)



Number at risk

	44474	44398	42934	40456	37800	35100	32455	30082	27766	24689	22354	20066	17471

D. Breast augmentation (per ICM group)†

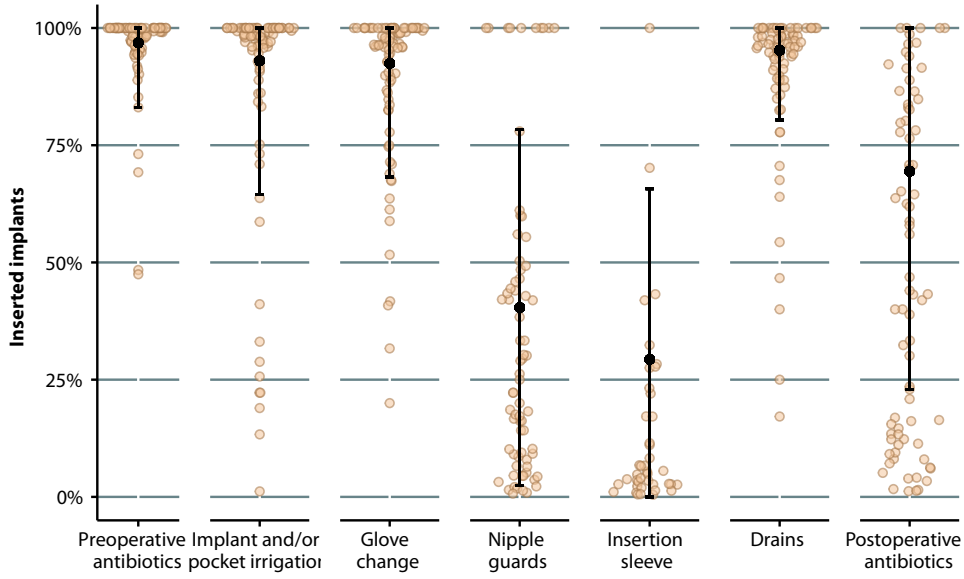


Number at risk

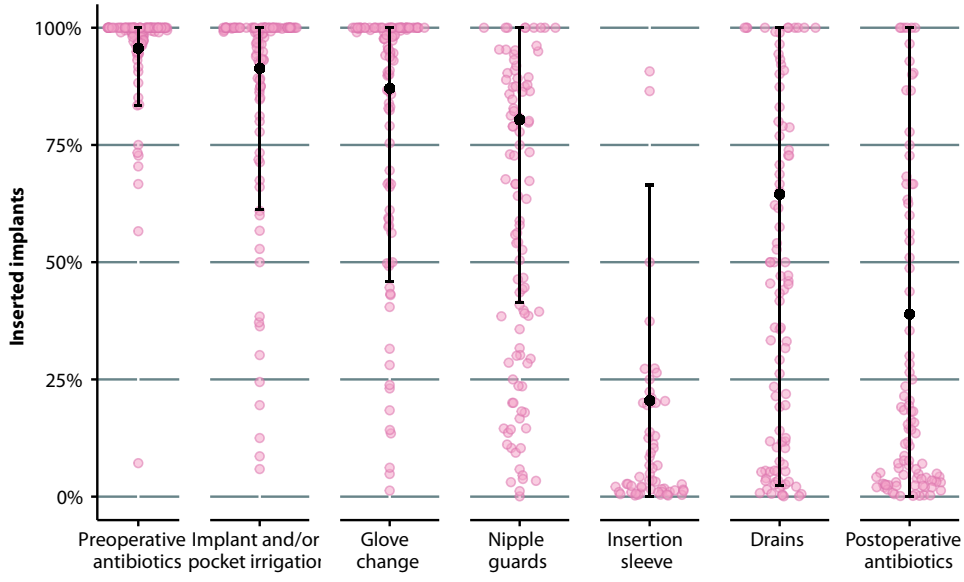
3 ICMs	20771	20742	19970	18754	17480	16257	15136	14043	12946	11255	10139	9022	7364
<3 ICMs	7904	7893	7755	7517	7268	7092	6838	6602	6374	6146	5913	5656	5325
>3 ICMs	15799	15763	15209	14185	13052	11751	10481	9437	8446	7288	6302	5388	4782

Figure 3. Nationwide variation in the proportion of implants being inserted with a particular infection control measure.
(The 95% confidence intervals are displayed around the nationwide mean in black.)

A. Breast reconstruction



B. Breast augmentation



of postoperative antibiotics (nationwide mean 69.4 percent, 95 percent CI 22.9-100), nipple guards (40.4 percent, 2.4-78.4), and an insertion sleeve (29.3 percent, 0-65.7).

For breast augmentations, the four most frequently used ICMs were preoperative antibiotics (nationwide mean 95.6 percent, 95 percent CI 83.4-100), implant and/or pocket irrigation (91.3 percent, 61.2-100), glove change (87.1 percent, 45.9-100), and nipple guards (80.4 percent, 41.4-100) (*Figure 3B*). Between the institutions, most variation was seen in the use of drains (nationwide mean 64.5 percent, 95 percent CI 2.4-100), postoperative antibiotics (38.9 percent, 0-100), and an insertion sleeve (20.5 percent, 0-66.5).

DISCUSSION

This nationwide population-based study included registry data from almost all healthcare institutions performing breast implant surgery in the Netherlands. For breast reconstruction, most surgeons used four different infection control measures (ICMs) and for breast augmentation three. The infection-related revision incidence was low (reconstruction: 2.1 percent, augmentation: 0.1 percent), and most infection-related revisions occurred within 2 and 2.5 months after breast augmentation and reconstruction, respectively. These numbers are in line with current literature.[9,10,12] The use of different ICMs varied considerably between institutions.

Interestingly, the impact of the number and combinations of ICMs used on the infection-related revision incidence remained unclear, given that it was statistically unable to properly adjust for confounding factors and limit confounding by indication due to the low event rate. Although it seemed that implants inserted with more than 4 ICMs during breast reconstruction had a higher chance of infection-related revision, it is more likely that this was due to higher patient age, ASA classification, and BMI. If proper adjustment for baseline characteristics would have been possible, the found effect would probably disappear.

The use of more ICMs during breast reconstruction compared to breast augmentation supports the hypothesis that more ICMs are used in higher-risk patients (i.e., confounding by indication). However, in a post hoc analysis, no consistent association was found between high-risk baseline characteristics and the use of more ICMs (data not shown). Therefore, another explanation is more likely. In the Netherlands, most healthcare institutions have an infection prevention unit, providing strict protocols based on (inter)national guidelines.[18] As a result, most surgeons have developed a standard practice for all patients, using at least the ICMs prescribed by their local protocol. In some specific situations, possibly one or two additional ICMs are used. For example, the use of postoperative antibiotic prophylaxis if surgery lasted substantially longer than expected, or the use of a Keller funnel

if polyurethane-coated implants were inserted. However, it is unlikely that surgeons use fewer ICMs than advised by their infection prevention protocols, regardless of the patient's risk profile.

These institutional infection prevention protocols could also explain the considerable variation between Dutch healthcare institutions in the use of each ICM. Most guidelines and studies have reported the potential beneficial use of preoperative antibiotic prophylaxis, glove change, implant and/or pocket irrigation, and in the case of breast reconstruction, the use of drains. However, to the best of our knowledge, no high-level evidence has been obtained proving the advantage or disadvantage of postoperative prophylactic antibiotics, nipple guards, or insertion sleeves.[18-21,35,36] Therefore, local protocols can vary, resulting in nationwide variation.

Additionally, some surgeons might consistently use more ICMs than proven in literature because of the hypothesized bacterial etiology of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) and capsular contracture.[24,29,37,38] A so-called, non-evidence-based 14-point plan was proposed by Deva et al. in 2013 to stimulate using 14 steps to reduce implant infections and hypothetically BIA-ALCL.[38] These developments may have caused surgeons to practice more defensive medicine over the years, as was evident from our data showing increased use of ICMs in breast reconstruction and breast augmentation procedures.

For now, it remains unclear how the use of each ICM and the variation in current practice impacts the quality of care provided. Although this study included data from over 52000 implants, infection-related revision incidence was too low to allow for statistical testing of differences, appropriately adjusting for confounding factors, limiting confounding by indication, and taking the various combinations of ICMs into account. The low infection-related revision incidence could reflect high-quality standards. Further reduction of infection-related revisions may then be difficult to achieve. Studying this in even larger study populations may also mean that even if differences are statistically significant, they are not necessarily clinically relevant. Therefore, one might even explore reducing the number of non-evidence-based ICMs to reduce costs and variation. On the other hand, exploring the underlying reasons for the observed variation is an important next step for improving guidelines and the quality of care for patients in both reconstructive and cosmetic breast implant surgery.

Strengths and Limitations

This is the first study investigating the national variation in the use of seven commonly used ICMs, using prospectively collected real-world data from a nationwide population-based registry, including both breast reconstructions and augmentations. Consequently,

our findings reflect daily clinical practice in all sorts of hospitals and private clinics in the Netherlands. Additionally, infection-related revisions beyond 30 postoperative days were taken into account because a substantial proportion of infections occur after 30 days.[12] Finally, the DBIR uses definitions similar to all breast implant registries affiliated with the International Collaboration of Breast Registry Activities (ICOBRA).[30] This improves comparability and probability of data pooling for future studies that use data from these affiliated registries.

However, this study is not exempt from limitations. Registration of all inserted and explanted breast implants in DBIR is mandatory for board-certified plastic surgeons. The registration of inserted implants can be externally validated using sales data, for example. The external validation of explanted implants, however, is more difficult as reliable tools are unavailable. Therefore, revision surgeries might be underreported without us knowing. Although the presented revision incidences are in line with current literature, they need to be interpreted as a minimum incidence. Second, reconstructions after non-nipple sparing mastectomy are not eligible for nipple guards. However, in DBIR, the distinction between nipple-sparing vs. non-nipple-sparing mastectomy has not been registered between 2015 and 2019. Therefore, the actual proportion of nipple guards used in breast reconstruction after a nipple-sparing mastectomy might be higher than presented in this study.

CONCLUSION

Although the use of different ICMs varied considerably between institutions, the incidence of infection-related revisions after breast implant surgery was low. Most infection-related revisions occurred within 2 to 2.5 months. Most surgeons used 4 ICMs for breast reconstruction and 3 ICMs for breast augmentation. As it remains unclear how the variation in ICM-use impacts the quality of care provided, further exploration of the underlying reasons is needed.

REFERENCES

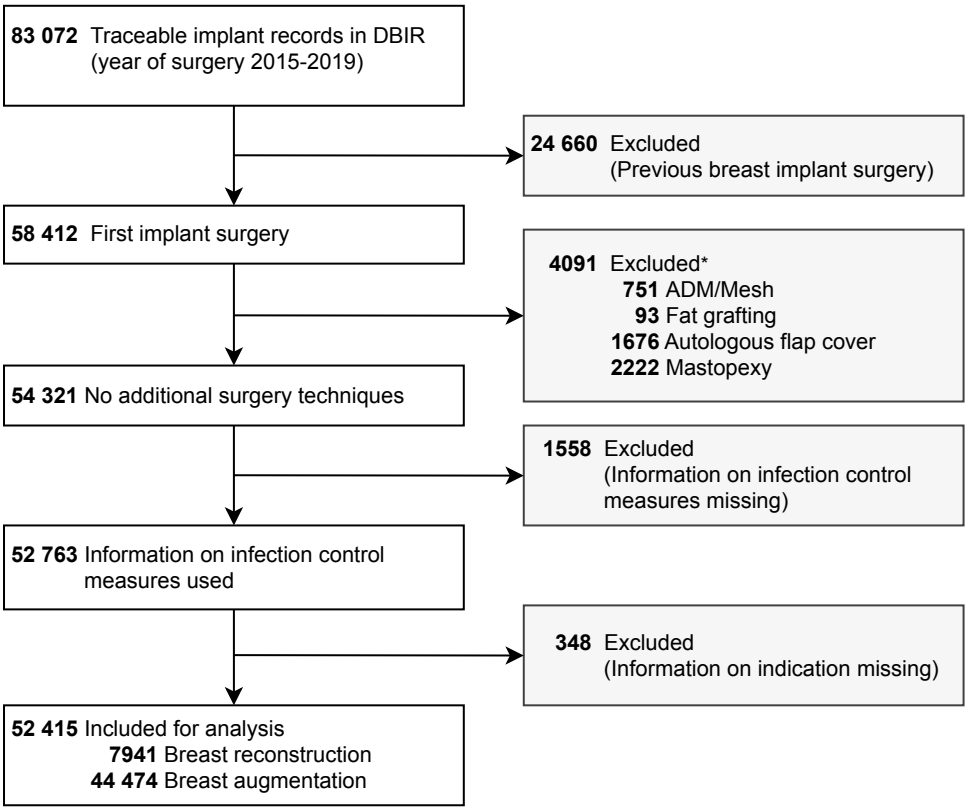
1. American Society of Plastic Surgeons. Plastic surgery statistics report 2019. ASPS National Clearinghouse of Plastic Surgery Procedural Statistics. Jun 2020.
2. International Society of Aesthetic Plastic Surgery. ISAPS Global Survey Results 2018. 2019.
3. The British Association of Aesthetic Plastic Surgeons. BAAPS Audit Results 2019. updated May 20, 2019. Available from: https://baaps.org.uk/media/press_releases/1708/cosmetic_surgery_stats_number_of_surgeries_remains_stable_amid_calls_for_greater_regulation_of_quick_fix_solutions.
4. de Boer M, van Middelkoop M, Hauptmann M, van der Bijl N, Bosmans JAW, Hendriks-Brouwer N, et al. Breast Implant Prevalence in the Dutch Female Population Assessed by Chest Radiographs. Aesthet Surg J. 2019.
5. Becherer BE, Rakhorst HA, Mureau MAM, Hommes JE, Hoornweg MJ, Keuter XHA, et al. Dutch Breast Implant Registry (DBIR)–Annual Report (2015-2017). Dutch Institute for Clinical Auditing (DICA); November 2018.
6. Spronk PER, Becherer BE, Hommes J, Keuter XHA, Young-Afat DA, Hoornweg MJ, et al. How to improve patient safety and quality of care in breast implant surgery? First outcomes from the Dutch Breast Implant Registry (2015–2017). Plast Reconstr Aesthet Surg. 2019;72(10):1607-15.
7. Fischer JP, Wes AM, Tuggle CT, Serletti JM, Wu LC. Risk analysis of early implant loss after immediate breast reconstruction: a review of 14,585 patients. J Am Coll Surg. 2013;217(6):983-990.
8. McCarthy CM, Mehrara BJ, Riedel E, Davidge K, Hinson A, Disa JJ, et al. Predicting Complications following Expander/Implant Breast Reconstruction: An Outcomes Analysis Based on Preoperative Clinical Risk. Plast and Reconstr Surg. 2008;121(6):1886-1892.
9. Wilkins EG, Hamill JB, Kim HM, Kim JY, Greco RJ, Qi J, et al. Complications in Postmastectomy Breast Reconstruction: One-year Outcomes of the Mastectomy Reconstruction Outcomes Consortium (MROC) Study. Ann Surg. 2018;267(1):164-170.
10. Henriksen TF, Holmich LR, Fryzek JP, Friis S, McLaughlin JK, Høyer AP, et al. Incidence and severity of short-term complications after breast augmentation: results from a nationwide breast implant registry. Ann Plast Surg. 2003;51(6):531-539.
11. Qureshi AA, Broderick KP, Belz J, Funk S, Reaven N, Brandt KE, et al. Uneventful versus Successful Reconstruction and Outcome Pathways in Implant-Based Breast Reconstruction with Acellular Dermal Matrices. Plast Reconstr Surg. 2016;138(2):173e-183e.
12. Piper ML, Roussel LO, Koltz PF, Wang F, Singh K, Chin R, et al. Characterizing infections in prosthetic breast reconstruction: A validity assessment of national health databases. J Plast Reconstr Aesthet Surg. 2017;70(10):1345-1353.
13. Lovecchio F, Jordan SW, Lim S, Fine NA, Kim JY. Risk Factors for Complications Differ Between Stages of Tissue-Expander Breast Reconstruction. Ann Plast Surg. 2015;75(3):275-280.

14. Hirsch EM, Seth AK, Kim JY, Dumanian GA, Mustoe TA, Galiano RD, et al. Analysis of risk factors for complications in expander/implant breast reconstruction by stage of reconstruction. Plast Reconstr Surg. 2014;134(5):692e-699e.
15. Alderman AK, Wilkins EG, Kim HM, Lowery JC. Complications in postmastectomy breast reconstruction: two-year results of the Michigan Breast Reconstruction Outcome Study. Plast Reconstr Surg. 2002;109(7):2265-2274.
16. Henriksen TF, Fryzek JP, Hölmich LR, McLaughlin JK, Kjøller K, Høyer AP, et al. Surgical intervention and capsular contracture after breast augmentation: a prospective study of risk factors. Ann Plast Surg. 2005;54(4):343-351.
17. Darragh L, Robb A, Hardie CM, McDonald S, Valand P, O'Donoghue JM. Reducing implant loss rates in immediate breast reconstructions. Breast. 2017;31:208-213.
18. Bauer MP, Garde van de EMW, Kasteren van MEE, Prins JM, Vos MC. Richtlijn Peri-operatieve profylaxe (guideline perioperative prophylaxis). Stichting Werkgroep Antibioticabeleid (SWAB); 2018 Juli 2019.
19. Douek M, Mylvaganam S, Ooi J, Rusby J, Shah E, Turton P, et al. Antibiotic Prophylaxis in Breast Surgery. Association of Breast Surgery; 2015.
20. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013;70(3):195-283.
21. Alderman A, Gutowski K, Ahuja A, Gray D, Postmastectomy Expander Implant Breast Reconstruction Guideline Work Group. ASPS clinical practice guideline summary on breast reconstruction with expanders and implants. Plast Reconstr Surg. 2014;134(4):648e-655e.
22. Bauer MP, Garde van de EMW, Kasteren van MEE, Prins JM, Vos MC. Richtlijn Peri-operatieve profylaxe. Stichting Werkgroep Antibioticabeleid (SWAB); 2017 June 2018.
23. Frois AO, Harbour PO, Azimi F, Young J, Chan B, Mak C, et al. The Role of Antibiotics in Breast Pocket Irrigation and Implant Immersion: A Systematic Review. Plast Reconstr Surg Glob Open. 2018;6(9):e1868.
24. Walker JN, Hanson BM, Myckatyn TM. Commentary on: Optimizing Breast Pocket Irrigation: The Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) Era. Aesthet Surg J. 2019.
25. Epps MT, Langsdon S, Pels TK, Lee TM, Thurston T, Brzezienski MA. Antimicrobial Irrigation and Technique during Breast Augmentation: Survey of Current Practice. Plast Reconstr Surg Glob Open. 2019;7(8):e2310.
26. Prantl L, Momeni A, Brebant V, Kuehlmann B, Heine N, Biermann N, et al. Recommendations for the Use of Antibiotics in Primary and Secondary Esthetic Breast Surgery. Plast Reconstr Surg Glob Open. 2020;8(1):e2590.
27. Rakhorst HA, Mureau MAM, Cooter RD, McNeil J, van Hooff M, van der Hulst R, et al. The new opt-out Dutch National Breast Implant Registry–Lessons learnt from the road to implementation. J Plast Reconstr Aesthet Surg. 2017;70(10):1354-1360.
28. Hoeijmakers F, Beck N, Wouters M, Prins HA, Steup WH. National quality registries: how to improve the quality of data? J Thorac Dis. 2018;10(Suppl 29):S3490-S3499.

29. Becherer BE, Rakhorst HA, Mureau MAM, Hommes JE, van Bommel ACM, Hoornweg MJ, et al. Dutch Breast Implant Registry (DBIR)–Annual Report 2018. Dutch Institute for Clinical Auditing (DICA); November 2019.
30. Spronk PE, Begum H, Vishwanath S, Crosbie A, Earnest A, Elder E, et al. Toward International Harmonization of Breast Implant Registries: ICOBRA global common dataset. Plast Reconstr Surg. 2020;146(2):255-67.
31. van Buuren S. Flexible Imputation of Missing Data, Second Edition. 2 ed: Chapman and Hall/CRC; 2018 July 16, 2018. 416 p.
32. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
33. Rubin DB. Multiple Imputation for nonresponse in Surveys. New York: John Wiley & Sons, Inc; 1987.
34. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999;94(446):496-509.
35. Nederlandse Vereniging voor Plastische Chirurgie. Richtlijn borstvergroting, Herziene versie 4 april 2014.
36. Lynch JM, Sebai ME, Rodriguez-Unda NA, Seal S, Rosson GD, Manahan MA. Breast Pocket Irrigation with Antibiotic Solution at Implant Insertion: A Systematic Review and Meta-Analysis. Aesthetic Plast Surg. 2018;42(5):1179-1186.
37. Culbertson EJ, Felder-Scott C, Deva AK, Greenberg DE, Adams WP. Optimizing Breast Pocket Irrigation: The Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) Era. Aesthet Surg J. 2019.
38. Deva AK, Adams WP, Jr., Vickery K. The role of bacterial biofilms in device-associated infection. Plast Reconstr Surg. 2013;132(5):1319-1328.

SUPPLEMENTARY DATA

Supplementary figure 1. Flow chart of breast implant selection.
*(*More than one additional surgery technique could be registered per record. DBIR, Dutch Breast Implant Registry; ADM, acellular dermal matrix.)*



Supplementary table 1. Data dictionary DBIR.

LABEL	VARIABLE AS STATED IN DBIR	DEFINITION
Age	Cclculated manually	Calculated in years, using the date of surgery and date of birth.
ASA classification	surgasa	American Society of Anesthesiologists' identification system for a patient's medical status.
body mass index	bmi	Is calculated automatically when height (in centimeters) and weight (in kilograms) of the patient are filled in.
smoking status	nicotineabuse	As identified by the patient.
previous radiotherapy	prevradio	Radiotherapy to the breast or chest wall at any time prior to the current device operation.
year of surgery	calculated manually	Derived from the variable [operdate].
indication	indication	The reason for surgery: - Cosmetic augmentation = cosmetic surgery for enlarging breasts. - Reconstruction post mastectomy for cancer = surgery to recreate a breast after one or both breasts are removed as a treatment for breast cancer. - Reconstruction post prophylactic mastectomy = surgery to remove one or both breasts to reduce the risk of developing breast cancer. - Reconstruction benign = surgery to restore or create shape and symmetry in patients with loss or absence of all or some breast tissue due to benign breast conditions, congenital deformity, tuberous breast, or gender reassignment surgery.
first implant surgery	first	Yes = primary surgery: initial insertion of a new device, i.e. an implant or tissue expander. No = insertion of a new device in a patient who has had previous breast implant surgery.
healthcare institution volume	calculated manually	Calculated per healthcare institution, per year, by counting the total number of implant procedure records (regardless of the operation indication).
laterality	surgside	The left and/or right breast.
number of infection measures (ICMs) used	calculated manually	Counted the number of applied infection control measures using the variables [systantibiot = use of antibiotics i.v. before incision], [postopantibiot = use of antibiotics i.v. at any time after 3 hours post-surgery], [antisepticrinse = rinse of the surgically created pocket or implant before implant insertion with antiseptic solution, antibiotic solution or both], [kellerfunnel = a skin barrier protector such as a Keller funnel], [nippleguards = the use of adhesive film dressing covering the nipple-areola complex to prevent perioperative expression of bacteria from nipple ducts contaminating the operative field. In case of no nipples: no nipple guards], [glovchanginsert = change of gloves immediately prior to the insertion of the implant], [drains = use of drains].

LABEL	VARIABLE AS STATED IN DBIR	DEFINITION
incision site	incissite	The site where the incision is placed: - Inframammary = an incision in or beneath the infra-mammary fold. - Mastectomy scar = an incision through an existing mastectomy incision (nipple-sparing o non-nipple sparing). - Areolar = an incision around the areola. - Other = any other incision site, such as an axillary incision.
plane	plane	The surgical plane in which an implant will be inserted: - Sub glandular = beneath the gland and above the muscular fascia. - Subcutaneous or subfascial = directly beneath the subcutis or above the pectoralis muscle but below the pectoralis fascia. - Completely covered with PM = above chest wall and below the pectoralis major muscle. - Partially covered with PM = partially beneath pectoralis major muscle and breast parenchyma.
ADM/Mesh	sheet	The use of either an: - ADM = acellular dermal matrix. - Mesh = absorbable or non-absorbable synthetic mesh. Both are medical devices used in breast implant surgery where the mesh or matrix provides a soft tissue scaffold.
fat grafting	fatgrafting	Transfer of aspirated fat to the breast region.
autologous flap cover	calculated manually	If either the variable [ldcover = Latissimus Dorsi flap used for current breast implant surgery that covers an implantable breast device or adds volume to the breast mound] or [flapcover-other = any other flap used for current breast implant surgery that covers an implantable breast device or adds volume to the breast mound] was selected.
mastopexy	mastopexy	Breast lift.
implant type	implanttype	Permanent breast implant or tissue expander.
texture	calculated manually	Combination of the variables [texture = the surface texture of the device being inserted or explanted] and [coating = breast implants with a polyurethane coating are Polytech and Silimed for example].
infection-related revision	wound	Revision due to an infection associated with a breast implant which leads to its explantation or revision. Usually involves redness, localized pain or tenderness, abscess or persistent serous liquid formation around the implant.

**An extended version of the data dictionary can be downloaded from https://support.mrdm.nl/documentatie/*

Supplementary table 2. Raw data of patient, surgery, and implant characteristics at time of primary implant insertion.

	Breast Reconstruction (*n* = 7941)	**Breast Augmentation** (*n* = 44474)
Intervention of Interest		
Number of ICMs (median, IQR)	4 (4-5)	3 (3-4)
Missing	0 (0)	0 (0)
Patient Characteristics		
Age in years (mean, SD)	48.0 (11.9)	31.4 (9.3)
Missing	28 (0.4)	235 (0.5)
ASA classification		
I	5153 (64.9)	41739 (93.8)
II	2447 (30.8)	2450 (5.5)
III+	237 (3.0)	70 (0.2)
Missing	104 (1.3)	215 (0.5)
Body mass index in kg/m² (median, IQR)*	24.0 (21.8-26.9)	21.5 (20.1-23.4)
Missing	295 (7.9)	1229 (5.3)
Smoking status*		
Not smoking	2570 (68.7)	12400 (53.3)
Smoking	393 (10.5)	3205 (13.8)
Missing	779 (20.8)	7676 (32.9)
Previous radiotherapy		
No	6470 (81.5)	43143 (97.0)
Yes	379 (4.8)	96 (0.2)
Missing	1280 (13.7)	1235 (2.8)
Surgery Characteristics		
Year of surgery		
2015	1280 (16.1)	5413 (12.2)
2016	1756 (22.1)	8576 (19.3)
2017	1708 (21.5)	10019 (22.5)
2018	1555 (19.6)	10170 (22.9)
2019	1642 (20.7)	10296 (23.1)
Missing	0 (0)	0 (0)
Healthcare institution volume per year		
<100 implant surgeries	2477 (31.2)	2504 (5.6)
100-249 implant surgeries	3936 (49.5)	6708 (15.1)
250-500 implant surgeries	1190 (15.0)	11610 (26.1)
>500 implant surgeries	338 (4.3)	23652 (53.2)
Missing	0 (0)	0 (0)

	Breast Reconstruction (*n* = 7941)	**Breast Augmentation** (*n* = 44474)
Laterality		
Unilateral	4632 (58.3)	262 (0.6)
Bilateral	3309 (41.7)	44208 (99.3)
Missing	0 (0)	4 (<0.1)
Incision site		
Inframammary	970 (12.2)	43703 (98.3)
Mastectomy scar	5341 (67.3)	245 (0.6)
Areolar	647 (8.1)	106 (0.2)
Other	310 (3.9)	280 (0.6)
Missing	673 (8.5)	140 (0.3)
Plane		
Subglandular	0 (0)	6461 (14.5)
Subcutaneous or subfascial	428 (5.5)	3579 (8.1)
Completely covered with PM	4431 (55.7)	6850 (15.4)
Partially covered with PM	2162 (27.2)	26911 (60.5)
Missing	920 (11.6)	673 (1.5)
Implant Characteristics		
Inserted implant type		
Breast implant	2566 (32.3)	44358 (99.7)
Tissue expander	5375 (67.7)	116 (0.3)
Missing	0 (0)	0 (0)
Texture		
Textured	7005 (88.2)	39822 (89.5)
Smooth	101 (1.3)	2739 (6.2)
Polyurethane	195 (2.5)	1321 (3.0)
Missing	640 (8.1)	592 (1.3)

*Values in parentheses are percentages unless indicated otherwise. ICM, infection control measure; IQR, interquartile range; SD, standard deviation; ASA, American society of anesthesiologists; PM, pectoralis major. *Registered since September 2017 and therefore presented for a smaller population (reconstruction: n=3742, augmentation: n=23281).*

5

CHAPTER 5

REVISION INCIDENCE AFTER IMMEDIATE DIRECT-TO-IMPLANT VERSUS TWO-STAGE IMPLANT-BASED BREAST RECONSTRUCTION: RESULTS FROM A NATIONWIDE BREAST IMPLANT REGISTRY.

B.E. Becherer
E. Heeg
D.A. Young-Afat
M.T.F.D. Vrancken Peeters
H.A. Rakhorst
M.A.M. Mureau
on behalf of the Dutch Breast Implant Registry (DBIR) group

Submitted.

ABSTRACT

Background. In immediate implant-based breast reconstruction (IBBR), large variation is observed in current practices between a direct-to-implant or two-stage approach. This population-based study aimed to compare unplanned short- and long-term revision incidence between direct-to-implant and two-stage IBBR in the Netherlands.

Methods. All patients with immediate IBBR following a mastectomy between 2015 and 2019 were selected from the nationwide Dutch Breast Implant Registry (DBIR). Short- and long-term unplanned revision incidences were studied per immediate IBBR, including revision indications and the total number of additional operations. Confounding by indication was limited using propensity score matching.

Results. A total of 4512 breast implants (3948 women) were included, of which 2100 (47 percent) for direct-to-implant IBBR and 2412 (53 percent) for two-stage IBBR. Median (IQR) follow-up was 29 (16-45) months and 33 (21-47) months, respectively. Short-term revision incidence was 4.0 percent and 11.7 percent, respectively (conditional OR 0.31, 95% CI 0.23-0.42). Long-term revision incidence was 10.6 percent (95% CI 9.2-12.1) and 16.4 percent (95% CI 14.8-17.9), respectively. In the propensity score matched cohort, similar results were found. In the direct-to-implant group, more breasts were reconstructed within the planned number of operations than in the two-stage group.

Conclusion. Unplanned revision surgery occurred less often after direct-to-implant IBBR, and more breasts were reconstructed within the planned number of operations compared to two-stage IBBR. These results, based on real-world data, are important for improving patient counseling and shared decision-making.

INTRODUCTION

Immediate postmastectomy breast reconstruction is becoming increasingly popular, with up to 50 percent of mastectomy patients undergoing this type of reconstruction in current practice.[1,2] Although autologous techniques are increasingly being used, immediate implant-based breast reconstruction (IBBR) is still most often performed (70-90 percent).[1-5] Immediate IBBR can be achieved either using a one-stage direct-to-implant approach or a two-stage technique with a tissue expander (TE), which is replaced by a definite breast implant during a second surgery.

There is an ongoing debate about the differences in complications and cosmetic outcomes between direct-to-implant and two-stage breast reconstruction, as direct comparisons in randomized controlled trials (RCTs) have not been performed.[6-9] Second, not all patients are eligible for both reconstruction techniques, resulting in a selection bias. Possible advantages of direct-to-implant IBBR include fewer outpatient clinic visits and fewer surgeries, expected lower overall costs, and a quicker return to the patient's social and working life.[10,11] Possible disadvantages are difficulties in using implant sizes larger than the original breast(s), higher probability of asymmetry, and the potentially higher risk of adverse events, especially if ADMs or meshes are used.[12,13]

The latest evidence-based Dutch guideline for breast reconstruction from 2015 states that it is difficult to make evidence-based recommendations due to a lack of high-quality evidence.[14] This lack of high-quality evidence may contribute to unwanted variation in current practices among healthcare providers. These arguments emphasize the need for a better understanding of the differences in risks and outcomes to improve patient counselling and quality of care. Therefore, this study aimed to compare revision incidence, revision indications, and the additional number of operations per breast between direct-to-implant and two-stage IBBR in a nationwide, population-based cohort using the Dutch Breast Implant registry (DBIR).

METHODS

Design and Study Population

This observational cohort study included all women who had been prospectively registered in the DBIR after undergoing a direct-to-implant or two-stage immediate IBBR between January 1, 2015, and December 31, 2019. Indications for an immediate IBBR were mastectomy for breast cancer or prophylactic mastectomy.

Patients who had undergone reconstruction for a benign condition, who had received any previous breast implant surgery, and in whom additional surgical techniques (fat grafting, mastopexy or autologous flap cover) had been used during implant insertion, were excluded from analysis.

Of the women with a planned two-stage IBBR, information on both the first stage (tissue expander insertion) and second stage (tissue expander exchange for permanent breast implant) was necessary for inclusion.

Data Collection: the Dutch Breast Implant Registry

The DBIR is a nationwide, population-based registry. Since 2015, patient, surgery, and implant characteristics are prospectively collected of all patients undergoing breast implant surgery in the Netherlands for breast reconstruction or breast augmentation. All operations that concern implant insertion, repositioning, replacement or explantation have to be registered. More details about the registry have been described previously.[1,15,16] Currently, 100 percent (n=74) of the hospitals and 95 percent (n=37) of the private clinics where breast implant surgery is being performed are included in DBIR. For the current study, the last data update was on May 8, 2020.

Definitions

Direct-to-implant IBBR was defined as the insertion of a permanent breast implant during the same operation as the mastectomy. Two-stage IBBR was defined as the insertion of a tissue expander (TE) during the same operation as the mastectomy, followed by a second operation in which a permanent breast implant replaced the TE.

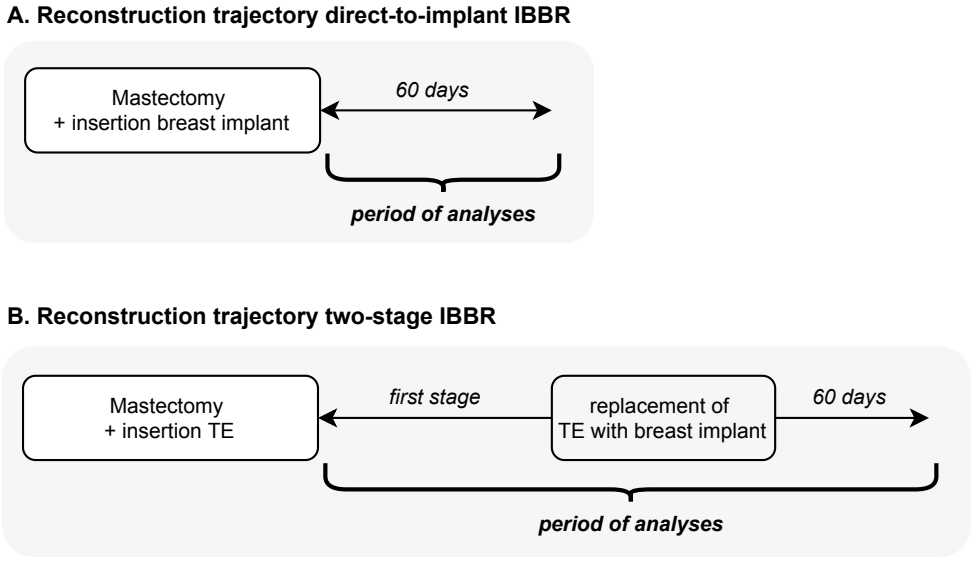
Completion of each reconstruction trajectory was defined as the moment a permanent breast implant was inserted. The reconstruction trajectory of a two-stage IBBR was defined as the time between mastectomy with immediate TE insertion and TE replacement with a permanent breast implant. Revision surgery was defined as the first unplanned reoperation after insertion, in which the breast implant or TE was repositioned, explanted or replaced. Indications for an unplanned revision were mastectomy skin flap necrosis, skin scarring problems, autologous flap problems, deep wound infections, seroma or hematoma, capsular contracture, newly diagnosed breast cancer, BIA-ALCL, breast pain, asymmetry, dissatisfaction with volume, patient-requested implant removal due to nonspecific health symptoms, device malposition, and device rupture or deflation.

Exact definitions of all patient, surgery, revision, and implant variables used for analysis can be found in the DBIR Data Dictionary (*Supplementary table 1*).

Outcome Measures

The primary outcome was the short-term revision incidence of both IBBR techniques during the time from mastectomy until 60 days after the last planned surgery in each reconstruction trajectory (*Figure 1*). A time interval of 60 days was chosen because a substantial number of complications in breast implant surgery occur after 30 days.[17,18] Subsequently, the long-term cumulative revision incidence within two years after mastectomy, revision indications, and the total number of additional operations per breast were evaluated for both IBBR techniques. Potential confounding factors were identified based on existing literature and clinical rationale. A Directed Acyclic Graph (DAG) was used to visualize this process before performing analyses.[19]

Figure 1. Schematic view of the two analyzed reconstruction trajectories: from mastectomy and immediate IBBR until 60 days after completion of the reconstruction.
(IBBR, implant-based breast reconstruction; TE, tissue expander.)



Statistical Analysis

All analyses were performed with the implant as the unit of analysis, using R software, version 1.4.1106-©2009-2021, RStudio, Inc. Missing data patterns were evaluated, resulting in the assumption of data being missing at random. Multiple imputation by chained equations was performed ('mice' package, version 3.13.0).[20,21] The outcome variable itself was not imputed. Statistical models were fitted and results were pooled following Rubin's rules.[22] See *Supplementary table 2* for non-imputed data.

Baseline characteristics were compared between groups using Student's t-tests, Mann Whitney U tests, χ^2 tests or Fisher's exact tests accordingly. Two-sided P-value <0.050 was considered statistically significant.

To assess the likelihood of short-term revision, multivariable logistic regression analyses were performed ('stats' package, version 4.0.2). Subsequently, to account for clustering of patients and implants within healthcare institutions which were likely to be correlated with practices performed, a conditional OR with 95 percent confidence interval (CI) was calculated using a mixed-effects logistic regression model ('lme4' package, version 1.1-26). In this mixed-effects model, confounding factors that were distributed differently between the revision and no-revision groups were entered as fixed effects and healthcare institutions were included as random intercepts.

The crude, long-term cumulative revision incidence was calculated using Nelson-Aalen estimates. Implants without any revision at closure of the dataset on May 8, 2020, were censored. After reassuring the proportional hazard assumption was met, a hazard ratio (HR) was calculated using a Cox proportional hazards model.

Sensitivity Analysis

Two sensitivity analyses were performed. First, the E-value was calculated ('EValue' package, version 4.1.2). An E-value assesses the minimum strength an unmeasured confounding factor must have, to negate the observed treatment-outcome association.[23] Second, propensity score matching (PSM) was used to mimic pseudo-randomization and assess the likelihood of short- and long-term revision. By using PSM, potential confounding by indication is limited.[24,25] Subsequently, a logistic regression model was used to calculate the propensity score for undergoing direct-to-implant IBBR using all preoperative covariates: age, ASA classification, BMI, smoking status, previous radiotherapy, postoperative radiotherapy planned, year of surgery, healthcare institution, healthcare institution volume, reconstruction indication, and laterality. In the PSM analyses, records with any missing preoperative characteristic were excluded. Matching was performed using a 1:1 ratio with a calliper width of 0.2 times the standard deviation of the logit ('MatchIt' package, version 4.1.0). Potential imbalances before and after matching were assessed using standardized mean differences (SMD).[26] A baseline characteristic with an SMD of 10 percent or more was considered imbalanced between the direct-to-implant and two-stage group.

RESULTS

A total of 3948 patients and 4512 breast implants met the inclusion criteria (*Supplementary figure 1*). 3710 patients (94.0 percent) underwent immediate IBBR after mastectomy for

breast cancer and 238 (6.0 percent) after prophylactic mastectomy. These reconstructions were performed in 75 healthcare institutions with a mean volume per institution of 111 breast implant surgeries per year (range 13-546).

A total of 2100 (46.5 percent) breast implants were inserted for a direct-to-implant IBBR, and 2412 (53.5 percent) TE's were inserted for a two-stage IBBR. Direct-to-implant IBBR was more frequently performed in younger, non-smoking patients, if postoperative radiotherapy was planned, in bilateral procedures, in case of nipple-sparing surgery, with partial PM coverage, when using fewer infection control measures, with the use of an ADM/mesh, in more recent years, and in healthcare institutions with a volume of >200 implant surgeries per year (*Supplementary table 3*).

Short-Term Revision Incidence

Of 2100 breast implants inserted during direct-to-implant IBBR, 84 (4.0 percent) underwent unplanned revision surgery within 60 days after insertion of the breast implant. Of 2412 breasts that underwent two-stage IBBR, 281 (11.7 percent) had an unplanned revision within 60 days after completion of the entire reconstruction trajectory. The majority of these unplanned revisions occurred during the first stage of a two-stage reconstruction (n=259) (*Figure 2*).

Revision surgery was more frequently observed after two-stage IBBR, in patients with higher age, ASA classification, and BMI, in patients who smoked, in middle-volume healthcare institutions (50-200 implant surgeries per year), after non-nipple sparing surgery, if the implant was not completely covered with PM, and if an ADM/Mesh was used (*Table 1*). Implants inserted during a direct-to-implant procedure had a lower likelihood of short-term revision surgery compared with a two-stage procedure (unadjusted OR 0.32, 95% CI 0.25-0.41; adjusted OR 0.27, 95% CI 0.20-0.36; conditional OR 0.31, 95% CI 0.23-0.42) (*Table 2*).

Long-Term Revision Incidence

The median (IQR) follow-up time was 29 (16-45) months in the direct-to-implant group and 33 (21-47) months in the two-stage group. After direct-to-implant IBBR, the crude cumulative unplanned revision incidence within two years was 10.6 percent (n=220, 95% CI 9.2-12.1). Within the two-stage group, this was 16.4 percent (n=406, 95% CI 14.8-17.9) (*Figure 3A*). A hazard ratio could not be calculated, because the proportional hazard assumption was not met.

Figure 2. Short-term (≤60 days) revision incidence per breast reconstruction trajectory.

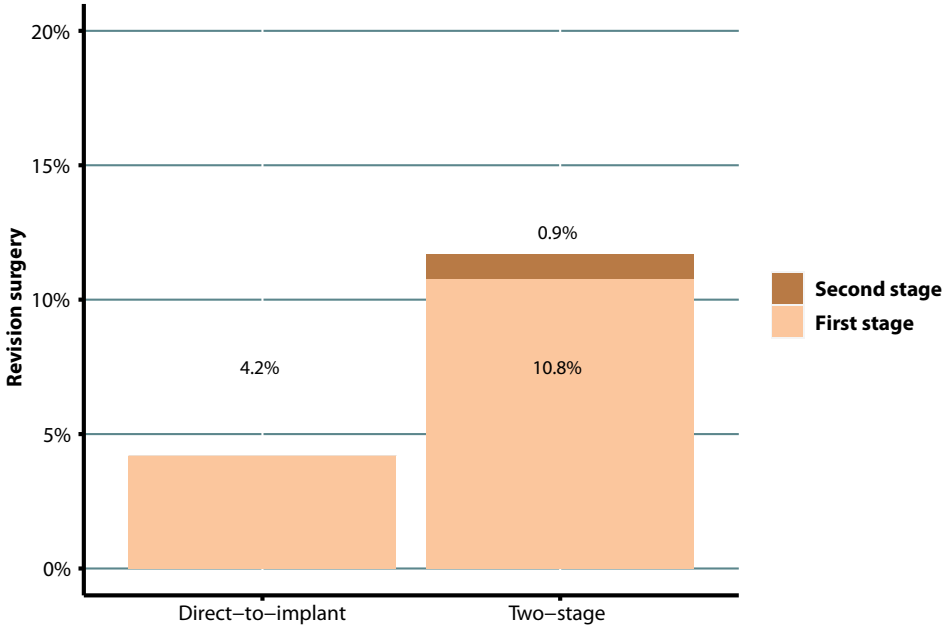


Table 1. Patient and surgery factors at time of mastectomy and immediate IBBR, per group with and without short-term (≤60 days) revision surgery after completion of the reconstruction trajectory.

	Total group (*n*=4512)	**No short-term revision** (*n*=4147, 91.9%)	**Short-term revision** (*n*=365, 8.1%)	***P*-value**
Intervention of Interest				
Type of IBBR				
Direct-to-implant	2100 (46.5)	2016 (48.6)	84 (23.0)	<0.001
Two-stage	2588 (53.5)	2131 (51.4)	281 (77.0)	
Patient Characteristics				
Mean age (years, SD)	49.0 (11.3)	48.8 (11.3)	51.0 (10.5)	<0.001
ASA classification				
I	2878 (63.8)	2694 (65.0)	184 (50.4)	<0.001
II	1500 (33.2)	1338 (32.3)	162 (44.4)	
III+	134 (3.0)	115 (2.7)	19 (5.2)	
Median body mass index (kg/m², IQR)	23.0 (20.5-25.8)	22.9 (20.4-25.5)	24.6 (22.1-28.1)	<0.001
Smoking status				
Not smoking	3852 (85.4)	3567 (86.0)	285 (78.1)	<0.001
Smoking	660 (14.6)	580 (14.0)	80 (21.9)	

	Total group (*n*=4512)	**No short-term revision** (*n*=4147, 91.9%)	**Short-term revision** (*n*=365, 8.1%)	***P*-value**
Previous radiotherapy				
No	4297 (95.2)	3956 (95.4)	341 (93.4)	0.118
Yes	215 (4.8)	191 (4.6)	24 (6.6)	
Surgery Characteristics				
Healthcare institution volume (per year)				
<50 implant surgeries	506 (11.2)	463 (11.2)	43 (11.8)	0.003
50-99 implant surgeries	783 (17.4)	702 (16.9)	81 (22.2)	
100-200 implant surgeries	1824 (40.4)	1667 (40.2)	157 (43.0)	
>200 implant surgeries	1399 (31.0)	1315 (31.7)	84 (23.0)	
Reconstruction indication				
Breast cancer	4094 (90.7)	3764 (90.8)	330 (90.4)	0.897
Prophylactic mastectomy	418 (9.3)	383 (9.2)	35 (9.6)	
Laterality				
Unilateral	2933 (65.0)	2686 (64.8)	247 (67.7)	0.291
Bilateral	1579 (35.0)	1461 (35.2)	118 (32.3)	
Incision site				
Nipple sparing	1035 (22.9)	966 (23.3)	69 (18.9)	0.043
Non-nipple sparing	3193 (70.8)	2914 (70.3)	279 (76.4)	
Other	284 (6.3)	267 (6.4)	17 (4.7)	
Plane				
Completely covered with PM muscle	2490 (55.2)	2314 (55.8)	176 (48.2)	0.001
Partially covered with PM muscle	1848 (41.0)	1684 (40.6)	164 (44.9)	
Other	174 (3.8)	149 (3.6)	25 (6.9)	
Number of applied ICMs during implant insertion				
<4	910 (20.2)	845 (20.4)	65 (17.8)	0.121
4	1557 (34.5)	1441 (34.7)	116 (31.8)	
>4	2045 (45.3)	1861 (44.9)	184 (50.4)	
ADM/Mesh				
No	4045 (89.6)	3705 (89.3)	340 (93.2)	0.028
Yes	467 (10.4)	442 (10.7)	25 (6.8)	

Values in parentheses are percentages, unless indicated otherwise. IBBR, implant-based breast reconstruction; SD, standard deviation; ASA, American society of anesthesiologists; IQR, interquartile range; PM, pectoralis major; ICMs, infection control measures; ADM, acellular dermal matrix.

Table 2. Likelihood of short-term revision surgery after completion of the reconstruction trajectory.

Direct-to-implant IBBR (*n*=2100 implants) Two-stage IBBR (*n*=2412 implants)	**OR**
Unadjusted (univariable logistic regression model)	
Two-stage	1 (reference)
Direct-to-implant	0.32 (0.25-0.41)
Adjusted (multivariable logistic regression model)	
Age	0.32 (0.25-0.42)
Age & ASA	0.32 (0.25-0.41)
Age, ASA, & BMI	0.32 (0.25-0.41)
Age, ASA, BMI & smoking	0.32 (0.25-0.42)
Age, ASA, BMI, smoking & institution volume	0.33 (0.25-0.43)
Age, ASA, BMI, smoking, institution volume & incision site	0.33 (0.25-0.43)
Age, ASA, BMI, smoking, institution volume, incision site & plane	0.27 (0.20-0.35)
Age, ASA, BMI, smoking, institution volume, incision site, plane & ADM/Mesh	0.27 (0.20-0.36)
Conditional (mixed-effects logistic regression model)	
Age, ASA, BMI, smoking, institution volume, incision site, plane, ADM/Mesh & health-care institution*	0.31 (0.23-0.42)

*Values in parentheses are 95 percent confidence intervals. *The conditional OR was obtained by entering age, ASA classification, BMI, smoking, institution volume, incision site, plane, ADM/Mesh as fixed effects into the model, and healthcare institution as random effect. IBBR, implant-based breast reconstruction; ASA, American society of anesthesiologists' classification; BMI, body mass index; ADM, acellular dermal matrix.*

Revision Indications

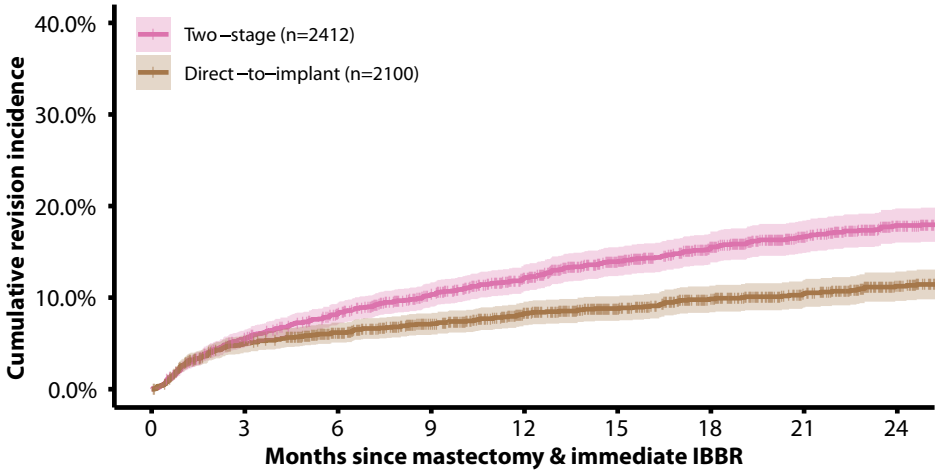
Within 60 days after direct-to-implant IBBR, most frequently registered revision indications were mastectomy skin flap necrosis and deep wound infections (*Table 3*). After 60 days, asymmetry, breast pain, and dissatisfaction with volume were most frequently observed.

During the complete first stage of a two-stage IBBR, revision surgery was mostly performed for deep wound infections and seroma or hematoma. Within 60 days of the second stage of two-stage IBBR, the majority of revisions was for seroma or hematoma, deep wound infections, and skin scarring problems. Over the longer term, asymmetry, breast pain, capsular contracture, and dissatisfaction with volume were mostly observed.

Very few implants were removed on patients' request due to nonspecific health symptoms. No implant removals for BIA-ALCL were registered.

Figure 3. Crude, long-term cumulative revision incidence after mastectomy and immediate direct-to-implant IBBR or immediate two-stage IBBR*.
*(*Curves include revisions during the first and second stage of the reconstruction trajectory. IBBR, implant-based breast reconstruction.)*

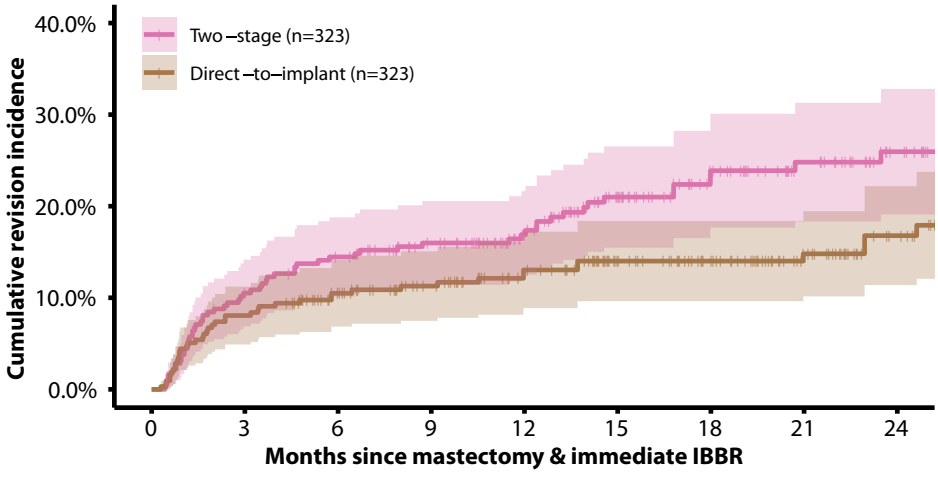
A. In the complete cohort



Number at risk

Two–stage	2412	2261	2171	2062	1927	1767	1607	1453	1299
Direct–to–implant	2100	1957	1825	1675	1551	1400	1271	1161	1059

B. In the matched cohort (sensitivity analysis



Number at risk

Two–stage	323	285	272	250	213	171	131	107	78
Direct–to–implant	323	298	267	242	218	183	158	124	95

Table 3. Indications* for short- and long-term revision surgery per reconstruction trajectory.

	Direct-to-implant IBBR		Two-stage IBBR		
	Short-term ≤60 days (*n*=84)	**Long-term >60 days** (*n*=136)	**During complete first stage** (*n*=259)	**Short-term ≤60 days second stage** (*n*=22)	**Long-term >60 days second stage** (*n*=125)
Deep wound infection	36 (43)	17 (13)	108 (42)	6 (26)	7 (6)
Seroma or hematoma	13 (16)	17 (13)	59 (23)	10 (46)	9 (7)
Mastectomy skin flap necrosis	45 (54)	14 (10)	44 (17)	1 (5)	4 (3)
Asymmetry	2 (2)	50 (37)	18 (7)	2 (9)	46 (37)
Breast pain	7 (8)	32 (24)	33 (13)	2 (9)	35 (28)
Capsular contracture	1 (1)	22 (16)	33 (13)	0 (0)	32 (26)
Skin scarring problems	11 (13)	5 (4)	28 (11)	5 (23)	10 (8)
Dissatisfaction with volume	2 (2)	29 (21)	8 (3)	1 (4)	28 (22)
Device malposition	2 (2)	25 (18)	16 (6)	0 (0)	24 (19)
Device rupture or deflation	2 (2)	9 (7)	43 (17)	1 (5)	5 (4)
Newly diagnosed breast cancer	5 (6)	10 (7)	10 (4)	1 (5)	1 (1)
Patient-requested implant removal due to nonspecific health symptoms	1 (1)	3 (2)	1 (<1)	0 (0)	1 (1)
BIA-ALCL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*Values in parentheses are percentages. *Multiple indications could be reported per revision procedure. IBBR, implant-based breast reconstruction; BIA-ALCL, Breast Implant–Associated Anaplastic Large Cell Lymphoma.*

Additional Operations

During the follow-up period, 1880 of 2100 breasts (89.5 percent) in the direct-to-implant IBBR cohort were reconstructed within one operation. Seventy-seven breasts (3.7 percent) needed one, 106 (5.0 percent) two, and 37 (1.8 percent) three or more additional operations.

In the two-stage IBBR group, 2006 of 2412 breasts (83.2 percent) were reconstructed within the planned two procedures. Hundred sixty-seven breasts (6.8 percent) needed one, 74 (3.1 percent) two, and 81 (3.4 percent) three or more additional operations. Eighty-four breasts (3.5 percent) needed revision surgery right after TE insertion and did not reach the second stage within the median follow-up.

Sensitivity Analysis

For the conditional OR of short-term revision surgery, the E-value was 5.9. This indicates that residual confounding could explain the observed association if an unidentified confounding factor exists with a relative risk association of at least 5.9. The E-value for the adjusted HR of long-term revision surgery could not be calculated because the proportional hazard assumption was not met.

After limiting confounding by indication using propensity score matching, the matched cohort included 646 records, of which 323 (50.0 percent) direct-to-implant and 323 (50.0 percent) two-stage records. While before matching, an imbalance in preoperative baseline characteristics was observed, no imbalances were observed after matching (*Supplementary table 4*). In the matched cohort, implants inserted during direct-to-implant IBBR had a lower conditional likelihood of short-term revision compared to a two-stage procedure (conditional OR 0.36, 95% CI 0.21-0.60). For the long-term, risk of revision surgery was 32 percent lower for implants inserted during direct-to-implant IBBR compared to two-stage IBBR (HR 0.68, 95% CI 0.46-0.99). The crude cumulative revision incidence at two years was 15.4 percent (95 % CI 10.8-19.9) after direct-to-implant IBBR and 22.9 percent (95% CI 17.4-28.0) after two-stage IBBR (*Figure 3B*).

DISCUSSION

This nationwide population-based study included close to 100 percent of all healthcare institutions performing breast reconstruction in the Netherlands. After adjusting for confounders and variation among centers, direct-to-implant IBBR was associated with a lower short-term and long-term unplanned revision incidence than two-stage IBBR. After limiting confounding by indication, comparable results were found. Additionally, in the direct-to-implant group, more breasts were reconstructed within the planned number of operations than in the two-stage group.

Interestingly, both Basta et al. and Lee et al. reported in their meta-analysis that direct-to-implant procedures were associated with a 1.24 (95 percent CI 1.02-1.53) and 1.25 (95 percent CI 0.40-3.89) higher likelihood of revision surgery, respectively, although the latter result was not statistically significant.[8,9] However, both meta-analyses included mainly single-center studies, with low numbers of reconstructions, high heterogeneity in follow-up time, and without adjusting for confounders or indication bias. And most importantly, the second stage of a two-stage IBBR was not always included.

Bennett et al. compared different types of IBBR during a two-year follow-up.[27] Re-operative complication rates were 19 percent after direct-to-implant IBBR and 16 percent after two-stage IBBR. Although these results were adjusted for confounders and variation among centers, selection bias (confounding by indication) was not limited, and the results were statistically not significant (OR 1.06, 95 percent CI 0.56-1.99). Other smaller studies reported comparable proportions of long-term revision surgery between the two IBBR groups (range 20-28 percent).[28,29] Nevertheless, comparing the current study results to previous studies remains difficult because many different outcome definitions are used, such as reconstructive failure, reoperation, or re-operative complications.[7,18,27,30]

There are two likely explanations for the lower risk of short- and long-term revision surgery in the direct-to-implant IBBR group compared to the two-stage group. First, the reconstruction trajectory of a two-stage IBBR is longer by definition, with two potentially hazardous events instead of one. Second, patient selection may have affected the probability of revision surgery. Direct-to-implant IBBR was more often performed in younger, non-smoking patients. Additionally, fewer infection control measures were used compared to two-stage IBBR, suggesting that direct-to-implant IBBR was more frequently performed in low-risk patients. However, in the propensity score matched cohort, in which pseudo-randomization was mimicked and the selection bias was limited, comparable results were found.

To further decrease the risk of short-term revision surgery after direct-to-implant IBBR, current findings suggest that one should focus specifically on mastectomy skin flap quality and prevention of deep wound infections. After two-stage IBBR, most short-term revisions were due to deep wound infections and seroma or hematoma formation. As most of these revision indications were related, different preventive strategies may be useful. For example, prophylactic intravenous tranexamic acid administration and a more aggressive surgical dead space management to prevent hematoma and seroma formation, respectively, and consequently deep wound infections.[31,32] Long-term outcomes of both IBBR techniques could be improved by focusing on patient selection and counseling, especially regarding the risk of asymmetry, breast pain and dissatisfaction with volume.

Strengths and Limitations

One of the strengths of this study is that real-world data was used from a nationwide population-based registry, including implants that were followed over time within different healthcare institutions. Consequently, the findings reflect daily clinical practice in the Netherlands. Randomized Controlled Trials are still the golden standard for comparative studies. However, RCTs are not always feasible if the outcome has a low event rate. As the next best alternative, selection and indication bias was limited using imputation techniques for missing data and propensity score matching to mimic pseudo-randomization. Also, clustering of patients and implants within healthcare institutions were taken into account. Finally, the DBIR uses definitions similar for all breast implant registries affiliated with the International Collaboration of Breast Registry Activities (ICOBRA), thereby improving comparability to future studies and meta-analyses using data from breast implant registries.[33]

There are several limitations. Registration of all inserted and explanted breast implants in DBIR is mandatory for board-certified plastic surgeons. The registration of inserted implants can be validated using industry sales data, for example. The validation of explanted implants, however, is more difficult as reliable tools are unavailable. Therefore, revision surgeries might be underreported without us knowing. Although it is unlikely that revisions

were less frequently registered for only one of the IBBR techniques, the presented revision incidences need to be interpreted as minimum incidences. Second, there may be residual confounding, due to missing potential confounders such as mastectomy skin flap quality, breast volume or mastectomy weight, surgeon's experience, and detailed information on (neo)adjuvant therapy.[3,18,34,35] However, the sensitivity analysis indicated that residual confounding could explain the observed association if an unidentified confounding factor with an OR of at least 5.9 would exist. The majority of the measured confounders had an OR below 2. Therefore, it is unlikely that unidentified confounders would drastically alter the conclusions.

Lastly, postoperative radiotherapy is associated with a higher risk of postoperative complications, and postoperative radiotherapy was registered in approximately 5% of our total study population. This low percentage is in line with the Dutch breast reconstruction guideline, which discourages immediate breast reconstruction if postoperative radiotherapy is indicated, especially with an implant.[14] Therefore, the generalizability of the results may be restricted in countries with different guidelines.

Future Research

In daily practice, healthcare institutions tend to prefer one technique over the other. Future studies should focus on nationwide variation in the use of both IBBR techniques and the underlying reasons. Insight into variation, patient selection, and outcomes helps to further improve guidelines and the quality of care provided.

CONCLUSIONS

Unplanned revision surgery occurred less often after direct-to-implant IBBR, and a higher proportion of breasts were reconstructed within the planned number of operations compared to two-stage IBBR. These population-based results are important to improve patient counseling and shared decision-making. Besides, they may help to start the discussion about whether a direct-to-implant approach should be considered more often.

REFERENCES

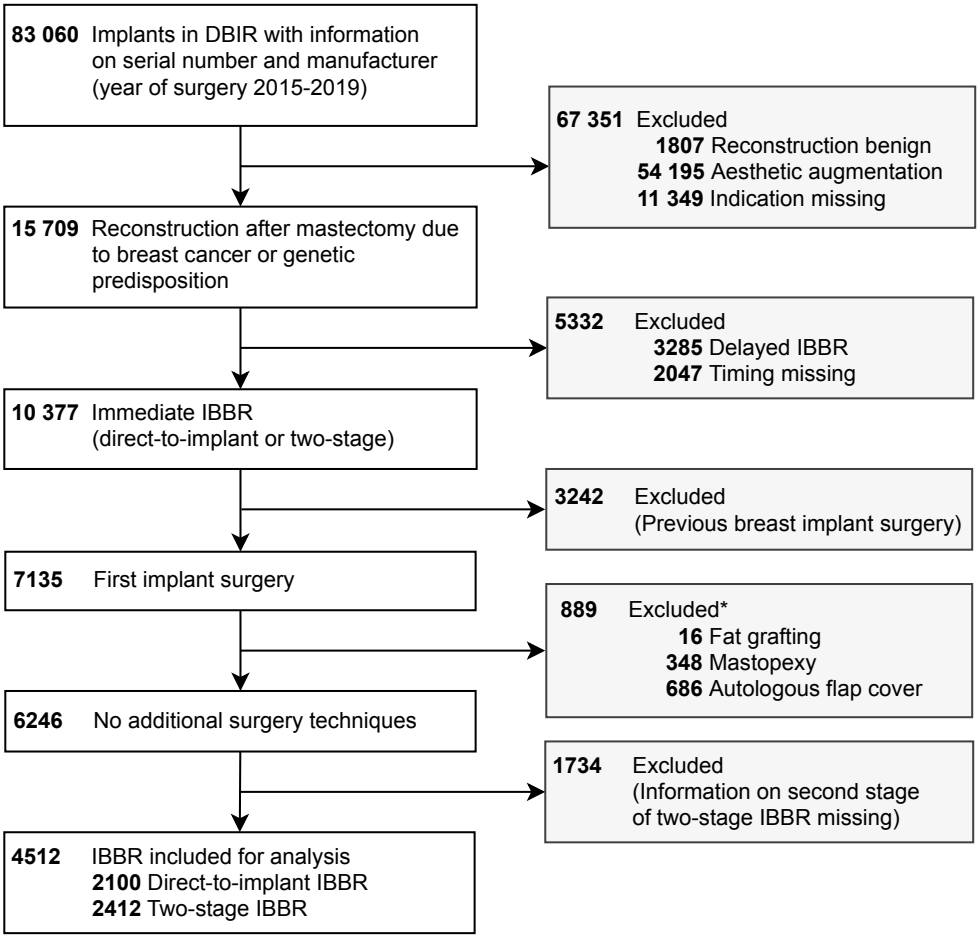
1. Becherer BE, Rakhorst HA, Mureau MAM, Hommes JE, van Bommel ACM, Hoornweg MJ, et al. Dutch Breast Implant Registry (DBIR)–Annual Report 2018. Dutch Institute for Clinical Auditing (DICA); November 2019.
2. Kamali P, Zettervall SL, Wu W, Ibrahim AMS, Medin C, Rakhorst HA, et al. Differences in the Reporting of Racial and Socioeconomic Disparities among Three Large National Databases for Breast Reconstruction. Plast Reconstr Surg. 2017;139(4):795-807.
3. Mylvaganam S, Conroy E, Williamson PR, Barnes NLP, Cutress RI, Gardiner MD, et al. Variation in the provision and practice of implant-based breast reconstruction in the UK: Results from the iBRA national practice questionnaire. Breast. 2017;35:182-90.
4. Ilonzo N, Tsang A, Tsantes S, Estabrook A, Thu Ma AM. Breast reconstruction after mastectomy: A ten-year analysis of trends and immediate postoperative outcomes. Breast. 2017;32:7-12.
5. Mandelbaum AD, Thompson CK, Attai DJ, Baker JL, Slack G, DiNome ML, et al. National Trends in Immediate Breast Reconstruction: An Analysis of Implant-Based Versus Autologous Reconstruction After Mastectomy. Ann Surg Oncol. 2020;27(12):4777-85.
6. Susarla SM, Ganske I, Helliwell L, Morris D, Eriksson E, Chun YS. Comparison of clinical outcomes and patient satisfaction in immediate single-stage versus two-stage implant-based breast reconstruction. Plast Reconstr Surg. 2015;135(1):1e-8e.
7. Davila AA, Mioton LM, Chow G, Wang E, Merkow RP, Bilimoria KY, et al. Immediate two-stage tissue expander breast reconstruction compared with one-stage permanent implant breast reconstruction: a multi-institutional comparison of short-term complications. J Plast Surg Hand Surg. 2013;47(5):344-9.
8. Basta MN, Gerety PA, Serletti JM, Kovach SJ, Fischer JP. A Systematic Review and Head-to-Head Meta-Analysis of Outcomes following Direct-to-Implant versus Conventional Two-Stage Implant Reconstruction. Plast Reconstr Surg. 2015;136(6):1135-44.
9. Lee KT, Mun GH. Comparison of one-stage vs two-stage prosthesis-based breast reconstruction: a systematic review and meta-analysis. Am J Surg. 2016;212(2):336-44.
10. Grover R, Padula WV, Van Vliet M, Ridgway EB. Comparing five alternative methods of breast reconstruction surgery: a cost-effectiveness analysis. Plast Reconstr Surg. 2013;132(5):709e-23e.
11. Krishnan NM, Fischer JP, Basta MN, Nahabedian MY. Is Single-Stage Prosthetic Reconstruction Cost Effective? A Cost-Utility Analysis for the Use of Direct-to-Implant Breast Reconstruction Relative to Expander-Implant Reconstruction in Postmastectomy Patients. Plast Reconstr Surg. 2016;138(3):537-47.
12. Killaars RC, Hommes J, van der Hulst RR, Tielemans HJ, Negenborn VL, Piatkowski A. Does 2-Stage Implant-Based Breast Reconstruction Allow for a Larger Volume of the Definite Implant Compared With 1-Stage Reconstruction? Ann Plast Surg. 2018;80(5):481-6.
13. Dikmans RE, Negenborn VL, Bouman MB, Winters HAH, Twisk JWR, Ruhé PQ, et al. Two-stage implant-based breast reconstruction compared with immediate one-stage implant-based breast

reconstruction augmented with an acellular dermal matrix: an open-label, phase 4, multicentre, randomised, controlled trial. Lancet Oncol. 2017;18(2):251-8.
14. Mureau MAM, Breast Reconstruction Guideline Working Group. Dutch breast reconstruction guideline. J Plast Reconstr Aesthet Surg. 2018;71(3):290-304.
15. Rakhorst HA, Mureau MAM, Cooter RD, McNeil J, van Hooff M, van der Hulst R, et al. The new opt-out Dutch National Breast Implant Registry–Lessons learnt from the road to implementation. J Plast Reconstr Aesthet Surg. 2017;70(10):1354-60.
16. Hoeijmakers F, Beck N, Wouters M, Prins HA, Steup WH. National quality registries: how to improve the quality of data? J Thorac Dis. 2018;10(Suppl 29):S3490-S99.
17. Piper ML, Roussel LO, Koltz PF, Wang F, Singh K, Chin R, et al. Characterizing infections in prosthetic breast reconstruction: A validity assessment of national health databases. J Plast Reconstr Aesthet Surg. 2017;70(10):1345-53.
18. Fischer JP, Wes AM, Tuggle CT, 3rd, Serletti JM, Wu LC. Risk analysis of early implant loss after immediate breast reconstruction: a review of 14,585 patients. J Am Coll Surg. 2013;217(6):983-90.
19. Suttorp MM, Siegerink B, Jager KJ, Zoccali C, Dekker FW. Graphical presentation of confounding in directed acyclic graphs. Nephrol Dial Transplant. 2015;30(9):1418-23.
20. van Buuren S. Flexible Imputation of Missing Data, Second Edition. 2 ed: Chapman and Hall/CRC; 2018 July 16, 2018. 416 p.
21. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
22. Rubin DB. Multiple Imputation for nonresponse in Surveys. New York: John Wiley & Sons, Inc; 1987.
23. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. JAMA. 2019;321(6):602-3.
24. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.
25. Gfrerer L, Mattos D, Mastroianni M, Weng QY, Ricci JA, Heath MP, et al. Assessment of patient factors, surgeons, and surgeon teams in immediate implant-based breast reconstruction outcomes. Plast Reconstr Surg. 2015;135(2):245e-52e.
26. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083-107.
27. Bennett KG, Qi J, Kim HM, Hamill JB, Pusic AL, Wilkins EG. Comparison of 2-Year Complication Rates Among Common Techniques for Postmastectomy Breast Reconstruction. JAMA Surg. 2018;153(10):901-8.
28. Roostaeian J, Sanchez I, Vardanian A, Herrera F, Galanis C, Da Lio A, et al. Comparison of immediate implant placement versus the staged tissue expander technique in breast reconstruction. Plast Reconstr Surg. 2012;129(6):909e-18e.

29. Clarke-Pearson EM, Lin AM, Hertl C, Austen WG, Colwell AS. Revisions in Implant-Based Breast Reconstruction: How Does Direct-to-Implant Measure Up? Plast Reconstr Surg. 2016;137(6):1690-9.
30. Hvilsom GB, Friis S, Frederiksen K, Steding-Jessen M, Henriksen TF, Lipworth L, et al. The clinical course of immediate breast implant reconstruction after breast cancer. Acta Oncol. 2011;50(7):1045-52.
31. Heyns M, Knight P, Steve AK, Yeung JK. A Single Preoperative Dose of Tranexamic Acid Reduces Perioperative Blood Loss: A Meta-analysis. Ann Surg. 2020;273(1);75-81.
32. Jordan SW, Khavanin N, Kim JY. Seroma in Prosthetic Breast Reconstruction. Plast Reconstr Surg. 2016;137(4):1104-16.
34. Spronk PE, Begum H, Vishwanath S, Crosbie A, Earnest A, Elder E, et al. Toward International Harmonization of Breast Implant Registries: ICOBRA global common dataset. Plast Reconstr Surg. 2020;146(2):255-67.
35. McCarthy CM, Mehrara BJ, Riedel E, Davidge K, Hinson A, Disa JJ, et al. Predicting Complications following Expander/Implant Breast Reconstruction: An Outcomes Analysis Based on Preoperative Clinical Risk. Plast Reconstr Surg. 2008;121(6):1886-92.
36. Fischer JP, Wes AM, Tuggle CT, Serletti JM, Wu LC. Risk analysis and stratification of surgical morbidity after immediate breast reconstruction. J Am Coll Surg. 2013;217(5):780-7.

SUPPLEMENTARY DATA

Supplementary figure 1. Flow chart of implant selection.
*(*More than one additional surgery technique could be registered per record. DBIR, Dutch Breast Implant Registry; IBBR, implant-based breast reconstruction; TE, tissue expander)*



Supplementary table 1. Data dictionary DBIR.

LABEL	VARIABLE AS STATED IN DBIR	DEFINITION
Type of IBBR	timingrec	- Immediate = at the same time as the mastectomy. - Delayed = at a later time than the mastectomy.
Age	Cclculated manually	Calculated in years, using the date of surgery and date of birth.
ASA classification	surgasa	American Society of Anesthesiologists' identification system for a patient's medical status.
body mass index	bmi	Is calculated automatically when height (in centimeters) and weight (in kilograms) of the patient are filled in.
smoking status	nicotineabuse	As identified by the patient.
previous radiotherapy	prevradio	Radiotherapy to the breast or chest wall at any time prior to the current device operation.
postoperative radiotherapy planned	postradio	If radiotherapy to the breast or chest wall is planned after the current device operation.
year of surgery	calculated manually	Derived from the variable [operdate].
healthcare institution volume	calculated manually	Calculated per healthcare institution, per year, by counting the total number of implant procedure records (regardless of the operation indication).
reconstruction indication	indication	The reason for surgery: - Cosmetic augmentation = cosmetic surgery for enlarging breasts. - Reconstruction post mastectomy for cancer = surgery to recreate a breast after one or both breasts are removed as a treatment for breast cancer. - Reconstruction post prophylactic mastectomy = surgery to remove one or both breasts to reduce the risk of developing breast cancer. - Reconstruction benign = surgery to restore or create shape and symmetry in patients with loss or absence of all or some breast tissue due to benign breast conditions, congenital deformity, tuberous breast, or gender reassignment surgery.
laterality	surgside	The left and/or right breast.
primary surgery	first	Yes = primary surgery: initial insertion of a new device, i.e., an implant or tissue expander. No = insertion of a new device in a patient who has had previous breast implant surgery.
incision site	calculated manually	The variable [incissite = the site where the incision is placed] was used to define whether the incision was nipple sparing (inframammary, areolar, mastectomy scar (nipple-sparing)) or non-nipple sparing (mastectomy scar (general), Latissimus Dorsi) or other (axillary, other).
plane	plane	- Completely covered with PM = above chest wall and below the pectoralis major muscle. - Partially covered with PM = partially beneath pectoralis major muscle. - Other = includes subcutaneous (directly beneath the subcutis) and subfascial (above pectoralis muscle but below pectoralis fascia).

LABEL	VARIABLE AS STATED IN DBIR	DEFINITION
number of applied infection measures (ICMs)	calculated manually	Counted the number of applied infection control measures using the variables [systantibiot = use of antibiotics i.v. before incision], [postopantibiot = use of antibiotics i.v. at any time after 3 hours post-surgery], [antisepticrinse = rinse of the surgically created pocket or implant before implant insertion with antiseptic solution, antibiotic solution or both], [kellerfunnel = a skin barrier protector such as a Keller funnel], [nippleguards = the use of adhesive film dressing covering the nipple-areola complex to prevent perioperative expression of bacteria from nipple ducts contaminating the operative field. In case of no nipples: no nipple guards], [glovchanginsert = change of gloves immediately prior to the insertion of the implant], [drains = use of drains].
ADM/Mesh	sheet	The use of either an: - ADM = acellular dermal matrix. - Mesh = absorbable or non-absorbable synthetic mesh. Both are medical devices used in breast implant surgery where the mesh or matrix provides a soft tissue scaffold.
autologous flap cover	calculated manually	If either the variable [ldcover = Latissimus Dorsi flap used for current breast implant surgery that covers an implantable breast device or adds volume to the breast mound] or [flapcover-other = any other flap used for current breast implant surgery that covers an implantable breast device or adds volume to the breast mound] was selected.
fat grafting	fatgrafting	Transfer of aspirated fat to the breast region.
mastopexy	mastopexy	Breast lift.
mastectomy skin flap necrosis	skinnecrosis	Necrosis of the mastectomy skin flap.
skin scarring	scarring	An abnormal or suboptimal cutaneous or dermal scarring. Includes keloid formation, hypertrophic scarring, poor scar contour or orientation causing distortion or compromise of the reconstructive or aesthetic result. Does NOT include capsular contracture.
deep wound infection	wound	An infection associated with a breast implant which leads to its explantation or revision. Usually involves redness, localized pain or tenderness, abscess or persistent serous liquid formation around the implant.
seroma or hematoma	seroma, seroma19, hematoma19	Seroma (an accumulation of serum around the implant) or hematoma (a collection of blood outside the blood vessels which can be localized in an organ, space or tissue).
device malposition	devmalpos	Any instance in which the implant is outside its intended position.
capsular contracture	capsular-noyes	The shrinkage of the foreign body encapsulation scar tissue that forms around artificial implants imbedded in body tissue.
newly diagnosed breast cancer	breastcancer	Any type of newly diagnosed breast cancer (including DCIS), which leads to the revision or explantation of the breast device.
breast pain	breastpain	As noted by the patient.
asymmetry	asymmetry	As determined by the patient and identifiable by the surgeon.
dissatisfaction with volume	dissatisfaction	Patient preference to change the size of the implant.

LABEL	VARIABLE AS STATED IN DBIR	DEFINITION
device rupture or deflation	devicedefrupt	Loss of implant shell integrity.
BIA-ALCL	anaplasticconf	Pathology proven BIA-ALCL = Breast Implant-Associated Anaplastic Large Cell Lymphoma. A CD30+, ALK-, T-cell derived lymphoma within the non-Hodgkin lymphoma group.
Patient-requested implant removal due to nonspecific health symptoms	asia	ASIA = Autoimmune Syndrome Induced by Adjuvants. Breast Implant Illness (BII) = term used by women who have breast implants and who self-identity and describe a variety of symptoms including (but not limited to) fatigue, chest pain, hair loss, headaches, chills, photosensitivity, chronic pain, rash, body odor, anxiety, brain fog, sleep disturbance, depression, neurologic issues and hormonal issues that they feel are directly connected to their breast implants.
implant type	implanttype	Permanent breast implant or tissue expander.

**An extended version of the data dictionary can be downloaded from https://support.mrdm.nl/documentatie/*

Supplementary table 2. Raw data of patient and surgery characteristics at time of mastectomy and immediate IBBR.

	Total group (*n*=4512)
Intervention of Interest	
Type of IBBR	
Direct-to-implant	2100 (46.5)
Two-stage	2412 (53.5)
Patient Characteristics	
Mean age (years, SD)	49.0 (11.3)
Missing	14 (0.3)
ASA classification	
I	2843 (63.0)
II	1480 (32.8)
III+	131 (2.9)
Missing	58 (1.3)
Median Body Mass Index* (kg/m², IQR)	23.7 (21.6-26.6)
Missing	188 (8.1)
Smoking status*	
Not smoking	1562 (67.3)
Smoking	215 (9.3)
Missing	544 (23.4)
Previous radiotherapy	
No	3669 (81.3)
Yes	176 (3.9)
Missing	667 (14.8)
Postoperative radiotherapy planned*	
No	1897 (81.7)
Yes	125 (5.4)
Missing	299 (12.9)
Surgery Characteristics	
Year of surgery	
2015	694 (15.4)
2016	898 (19.9)
2017	937 (20.7)
2018	1081 (24.0)
2019	902 (20.0)
Healthcare institution volume (per year)	
<50 implant surgeries	506 (11.2)
50-99 implant surgeries	783 (17.4)

	Total group (*n*=4512)
100-200 implant surgeries	1824 (40.4)
>200 implant surgeries	1399 (31.0)
Reconstruction indication	
Breast cancer	4094 (90.7)
Prophylactic mastectomy	418 (9.3)
Laterality	
Unilateral	2933 (65.0)
Bilateral	1579 (35.0)
Incision site	
Nipple sparing	922 (20.4)
Non-nipple sparing	2946 (65.3)
Other	211 (4.7)
Missing	433 (9.6)
Plane	
Completely covered with PM muscle	2202 (48.8)
Partially covered with PM muscle	1509 (33.4)
Other	147 (3.3)
Missing	654 (14.5)
Number of applied ICMs during implant insertion	
<4	908 (20.1)
4	1543 (34.2)
>4	2038 (45.2)
Missing	23 (0.5)
ADM/Mesh	
No	3559 (78.9)
Yes	414 (9.2)
Missing	539 (11.9)

*Values in parentheses are percentages, unless indicated otherwise. IBBR, implant-based breast reconstruction; SD, standard deviation; ASA, American society of anesthesiologists; IQR, interquartile range; PM, pectoralis major; ICMs, infection control measures; ADM, acellular dermal matrix. *Registered since September 2017 and therefore presented for a smaller population (n=2321).*

Supplementary table 3. Patient and surgery characteristics at time of mastectomy and immediate IBBR per reconstruction trajectory.

	Direct-to-implant IBBR (*n*=2100, 46.5%)	**Two-stage IBBR** (*n*=2412, 53.5%)	***P*-value**
Patient Characteristics			
Mean age (years, SD)	48.0 (11.4)	49.8 (11.2)	<0.001
ASA classification			0.161
I	1352 (64.4)	1526 (63.3)	
II	677 (32.2)	823 (34.1)	
III+	71 (3.4)	63 (2.6)	
Median Body Mass Index (kg/m², IQR)	23.0 (20.6-25.7)	22.9 (20.5-25.8)	0.864
Smoking status			<0.001
Not smoking	1838 (87.5)	2014 (83.5)	
Smoking	262 (12.5)	398 (16.5)	
Previous radiotherapy			0.447
No	1994 (95.0)	2303 (95.5)	
Yes	1106 (5.0)	109 (4.5)	
Postoperative radiotherapy planned			<0.001
No	1872 (89.1)	2323 (96.3)	
Yes	228 (10.9)	89 (3.7)	
Surgery Characteristics			
Year of surgery			<0.001
2015	280 (13.3)	414 (17.2)	
2016	400 (19.0)	298 (20.6)	
2017	415 (19.8)	522 (21.6)	
2018	451 (21.5)	630 (26.2)	
2019	554 (26.4)	348 (14.4)	
Healthcare institution volume (per year)			<0.001
<50 implant surgeries	240 (11.4)	266 (11.0)	
50-99 implant surgeries	361 (17.2)	422 (17.5)	
100-200 implant surgeries	647 (30.8)	1177 (48.8)	
>200 implant surgeries	852 (40.6)	547 (22.7)	
Reconstruction indication			0.151
Breast cancer	1891 (90.0)	2203 (91.3)	
Prophylactic mastectomy	209 (10.0)	209 (8.7)	
Laterality			0.030
Unilateral	1330 (63.3)	1603 (66.5)	
Bilateral	770 (36.7)	809 (33.5)	

	Direct-to-implant IBBR (*n*=2100, 46.5%)	**Two-stage IBBR** (*n*=2412, 53.5%)	***P*-value**
Incision site			<0.001
Nipple sparing	608 (29.0)	427 (17.7)	
Non-nipple sparing	1282 (61.0)	1911 (79.2)	
Other	210 (10.0)	74 (3.1)	
Plane			<0.001
Completely covered with PM muscle	855 (40.7)	1635 (67.8)	
Partially covered with PM muscle	1123 (53.5)	725 (30.1)	
Other	122 (5.8)	52 (2.2)	
Number of applied ICM's during implant insertion			<0.001
<4	599 (28.5)	311 (12.9)	
4	670 (31.9)	887 (36.8)	
>4	831 (39.6)	1214 (50.3)	
ADM/Mesh			<0.001
No	1727 (82.2)	2318 (96.1)	
Yes	373 (17.8)	94 (3.9)	

Values in parentheses are percentages, unless indicated otherwise. IBBR, implant-based breast reconstruction; SD, standard deviation; ASA, American society of anesthesiologists; IQR, interquartile range; PM, pectoralis major; ICMs, infection control measures; ADM, acellular dermal matrix.

Supplementary table 4. Preoperative patient and surgery characteristics at time of mastectomy and immediate IBBR, per reconstruction trajectory, before and after propensity score matching*.

	Before PSM			After PSM		
	Direct-to-implant IBBR *n*=684 (40.1)	**Two-stage IBBR** *n*=1022 (59.9)	***SMD†***	**Direct-to-implant IBBR** *n*=323 (50.0)	**Two-stage IBBR** *n*=323 (50.0)	***SMD†***
Patient Characteristics						
Mean age (years, SD)	48.1 (11.1)	48.6 (11.6)	0.04	48.0 (11.2)	48.3 (11.9)	0.03
ASA classification						
I	353 (51.6)	601 (58.8)	0.15	167 (51.7)	175 (54.2)	0.08
II	297 (43.4)	385 (37.7)		146 (45.2)	135 (41.8)	
III+	34 (5.0)	36 (3.5)		10 (3.1)	13 (4.0)	
Median Body Mass Index (kg/m², IQR)	23.3 (21.3-26.0)	23.7 (21.5-26.7)	0.15	23.6 (21.5-26.1)	23.8 (21.5-26.5)	0.03
Smoking status						
Not smoking	615 (89.9)	881 (86.2)	0.12	287 (88.9)	285 (88.2)	0.02
Smoking	69 (10.1)	141 (13.8)		36 (11.1)	38 (11.8)	
Previous radiotherapy						
No	653 (95.5)	984 (96.3)	0.04	303 (93.8)	308 (95.4)	0.07
Yes	3 (4.5)	38 (3.7)		20 (6.2)	15 (4.6)	
Postoperative radiotherapy planned						
No	619 (90.5)	985 (96.4)	0.24	300 (92.9)	302 (93.5)	0.03
Yes	65 (9.5)	37 (3.6)		23 (7.1)	21 (6.5)	

	Before PSM			After PSM		
	Direct-to-implant IBBR *n*=684 (40.1)	**Two-stage IBBR** *n*=1022 (59.9)	***SMD†***	**Direct-to-implant IBBR** *n*=323 (50.0)	**Two-stage IBBR** *n*=323 (50.0)	***SMD†***
Surgery Characteristics						
Year of surgery						
2015	2 (0.3)	1 (0.1)		1 (0.3)	0 (0)	
2016	6 (0.9)	4 (0.4)	0.23	3 (0.9)	4 (1.2)	0.09
2017	116 (17.0)	181 (17.7)		52 (16.1)	47 (14.6)	
2018	296 (43.3)	541 (52.9)		150 (46.4)	153 (47.4)	
2019	264 (38.5)	295 (28.9)		117 (36.2)	119 (36.8)	
Healthcare institution volume (per year)						
<50 implant surgeries	102 (14.9)	94 (9.1)		30 (9.3)	33 (11.2)	
50-99 implant surgeries	146 (21.3)	204 (20.0)	0.19	59 (18.3)	58 (18.0)	0.04
100-200 implant surgeries	297 (43.4)	475 (46.5)		138 (42.7)	140 (43.3)	
>200 implant surgeries	139 (20.4)	249 (24.4)		96 (29.7)	92 (28.5)	
Reconstruction indication						
Breast cancer	570 (83.3)	839 (82.1)	0.03	266 (82.4)	266 (82.4)	<0.01
Prophylactic mastectomy	114 (16.7)	183 (17.9)		57 (17.6)	57 (17.6)	
Laterality						
Unilateral	394 (57.6)	594 (58.1)	0.01	180 (55.7)	185 (57.3)	0.03
Bilateral	290 (42.4)	428 (41.9)		143 (44.3)	138 (42.7)	

*Values in parentheses are percentages, unless indicated otherwise. *Sub-selection of original non-imputed data, records with any missing preoperative characteristic were excluded. †Standardized mean differences of ≥0.1 represent disbalances in characteristics between groups. PSM, propensity score matching; IBBR, implant-based breast reconstruction; SMD, standardized mean difference; SD, standard deviation; ASA, American society of anesthesiologists; IQR, interquartile range.*

PART III

JOINING FORCES WITH OTHER REGISTRIES

CHAPTER 6

THE DUTCH BREAST IMPLANT REGISTRY: REGISTRATION OF BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA – A PROOF OF CONCEPT

B.E. Becherer*
M. de Boer*
P.E.R. Spronk
A.H. Bruggink
J.P. de Boer
F.E. van Leeuwen
M.A.M. Mureau
R.R.W.J. van der Hulst
D. de Jong*
H.A. Rakhorst*
*contributed equally as first and last author

Plast Reconstr Surg. 2019 May;143(5):1298-1306.

ABSTRACT

Background: The Dutch Breast Implant Registry (DBIR) was established in April 2015 and currently contains information on 38,000 implants in 18,000 women. As a clinical registry, it evaluates the quality of breast implant surgery, including adverse events such as breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). To examine the efficacy of DBIR, the capture rate of BIA-ALCL was compared to the registration of BIA-ALCL in the Dutch Nationwide Network and Registry of Histo- and Cytopathology (PALGA) as a gold standard, in combination with matching these databases to obtain complementary information.

Methods: All BIA-ALCL patients diagnosed and registered in The Netherlands in 2016 and 2017 were identified separately in the PALGA and DBIR databases. In addition, both databases were matched using indirect key identifiers. Pathologic information from PALGA and clinical and device characteristics from DBIR were obtained for all patients.

Results: Matching of both databases gave a capture rate of BIA-ALCL in DBIR of 100 percent (n=6) in 2016 and 70 percent (n=7) in 2017. In total, 17 patients were identified in PALGA, of which 14 patients were also identified in DBIR; three patients were not registered and 10 patients were registered false-positive. Of all confirmed patients, symptoms, staging results, treatment, and implant information were registered.

Conclusions: Currently, DBIR contains 2 full registration years and captures most of the BIA-ALCL patients despite overestimation. Therefore, pathology confirmation remains essential. By matching these databases, complementary clinical and implant information could be retrieved, establishing DBIR as an essential postmarketing surveillance system for health risk assessments.

INTRODUCTION

Breast implants are class III (high-risk) medical devices that are amongst the most applied medical devices in plastic surgery.[1-3] Recently, we could determine that, in The Netherlands, 3.3 percent of all women between ages 20 and 70 years carry breast implants.[4] Instigated by the ongoing discussion on possible health risks in women with breast implants, national and international stakeholders have called for the need for nationally covering breast implant registries.[3-11] The recently proven significantly elevated risk for breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) has underpinned the timeliness of these registries.[4,12-13] BIA-ALCL is a rare variant of T-cell non-Hodgkin lymphoma, occurring in the periprosthetic fluid or capsule of women with breast implants, with a calculated absolute risk of 1:35,000 at the age of 50 years to 1:7000 at the age of 75 years.[4] Many aspects of this disease remain unresolved, of which identification of specific patient groups and implant associations that infer a higher risk may be the greatest challenges.

For meaningful studies in such a rare disease, a big-data approach is essential. In this light, use of breast implant registries with an almost complete regional or national coverage is an essential tool in evaluating breast implant-related serious adverse events. Currently, only the breast implant registries in Sweden (Swedish Breast Implant Registry (BRIMP) since 2014), Australia (Australian Breast Device Registry (ABDR) since 2015) and the Netherlands (Dutch Breast Implant Registry (DBIR) since 2015) seem to be eligible sources for big data.[11,14-15]

The Dutch Breast Implant Registry (DBIR) is a national, prospective, opt-out registry, with mandatory registration of all breast implant surgery performed in The Netherlands.[14,16-17] Since the start of DBIR in April of 2015, approximately 18,000 patients and 38,000 breast implants have been registered until December of 2017. In contrast, the Dutch Nationwide Network and Registry of Histo- and Cytopathology (PALGA) was established in 1971 as a comprehensive registration of all national pathology reports, containing coded histocytologic and cytopathologic information from all pathology laboratories in The Netherlands, providing nationwide coverage since 1990.[18]

We investigated the efficacy of DBIR by measuring the capture rate of BIA-ALCL patients in DBIR compared to PALGA as a gold standard, providing an objective quality assessment of the national breast implant registration program. Second, we aimed to determine the compatibility of both databases in merging data, as a support for future research.

METHODS

Registries and timeframe

Anonymized data for this cross-sectional study were obtained using two databases: the DBIR and PALGA. DBIR was implemented nationwide in April of2015, and 2016 was the first full registration year in which "participation in DBIR" was used as a national quality indicator by the Dutch Health Care Inspectorate. BIA-ALCL cases were selected from two corresponding full registration years in both registries, starting on January 1, 2016, up to and including December 31, 2017.

Case-finding strategies

All registered BIA-ALCL cases in The Netherlands were identified using the query "anaplastic large cell lymphoma" and "breast" in the PALGA database as described previously.[4,19] In addition, all cases registered as a revision operation because of BIA-ALCL were selected from DBIR.

These data were obtained after a centrally approved request by the scientific board of DBIR, the Netherlands Society of Plastic Surgery and the scientific board of PALGA. The Medical Research Involving Human Subjects Act does not apply to this study.[18-19]

Matching patients in DBIR and PALGA

After separate data collection from PALGA and DBIR, the output of DBIR was validated using the identified cases in the PALGA database. Interdatabase comparison per identified case was performed manually, using three key variables: date of diagnosis (i.e., date of receipt of pathology samples) in PALGA versus operation date in DBIR (with a maximum range of 1 day), age at diagnosis in PALGA versus age at surgery in DBIR, and pathology laboratory in PALGA versus hospital location in DBIR.

Included variables

Subsequently, data from PALGA and DBIR were merged. From PALGA, information on the date of diagnosis, age at diagnosis, pathology laboratory, histopathologic and cytopathologic information on diagnosis, and detailed tumor characteristics was obtained. From DBIR, clinical information at revision surgery was collected, including patient characteristics (i.e., age, American Society of Anesthesiologists classification, smoking, body mass index, and information on previous breast surgery and/or radiotherapy), surgery characteristics (i.e., hospital identification code, date of operation, side of operation, type of intervention, indication for intervention, and operative technique), and device characteristics (i.e., device type, year of implantation, country of implantation, and manufacturer).[20]

RESULTS

Capture rate of BIA-ALCL

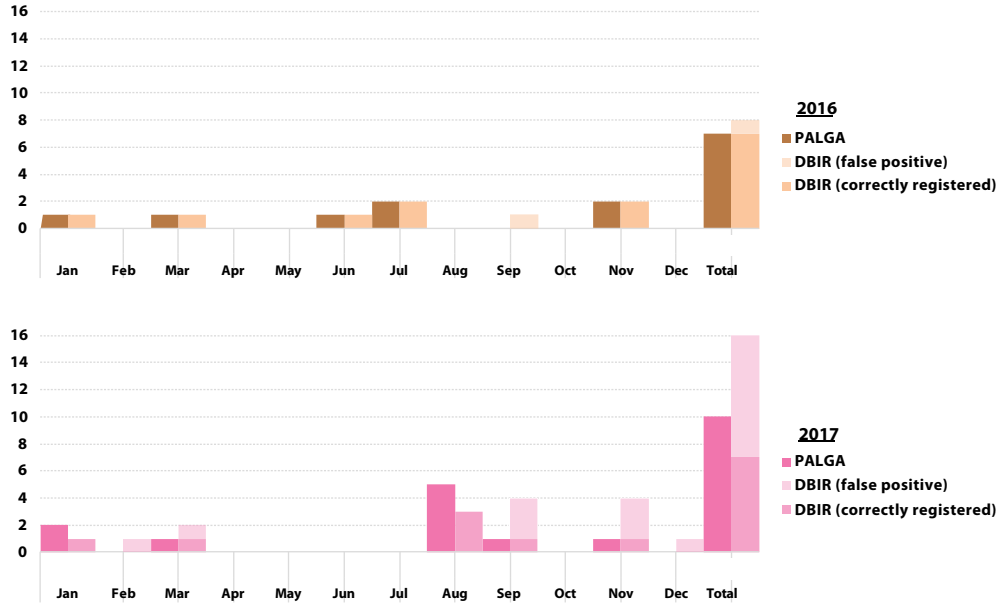
Between January 1, 2016, and December 31, 2017, 13,901 patients and 30,399 breast implants were registered in DBIR (6336 patients and 12,854 implants in 2016; 7565 patients and 17,745 implants in 2017). Of the 13,901 patients, 4039 patients underwent an unexpected revision surgery (2031 in 2016; 2008 in 2017). Registered implants were composed of new implants and revision surgery of breast implants inserted before and after the start of the registry. In the registry, indications for revision surgery are collected and categorized as unexpected or planned, such as the exchange of a tissue expander for an implant or autologous tissue. Of the women with an unexpected breast implant revision in DBIR, eight patients were reported to have BIA-ALCL in 2016 (0.3% percent) and 16 patients were reported to have BIA-ALCL in 2017 (0.8 percent). Between January 1, 2016, and December 31, 2017, 17 BIA-ALCL cases were identified in PALGA (n=7 in 2016; n=10 in 2017).

Matching of the patients reported with BIA-ALCL in both databases was performed successfully. All seven patients reported in PALGA in 2016 were correctly registered in DBIR (capture rate, 100 percent). In 2017, seven of 10 patients registered in PALGA were correctly registered in DBIR, whereas three were missing (capture rate, 70 percent; n=3 false-negative cases for DBIR). In both years, 10 additional patients were registered in DBIR (n=1 in 2016, and n=9 in 2017). In these patients, BIA-ALCL diagnosis was not histologically or cytologically confirmed and therefore not reported correctly in PALGA. These cases were considered false-positive for DBIR (*Figure 1*).

Combining clinical information from two databases

Combined histocytologic findings and patient, surgery, and implant characteristics of confirmed BIA-ALCL patients are listed in *Table 1*. The diagnosis of BIA-ALCL was obtained and confirmed after cytological analysis of periprosthetic seroma, histologic examination of the periprosthetic capsule, or large needle/incisional biopsy of a BIA-tumor mass. Of the 17 confirmed cases, median age at diagnosis and revision surgery was 56 years (interquartile range, 48 to 59 years; range, 33 to 75 years). Twelve patients presented with a seroma-associated type BIA-ALCL (T1N0M0), and five patients presented with a mass-associated type (T2 to T4), three of which had dissemination outside the breast.[21] Median time from implantation to lymphoma diagnosis was 9 years (interquartile range, 5.5 to 13.5 years; range, 1 to 18 years). In 12 patients, BIA-ALCL was the indication for revision surgery and registration in DBIR; in two patients, BIA-ALCL was an incidental finding at implant revision. Of five women, the primary indication for breast implants was known (n=3 aesthetic, n=2 reconstructive). Seven patients presented with asymmetry and seroma; in the other patients the symptoms were not registered. The reported capsular contracture grade varied between

Figure 1. Registered BIA-ALCL cases per year in the DBIR and PALGA databases (2016-2017).
(The number of registered BIA-ALCL cases per month in 2016 and 2017 in the PALGA database (dark green and dark blue), and the corresponding registrations in the DBIR database (light green and light blue). Registered cases in DBIR without a histopathologic confirmation in the PALGA database were labeled false-positive (hatched).)



grade I and grade IV (according to the Baker classification), and all patients underwent a capsulectomy and removal of the implant. Characteristics of the explanted implants were incomplete in the DBIR dataset before September of 2017, as this information has only been registered for explanted devices since its most recent update in September of 2017.

The accuracy of DBIR: false-positive and false-negative registrations

As derived from DBIR and PALGA registration logs, the false-positive registrations in DBIR (n=10) were entered based on a clinically suspected diagnosis of BIA-ALCL before histocytologic and/or cytopathologic assessment by the local and/or expert pathologist. However, once the negative pathology information became available, the registration was not corrected in DBIR.

The current registration procedure also explains the missing DBIR registrations (n=3), because novel lymphoma diagnoses were not updated in previously filed registrations at the time of surgery when lymphoma was not clinically suspected or realized. Even though DBIR is an opt-out registry with mandatory registration for all board-certified plastic surgeons in The Netherlands since January 1, 2016, we cannot exclude that some

Table 1. Complementary character of the DBIR and PALGA databases with histopathologic, clinical, and breast implant information per case (2016-2017).

	PALGA		DBIR	
Case	Pathological Report	Patient*	Surgery	Breast Implant (explanted)*
1	Periprosthetic seroma, CD30+, ALK1-. Anaplastic large cell lymphoma. Mass-associated type. TNM: T4N0M0	ASA classification: 2. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Left - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 2, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: N/A. Year of implantation: N/A. Country of implantation: The Netherlands.
2	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type TNM: T1N0M0	ASA classification: 2. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Left - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 4, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: N/A. Year of implantation: N/A. Country of implantation: Abroad (country unknown).
3	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Mass-associated type. TNM: T3N0M0	ASA classification: 2. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Left - Replacement with new implant. Indication for revision: Seroma and asymmetry. Additional findings: ALCL. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 1, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2013. Country of implantation: The Netherlands. NB: New implanted breast implant: Allergan, textured.
4	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 2. Smoking: N/A. BMI: N/A. revious RTx: No.	Primary indication for breast implants: Aesthetic. Side & Intervention: Right - Explantation only. Indication for revision: Seroma/Hematoma. Additional findings: ALCL. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 1, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2016. Country of implantation: The Netherlands.
5	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 2. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL. Additional findings: Asymmetry. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 1, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Sebbin Laboratoires. Year of implantation: 2012. Country of implantation: Belgium.

	PALGA	DBIR		
Case	Pathological Report	Patient*	Surgery	Breast Implant (explanted)*
6	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Mass-associated type. TNM: T4N1M0	ASA classification: 2. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Left - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 2, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2009. Country of implantation: The Netherlands.
7	Periprosthetic seroma and capsule. CD30+, ALK1-. Anaplastic large cell lymphoma. Mass-associated type TNM: T3N2M1	ASA classification: 3. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL. Additional findings: Seroma, Asymmetry, Breast pain. Device rupture: Yes. Silicone extravasation: Yes, intra-capsular. Capsular contracture: Grade 4, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2001. Country of implantation: The Netherlands.
8	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	Missing in DBIR		
9	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 1. Smoking: N/A. BMI: 29. Previous RTx: No.	Primary indication for breast implants: N/A. Side & Intervention: Left - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: N/A. Silicone extravasation: N/A. Capsular contracture: Grade 2, capsulectomy.	Type: N/A. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2007. Country of implantation: N/A.
10	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 1. Smoking: N/A. BMI: N/A. Previous RTx: No.	Primary indication for breast implants: Aesthetic. Side & Intervention: Left - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 4, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: Textured, silicone. Manufacturer: Allergan. Year of implantation: 2008. Country of implantation: N/A.

	PALGA		DBIR	
Case	Pathological Report	Patient*	Surgery	Breast Implant (explanted)*
11	Periprosthetic seroma and capsule. CD30+, ALK1-. Anaplastic large cell lymphoma. Mass-associated type. TNM: T2N0M1	ASA classification: 3. Smoking: N/A. BMI: 23. Previous RTx: No.	Primary indication for breast implants: Aesthetic. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL and asymmetry. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 4, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: N/A. Year of implantation: 1999. Country of implantation: N/A.
12	Periprosthetic seroma, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	Missing in DBIR		
13	Periprosthetic seroma and capsule, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	Missing in DBIR		
14	Periprosthetic seroma and capsule, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 1. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade N/A, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2004. Country of implantation: N/A.
15	Periprosthetic seroma and capsule, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: N/A. Smoking: N/A. BMI: N/A. Previous RTx: No.	Primary indication for breast implants: N/A. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 1, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: CUI implants. Year of implantation: 2003. Country of implantation: N/A.

	PALGA	DBIR		
Case	Pathological Report	Patient*	Surgery	Breast Implant (explanted)*
16	Periprosthetic seroma and capsule, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 1. Smoking: No. BMI: 32. Previous RTx: No.	Primary indication for breast implants: Reconstructive. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL and seroma. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: N/A, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: Textured, silicone. Manufacturer: Allergan. Year of implantation: 2008. Country of implantation: the Netherlands.
17	Periprosthetic seroma and capsule, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 1. Smoking: No. BMI: 26. Previous RTx: No.	Primary indication for breast implants: Reconstructive. Side & Intervention: Left - Replacement. Indication for revision: ALCL, seroma and asymmetry. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade N/A, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: Textured, silicone. Manufacturer: Allergan. Year of implantation: 2009. Country of implantation: the Netherlands. NB: new implanted breast implants: Allergan, smooth, silicone.

PALGA indicates Dutch Nationwide Network and Registry of Histo- and Cytopathology; DBIR, Dutch Breast Implant Registry; ASA, American Association of Anesthesiologists; BMI, body mass index, RTx, radiotherapy; BIA-ALCL, breast-implant associated anaplastic large cell lymphoma; N/A, not available.
*Variables registered since September 2017: BMI and smoking, and from the explanted devices texture, coating, and fill.

institutions still fail to reach a complete registration rate. This was not the case for the three missed lymphoma patients, however.

DISCUSSION

In the present study, the adverse event registration of BIA-ALCL in DBIR was validated using histopathologically confirmed BIA-ALCL cases from the national pathology registration database (i.e., PALGA). This showed the efficacy of registration of BIA-ALCL in DBIR to be 100 percent in 2016 and 70 percent in 2017, with a total of ten patients reported as false-positive, underpinning the importance of histopathologic or cytopathologic confirmation. Furthermore, both databases could be matched, resulting in a larger dataset with relevant variables for BIA-ALCL without the need for manual extraction of information from medical records. Data points included implant characteristics, surgery characteristics, and histopathologic information.[4,12-13,22-24]

Quality control strategies for breast implants in the DBIR design

DBIR has three purposes, all aiming to improve health care quality and patient safety. Besides the evaluation of health care provided, it contains data for recall purposes and determines the performance of all registered devices.[14] Because the quality and completeness of registered information depends on the accuracy of the registry and its users, control mechanisms are recommended.[25] To achieve maximal capture rates and improve data completeness, DBIR uses an opt-out structure, and is "Registration in the Dutch Breast Implant Registry" a mandatory quality indicator for the Dutch National Health Care Inspectorate since January 2016. A structure of mandatory input in all registration fields guarantees data completeness.

Besides quality control of submitted data, external validation of the registrations is at least as essential. Although no gold standard is known, several methods have been described, such as comparisons with locally held data, comparisons with other registries, or monitoring by dedicated personnel.[26-28] In DBIR, all registered implants used for implantation surgery have been compared with a selection of sales data from breast implant vendors in The Netherlands, resulting in an estimated capture rate of 75 percent in its first registration year (data not shown). However, validation of the capture rate of implants that are removed during revision surgery is more difficult, as validation tools with complete, reliable coverage for these operations are unavailable. Therefore, it was valuable to use the PALGA database, which has nationwide coverage, as an external validation tool for this particular group.

Complementarity of databases

Matching pathological data from the PALGA database with clinical and implant data from DBIR proved the complementarity of both databases. Eventually, this could serve as a basis system, substituting for the manual collection of case-based information and minimizing the burden of double registration. Because DBIR is a clinical audit, additional information such as body mass index, a history of smoking or previous radiotherapy of the breast, previous and subsequent implant operations, and additional findings at revision surgery is automatically asked for. Extensive information on other clinical history and (oncological) follow-up, however, is not (yet) registered and needs to be extracted from medical records when necessary.

Optimizing the quality of BIA-ALCL diagnoses in DBIR

This study has allowed us to identify various aspects of DBIR registration that will help to improve the quality of the database in the next registry update. Most importantly, 10 patients with a false-positive registration for BIA-ALCL were found, and in three registered patients the BIA-ALCL listing were missing and were considered false-negative. All misclassifications were caused by registrations based on clinical data at the time of surgery without manual correction after pathology reports were received. First, this underpins the importance of including cases with pathologically confirmed diagnoses in institutional and international/national databases in general. For DBIR in particular, we plan to include two registration fields for diagnosis: "BIA-ALCL pathologically confirmed" and "suspicion of BIA-ALCL, not pathologically confirmed". All patients without a definite diagnosis will be automatically tagged and the reporting physician will receive an alert to update the registration based on a final pathological diagnosis within 1 month after surgery. This procedure is currently being tested. To avoid false-negative registrations, all BIA-ALCL patients registered in the PALGA database will be matched to DBIR periodically.

Limitations

A limitation is the fact that a minimum period of 3 years is indicated for a properly functioning clinical audit with reliable data.[14] With 2 full registration years, DBIR is still relatively young, and data completeness needs to improve. Increasing compliance, data validation and awareness among plastic surgeons is continuously needed to ensure high-quality and completely registered data in the future.

Future perspectives

The results from this study imply that breast implant registries can be used as an objective, national medical device evaluation system, without financial disclosures, to function as post-marketing surveillance systems, once the collected data have been validated.[29] Longitudinal long-term data collections in regular medical device postapproval studies often do not have a sufficient sample size to detect rare diseases such as BIA-ALCL, do

not follow participants for a sufficient length of time, and are not equipped to identify influencing factors for the development or prevention of BIA-ALCL.

Although matching DBIR to PALGA was executed manually for this study, a real-time patient-based matching process is ideally desired. For that, however, solid data validity and more advanced information and communication technology structures are required. A trusted third party may assist in this, but proven reliable search queries and key variables are essential when realizing an automatic matching process. Eventually, the concept of such a combined dataset, either manually or automatically, might even be implemented internationally. However, different privacy laws could become an obstacle, requiring attention beforehand.

CONCLUSION

This study supports the potential of breast implant registries to identify serious adverse events, using BIA-ALCL as an example. Despite its short existence and still growing compliance, DBIR proved to be effective as a registration system for BIA-ALCL. It showed a 100 percent match in its first registration year, and 70 percent match in its second full registration year, as validated by PALGA, albeit at the costs of false-positive registrations, emphasizing the importance of histopathologic confirmation of the diagnosis. By matching databases with patient-related, tissue-related, and implant-related information, reliable complementary data could be retrieved. In the future, a mature DBIR could provide complementary data that can be used for surveillance, monitoring, and to further study severe adverse events such as BIA-ALCL.

REFERENCES

1. Spear S. The breast implant story. Ann Plast Surg. 2006;56(5):573-83
2. European Commission. Guidelines for conformity assessment of breast implants according to directive 93/42/EEC relating to medical devices. Available at: https://ec.europa.eu/docsroom/documents/10290/attachments/1/translations/en/renditions/pdf. Accessed April 11, 2018.
3. U.S. Food and Drug Administration. FDA Breast Implant Consumer Handbook: 2004. Timeline of breast implant activities. Available at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm064242.htm.L Accessed January 26, 2018.
4. de Boer M, van Leeuwen FE, Hauptmann M, Overbeek LIH, de Boer JP, Hijmering NJ, et al. Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast. JAMA Oncol. 2018;4(3):335-41.
5. Agence Fraincaise de sécurité sanitaire des produits de santé. Situation update on checking procedures performed by the health authorities on the Poly Implant Prothèse company. Available at : https://www.ansm.sante.fr/var/ansm_site/storage/original/application/e044aa9eb27fc2eca49b93165c9020ae.pdf. Accessed January 26, 2018.
6. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Scientific opinion on the safety of Poly Implant Prothèse (PIP) silicone breast Implants (2013 update). Available at: https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_043.pdf. Accessed October 30, 2017.
7. Venhuis BJ, Keizers P, Geertsma R, Woutersen M, Muller A, Pronk M. Risk analysis of particulate contamination on Silimed silicone-based breast implants. Bilthoven, The Netherlands: National Institute for Public Health and the Environment, 2015.
8. Australian Government, Department of Health, Therapeutic Goods Administration. Silimed medical devices (all–including breast implants): Available at: https://www.tga.gov.au/node/709665. Accessed October 20, 2017.
9. Cooter RD, Barker S, Carroll SM, Evans GR, von Fritschen U, Hoflehner H, et al. International importance of robust breast device registries. Plast Reconstr Surg. 2015;135(2):330-6.
10. Nahabedian MY. Discussion: International importance of robust breast device registries. Plast Reconstr Surg. 2015;135(2):337-8.
11. Hopper I, Ahern S, Best RL, McNeil J, Cooter RD. Australian Breast Device Registry: breast device safety transformed. ANZ J Surg. 2017;87(1-2):9-10.
12. Loch-Wilkinson A, Beath KJ, Knight RJW, Wessels WLF, Magnusson M, Papadopoulos T, et al. Breast Implant-Associated Anaplastic Large Cell Lymphoma in Australia and New Zealand: High-Surface-Area Textured Implants Are Associated with Increased Risk. Plast Reconstr Surg. 2017;140(4):645-54.
13. Doren EL, Miranda RN, Selber JC, Garvey PB, Liu J, Medeiros LJ, et al. U.S. Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Plast Reconstr Surg. 2017;139(5):1042-50.

14. Rakhorst HA, Mureau MAM, Cooter RD, McNeil J, van Hooff M, van der Hulst R, et al. The new opt-out Dutch National Breast Implant Registry–Lessons learnt from the road to implementation. J Plast Reconstr Aesthet Surg. 2017;70(10):1354-60.
15. BRIMP. The breast implant registry annual report 2016. Available at: https://stratum.registercentrum.se/Handlers/ResourceManager.ashx?ID=32482. Accessed April 11, 2018.
16. Hommes J, Mureau M, Harmsen M, Rakhorst H. ['Which breast implant do I have?'; the importance of the Dutch Breast Implant Registry]. Ned Tijdschr Geneeskd. 2015;160:A9728.
17. Dutch Institute for Clinical Auditing. About DBIR (Eng). Available at: https://dica.nl/dbir/about-dbir. Accessed January 26, 2018.
18. Casparie M, Tiebosch ATMG, Burger G, Blauwgeers H, van de Pol A, van Krieken JHJM, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol. 2007;29(1):19-24.
19. de Jong D, Vasmel WL, de Boer JP, Verhave G, Barbe E, Casparie MK, et al. Anaplastic large-cell lymphoma in women with breast implants. JAMA. 2008;300(17):2030-5.
20. Dutch Breast Implant Registry. Case report form DBIR-2017. Available at https://mrdm.nl/showcase/downloaden. Accessed January 26, 2018.
21. Clemens MW, Medeiros LJ, Butler CE, Hunt KK, Fanale MA, Horwitz S, et al. Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant-Associated Anaplastic Large-Cell Lymphoma.J Clin Oncol. 2016 Jan 10;34(2):160-8.
22. Miranda RN, Aladily TN, Prince HM, Kanagal-Shamanna R, de Jong D, Fayad LE, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol. 2014;32(2):114-20.
23. Brody GS, Deapen D, Taylor CR, Pinter-Brown L, House-Lightner SR, Andersen JS, et al. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. Plast Reconstr Surg. 2015;135(3):695-705.
24. Srinivasa DR, Miranda RN, Kaura A, Francis AM, Campanale A, Boldrini R, et al. Global Adverse Event Reports of Breast Implant-Associated ALCL: An International Review of 40 Government Authority Databases. Plast Reconstr Surg. 2017;139(5):1029-39.
25. Kolling C, Simmen B, Labek G, Goldhahn J. Key factors for a successful National Arthroplasty Register. J Bone Joint Surg Br. 2007;89(12):1567-73.
26. Cundall-Curry DJ, Lawrence JE, Fountain DM, Gooding CR. Data errors in the National Hip Fracture Database: a local validation study. Bone Joint J. 2016;98-B(10):1406-9.
27. Linder G, Lindblad M, Djerf P, Elbe P, Johansson J, Lundell L, et al. Validation of data quality in the Swedish National Register for Oesophageal and Gastric Cancer. Br J Surg. 2016;103(10):1326-35.
28. Fest J, Ruiter R, van Rooij FJ, van der Geest LG, Lemmens VE, Ikram MA, et al. Underestimation of pancreatic cancer in the national cancer registry–Reconsidering the incidence and survival rates. Eur J Cancer. 2017;72:186-91.
29. Faris O, Shuren J. An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials. N Engl J Med. 2017;376(14):1350-7.

CHAPTER 7

IMPROVING BREAST IMPLANT SAFETY THROUGH INTERNATIONAL COLLABORATION OF NATIONAL REGISTRIES – A REVIEW OF OVER 85,000 PATIENTS AND 200,000 IMPLANTS FROM FOUR COUNTRIES.

B.E. Becherer
I. Hopper
R.D. Cooter
B. Couturaud
U. von Fritschen
E. Mullen
A.G.B. Perks
A.L. Pusic
B. Stark
M.A.M. Mureau
H.A. Rakhorst

Submitted.

ABSTRACT

Background. Growing awareness about breast implant-related adverse events has stimulated the demand for large, independent data resources. For this, data from breast implant registries could be combined. However, that has never been achieved yet.

Methods. Real-world data from four currently active national breast implant registries were used. All permanent breast implants from the Australian, Dutch, Swedish and American registries were included. A sub-population present across all registries between 2015-2018 was subsequently selected, including only permanent breast implants inserted during primary surgery for breast reconstruction or augmentation in patients without previous breast device surgery. Nationwide coverage, patient and implant characteristics, infection control measures, and revision incidences were analyzed.

Results. A total of 207189 breast implants were registered. Nationwide coverage varied between 3-98 percent. The sub-population included 111590 implants (7 percent reconstruction, 93 percent augmentation). Across the registries, mean patient age varied between 41-51 years (P <0.001) for reconstruction and 31-36 years (P <0.001) for augmentation. Median BMI differed for reconstruction (P=0.007), but not for augmentation (P=0.080). Variation was observed in implant preferences across the countries and over the years. Infection control measures were most frequently registered in Australia. Cumulative revision incidence at two years ranged from 6-16 percent after reconstruction and 1-4 percent after augmentation.

Conclusion. For the first time, independent, population-based data from four breast implant registries were combined. This is a powerful step forward in optimizing international breast implant monitoring, evidence-based decision-making, and patient safety.

INTRODUCTION

Over the past three decades, a lack of reliable implant data has had a negative impact on patients with breast implants during controversies about breast implant safety, silicone safety, and post-market implant surveillance. This paucity of good data has led to a new generation of well-designed, independent national breast implant registries to generate better evidence-based information that will ultimately improve patient safety.[1-7] These registries have united in the International Collaboration of Breast Registry Activities (ICOBRA), which was founded by the Australasian Foundation for plastic surgery in 2012 to harmonize registry efforts internationally.[8,9]

The goals of ICOBRA are to enhance collaboration between breast implant registries worldwide, improve breast device monitoring, and optimize patient safety. To this end, ICOBRA developed a harmonized dataset containing standardized and well-defined core data points incorporated by the involved breast implant registries.[10] The use of a harmonized dataset by different registries facilitates collaborative international projects, specifically for uncommon events like BIA-ALCL, for which answers on etiology are yet to be found.

Although data have been collected in the separate registries and annual reports have been published, until now, data have not been combined for analysis.[11-15] Therefore, this study aimed to evaluate the potential of sharing data from active breast implant registries using the ICOBRA harmonized dataset. Included topics per registry were: nationwide coverage, number of registered implants, patient characteristics, implant characteristics, use of infection control measures, and cumulative revision incidence.

METHODS

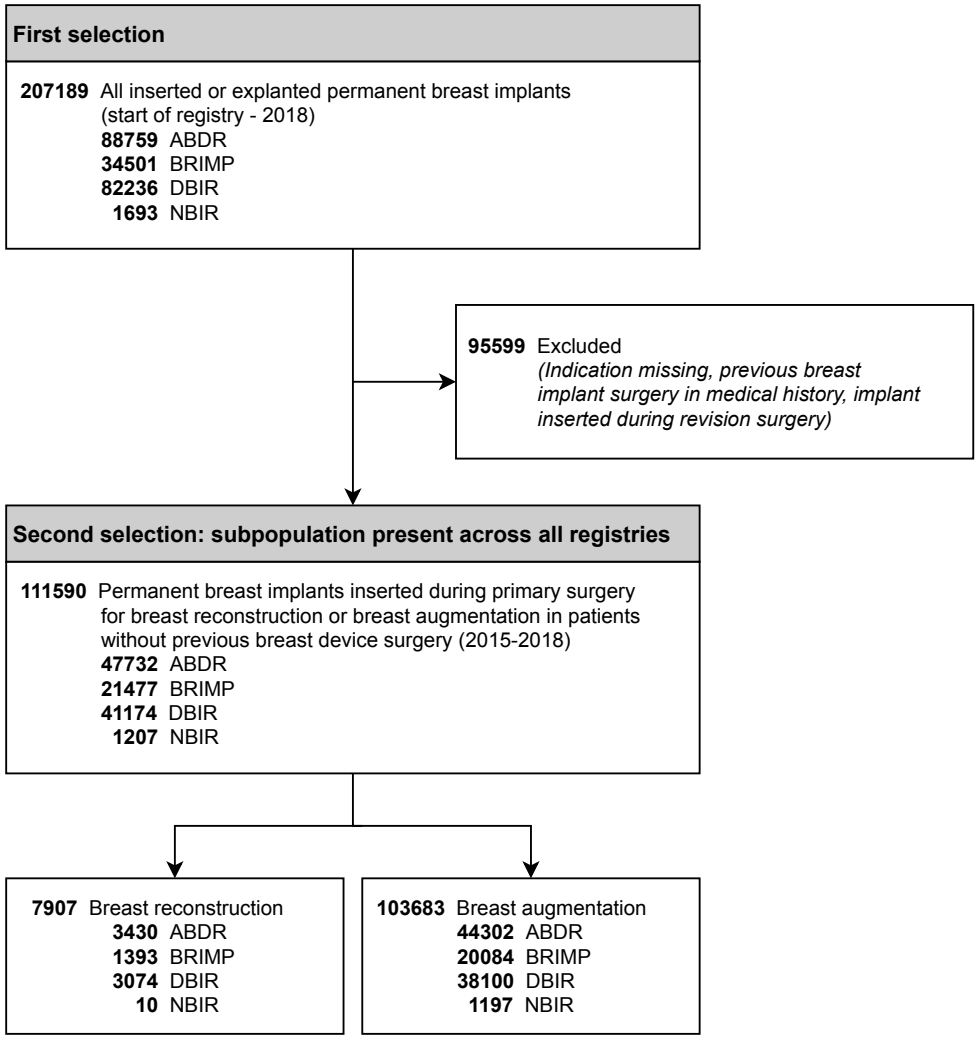
Breast implant registries

This observational study compiled data from the Australian Breast Device Registry (ABDR), the Breast Implant Register (BRIMP) from Sweden, the Dutch Breast Implant Registry (DBIR), and the National Breast Implant Registry (NBIR) from the United States. BRIMP started collecting data in 2014, ABDR and DBIR in 2015, and NBIR in October 2018. All four registries include permanent breast implants for breast reconstruction and breast augmentation. ABDR and DBIR include (temporary) tissue expanders as well. The registries use opt-out consent for patients and are united in the International Collaboration of Breast Registry Activities (ICOBRA).[8] More details about the registries may be found in previous work.[2,3,6,11,13,15-18]

Study population

For this observational, population-based cohort study, only permanent breast implants were included; temporary tissue expanders were excluded as BRIMP and NBIR do not register these devices. Subsequently, two selection steps were made (*Figure 1*). First, all permanent breast implants which had been prospectively registered as insertion or revision surgery between the start of each registry and December 31, 2018, were included. Second, a sub-population present across all four registries was selected to ensure uniformity of the gathered information. These included only permanent breast implants inserted during

Figure 1. Flow chart of implant selection.
(ABDR, Australian Breast Device Registry; BRIMP, Breast Implant Registry from Sweden; DBIR, Dutch Breast Implant Registry; NBIR, National Breast Implant Registry from the United States of America.)



primary surgery for breast reconstruction or breast augmentation in patients without a previous breast implant or tissue expander between 2015 and 2018.

Outcomes

The included outcomes were based on the existing overlap in the annual reports of the registries. From the essential topics registry validation, patient characteristics, implant characteristics, surgery techniques, and postoperative outcomes, the following six outcomes were included: 1) nationwide coverage of each registry, 2) total number of registered permanent breast implants, 3) patient age and BMI, 4) implant shape, shell and fill, 5) use of infection control measures (ICMs), and 6) cumulative revision incidence.

Definitions

Nationwide coverage of each registry was defined as the number of participating institutions in relation to the eligible number of institutions performing breast implant surgery in 2018. In Sweden, the eligible number of institutions could not be obtained. Implant insertion was defined as the insertion of a new breast implant in a breast without an implant or as replacement of an in-situ device. Primary implant surgery was defined as the first operation recorded in the registry in which a new breast implant was inserted in a patient without any previous breast implant or tissue expander insertion. Revision surgery was defined as the first reoperation after insertion in which an implant was repositioned, explanted, or replaced with a new implant or autologous tissue, regardless of the revision indication. Breast reconstruction included a reconstruction after mastectomy due to breast cancer or genetic predisposition and after a congenital deformity such as tuberous breasts or benign conditions such as gender-affirming surgery. Breast augmentation was defined as a unilateral or bilateral procedure for enlarging the breast(s). Exact definitions of all variables used for analysis are based on the ICOBRA harmonized dataset (*Supplementary table 1*).[10]

Combining data

The scripts for the analyses were developed collaboratively by the registries' data analysts. Subsequently, analyses were performed at registry level, after which the results were anonymously combined in aggregated analyses. Using this technique, data from each registry were protected for transfer across international borders according to the General Data Protection Regulation (GDPR) and Health Insurance Portability and Accountability Act (HIPAA).

Statistical analysis

Analyses were performed with breast implants as the unit of analysis. Missing data were left untouched to reflect the actual data that were present in the registries.

The total number of registered permanent breast implants in each registry was calculated by counting all inserted and explanted breast implant records.

Patient mean age was compared between the registries using a one-way ANOVA test (normal distribution) and a Kruskal-Wallis test (non-normal distribution). Differences in patient median body mass index (BMI) were compared between the registries using a Kruskal-Wallis H test, with BMI as the ordinal dependent variable. Two-sided *P*-values <0.050 were considered statistically significant.

Characteristics of the used breast implants were evaluated by implant shape, shell, and fill, and visualized in combined bar charts. The use of different infection control measures was calculated by registry and visualized in a combined bar chart.

The crude, cumulative revision incidence was analyzed using Nelson-Aalen estimates. *Revision time* was defined as the time from implant insertion to the first registered revision. Implants without revision surgery had their follow-up time censored at the date of data extraction. Implants without an implantation record were excluded.
No risk adjustment was undertaken for the analyses because the registries' differences in maturity do not yet allow this. Aggregated analyses were performed using R software, version 1.3.959 – © 2009-2020, RStudio, Inc.

Cautionary note

Although the registries are united in ICOBRA and have incorporated the minimum harmonized dataset, they run independently and have different data collection forms and methods. This study represents what is registered in each registry. However, depending on registry maturity, capture rate, data completeness, and data validity, registries do not entirely reflect each country's actual practice yet. This has to be kept in mind before comparing results.

RESULTS

Nationwide coverage

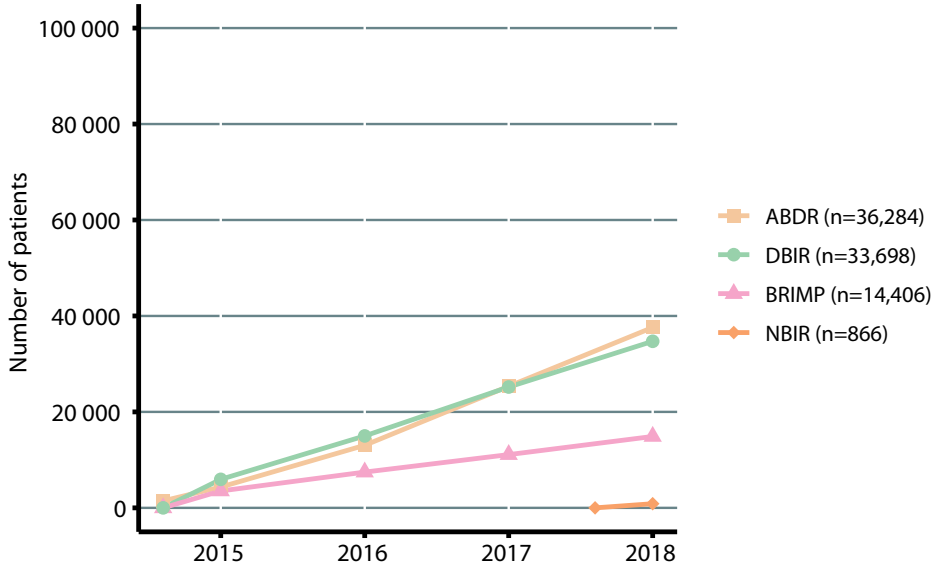
On December 31st, 2018, the ABDR captured 85 percent (n=280 of 329) of the eligible institutions, BRIMP included 46 institutions (eligible number unknown), DBIR captured 98 percent (n=110 of 112) of the institutions, and NBIR 2.5 percent (n=156 of 6185).

Total number of registrations

By the end of 2018, a total of 207189 permanent breast implants and 85254 patients were registered, including implantations, revisions, and explantations (*Figure 1)*. Of these, 88759 implants (36284 patients) were registered in ABDR, 34501 implants (14406 patients) in BRIMP, 82236 implants (33698 patients) in DBIR, and 1693 implants (866 patients) in NBIR (*Figure 2*).

Figure 2. Total number of registered patients and permanent breast implants since the start of each registry, including implantation and revision records.
(ABDR, Australian Breast Device Registry; BRIMP, Breast Implant Registry from Sweden; DBIR, Dutch Breast Implant Registry; NBIR, National Breast Implant Registry from the United States of America.)

A. Registered patients



B. Registered implants

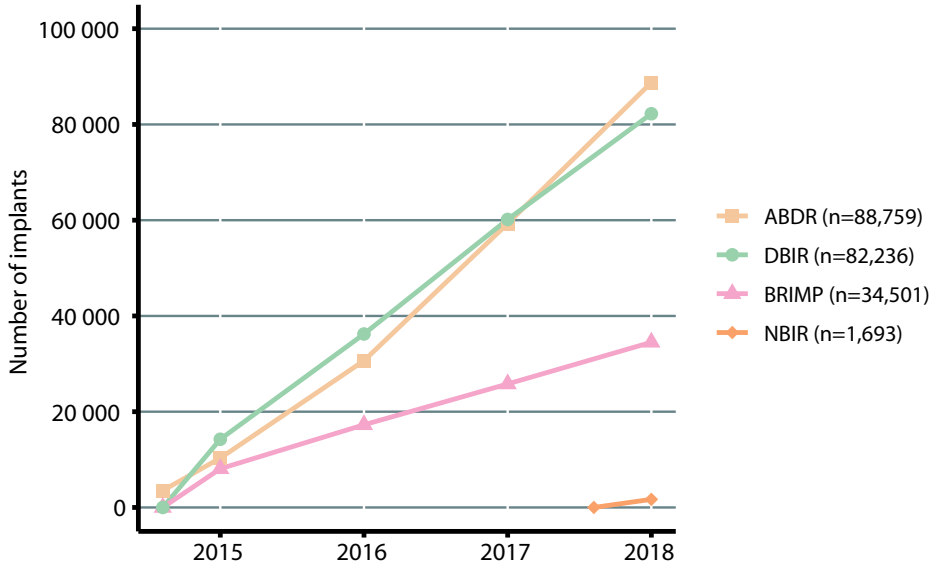
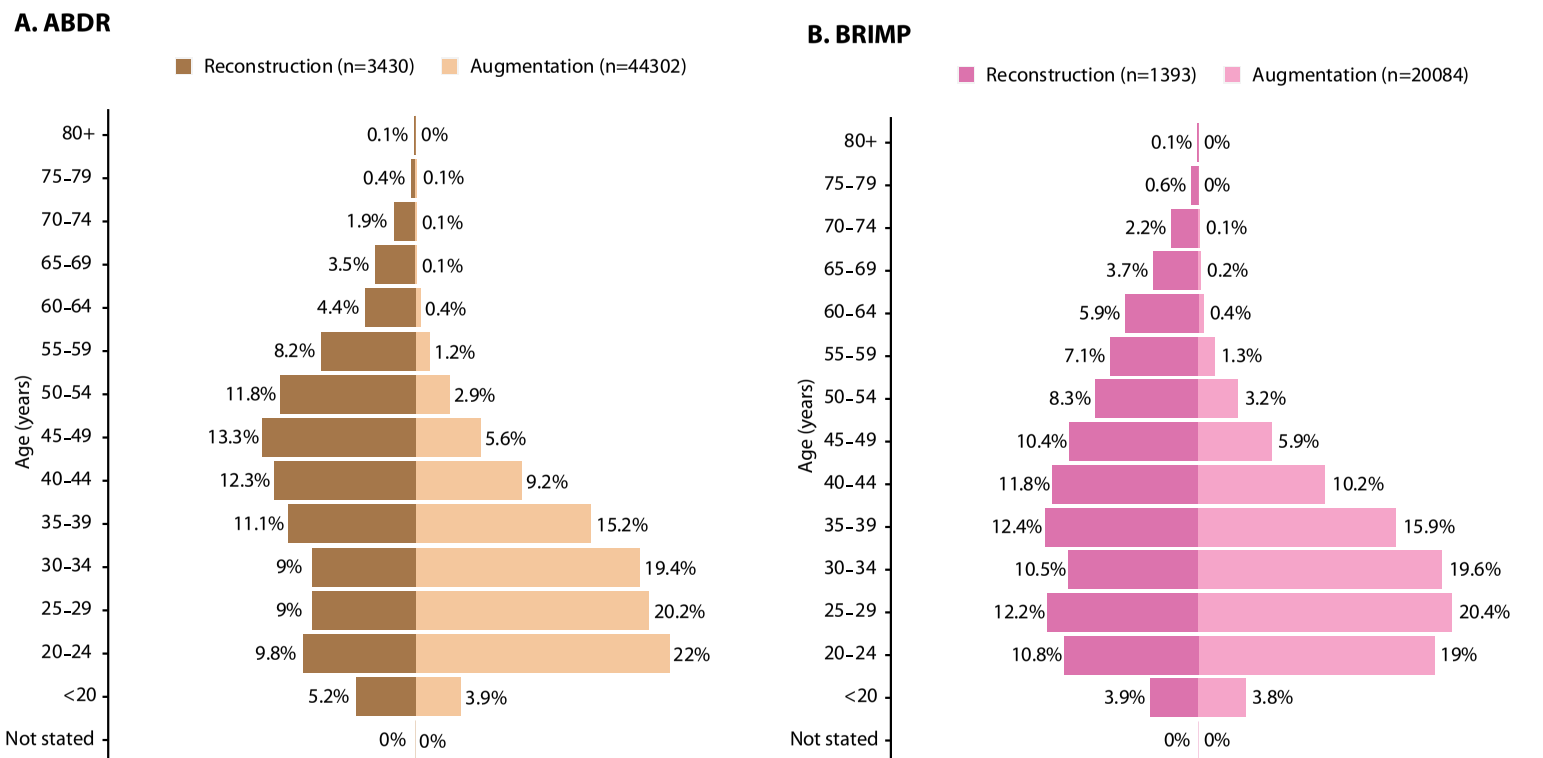
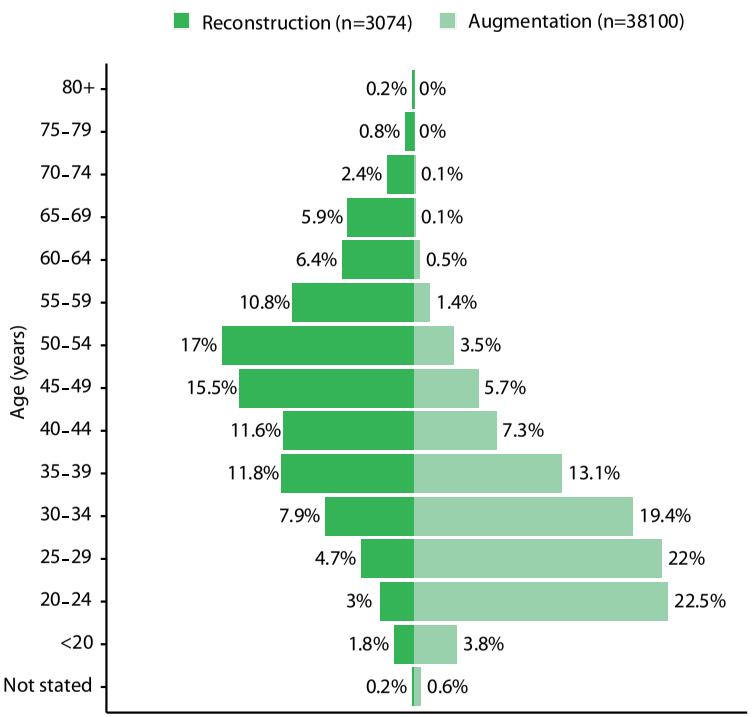


Figure 3. Patient age distribution per primary inserted permanent breast implant.
(Differences in mean age between registries: breast reconstruction P-value <0.001, breast augmentation P-value <0.001. ABDR, Australian Breast Device Registry; BRIMP, Breast Implant Registry from Sweden; DBIR, Dutch Breast Implant Registry; NBIR, National Breast Implant Registry from the United States of America.)



C. DBIR


Reconstruction (n=3074)
Augmentation (n=38100)
Age (years)
80+
75–79
70–74
65–69
60–64
55–59
50–54
45–49
40–44
35–39
30–34
25–29
20–24
<20
Not stated
0.2%
0%
0.8%
0%
2.4%
0.1%
5.9%
0.1%
6.4%
0.5%
10.8%
1.4%
17%
3.5%
15.5%
5.7%
11.6%
7.3%
11.8%
13.1%
7.9%
19.4%
4.7%
22%
3%
22.5%
1.8%
3.8%
0.2%
0.6%

D. NBIR

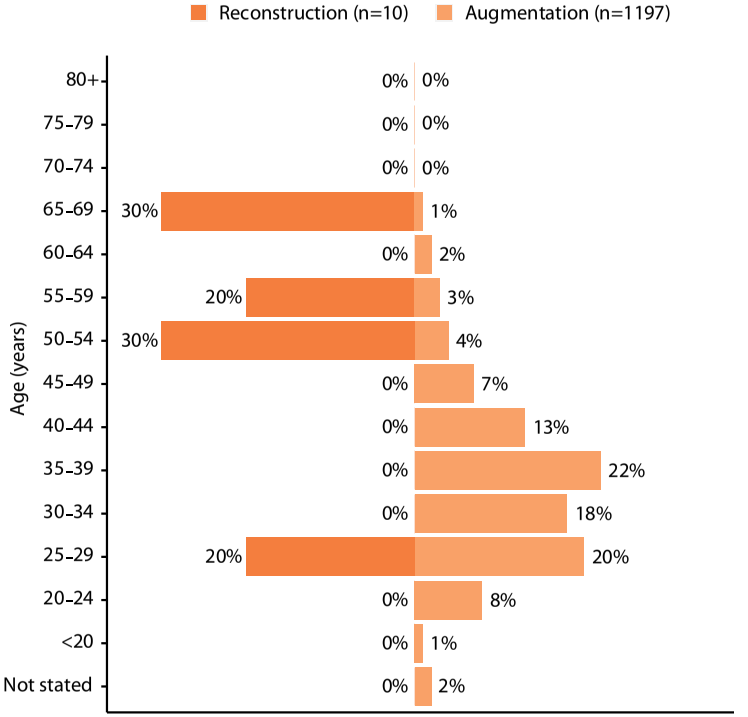
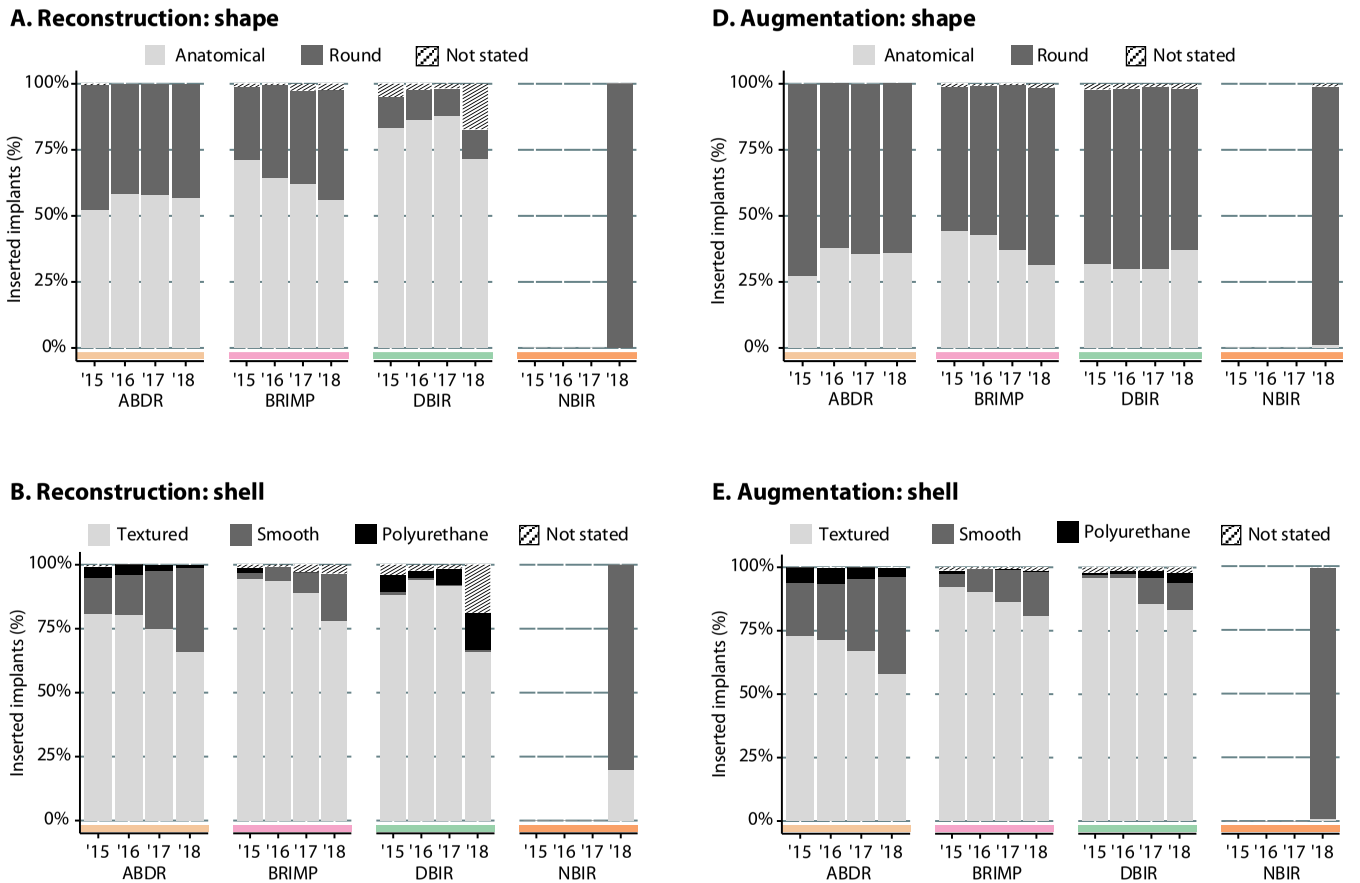

Reconstruction (n=10)
Augmentation (n=1197)
Age (years)
80+
75–79
70–74
65–69
60–64
55–59
50–54
45–49
40–44
35–39
30–34
25–29
20–24
<20
Not stated
0%
0%
0%
0%
0%
0%
30%
1%
0%
2%
20%
3%
30%
4%
0%
7%
0%
13%
0%
22%
0%
18%
20%
20%
0%
8%
0%
1%
0%
2%

Figure 4. Characteristics of primary inserted permanent breast implants.
([a]Other includes hydrogel filled implants or a combination of silicone and saline. ABDR, Australian Breast Device Registry; BRIMP, Breast Implant Registry from Sweden; DBIR, Dutch Breast Implant Registry; NBIR, National Breast Implant Registry from the United States of America.)



C. Reconstruction: fill [a]
Silicone
Saline
Other
Not stated
Inserted implants (%)
100%
75%
50%
25%
0%
'15 '16 '17 '18
ABDR
BRIMP
DBIR
NBIR
F. Augmentation: fill [a]

Patient characteristics in primary implant surgery

Subsequently, 111590 permanent breast implants and 57574 patients met the second selection criterion of primary breast implant insertion for breast reconstruction or augmentation between 2015-2018 (*Figure 1*). Of these, 47732 implants were included by ABDR, 21477 by BRIMP, 41174 by DBIR, and 1207 by NBIR.

For breast reconstruction, the mean age (SD) in ABDR, BRIMP, DBIR, and NBIR was 42.0 (14.1), 41.3 (14.4), 48.8 (12.6), and 51.4 years (13.4), respectively (*P*-value <0.001). For breast augmentation, mean age (SD) was 32.3 (9.2), 32.8 (9.3), 31.6 (9.4), and 35.9 years (9.8), respectively (*P*-value <0.001) (*Figure 3*).

Between BRIMP, DBIR, and NBIR, median body mass index (BMI) differed for breast reconstruction (*P*-value = 0.007), but not for breast augmentation (*P*-value = 0.080) (*Supplementary table 2)*. In ABDR, BMI was not registered. Most reconstructions and augmentations in BRIMP were performed in patients with a BMI of 25-29.9 kg/m^2 (n=862, 61.9 percent and n=2229, 78.7 percent, respectively). In DBIR, most reconstructions and augmentations were performed in patients with a BMI of 18.5-24.9 kg/m^2 (n=375, 56.0 percent and n=8335, 74.9 percent, respectively). In NBIR, BMI was not registered for the majority of breast reconstructions. During breast augmentation, BMI mainly was 18.5-24.9 kg/m2 (n=714, 6.0 percent).

Implant characteristics

Generally, a large variation in implant preference was observed. Over time, an increase in the use of round and smooth implants was observed in all countries.

Overall, primary breast reconstruction was most frequently performed with anatomically shaped, textured, silicone-filled implants, except in NBIR (*Figure 4ABC*). In ABDR, 57.1 percent (n=1959) of the implants were anatomically shaped, 73.8 percent (n=2532) textured, and 99.5 percent (n=3412) silicone-filled. In BRIMP, this was 63.8 percent (n=889), 89.4 percent (n=1245), and 93.9 percent (n=1309), respectively. In DBIR, 83.0 percent (n=2550), 86.1 percent (n=2646), and 76.2 percent (n=2343), respectively. In NBIR, all implants were round (n=10, 100 percent), mostly smooth (n=8, 80 percent), and silicone-filled (n=10, 100 percent).

For primary breast augmentation, round, textured, silicone-filled implants were most frequently registered, except in NBIR (*Figure 4DEF*). In ABDR, 64.2 percent (n=28456) of the implants were round, 65.9 percent (n=29173) textured, and 98.9 percent (n=43827) silicone-filled. In BRIMP, this was 60.0 percent (n=12045), 87.4 percent (n=17570), 98.4 percent (n=19784), respectively. In DBIR, 66.0 percent (n=25160), 89.2 percent (n=33972),

Figure 5. Infection control measures used per primary inserted permanent breast implant.
(In Sweden, glove change, nipple guards, and an insertion sleeve are applied but not captured in BRIMP and therefore not included in this figure. NBIR did not have enough data to be included in this figure. ABDR, Australian Breast Device Registry; BRIMP, Breast Implant Registry from Sweden; DBIR, Dutch Breast Implant Registry)

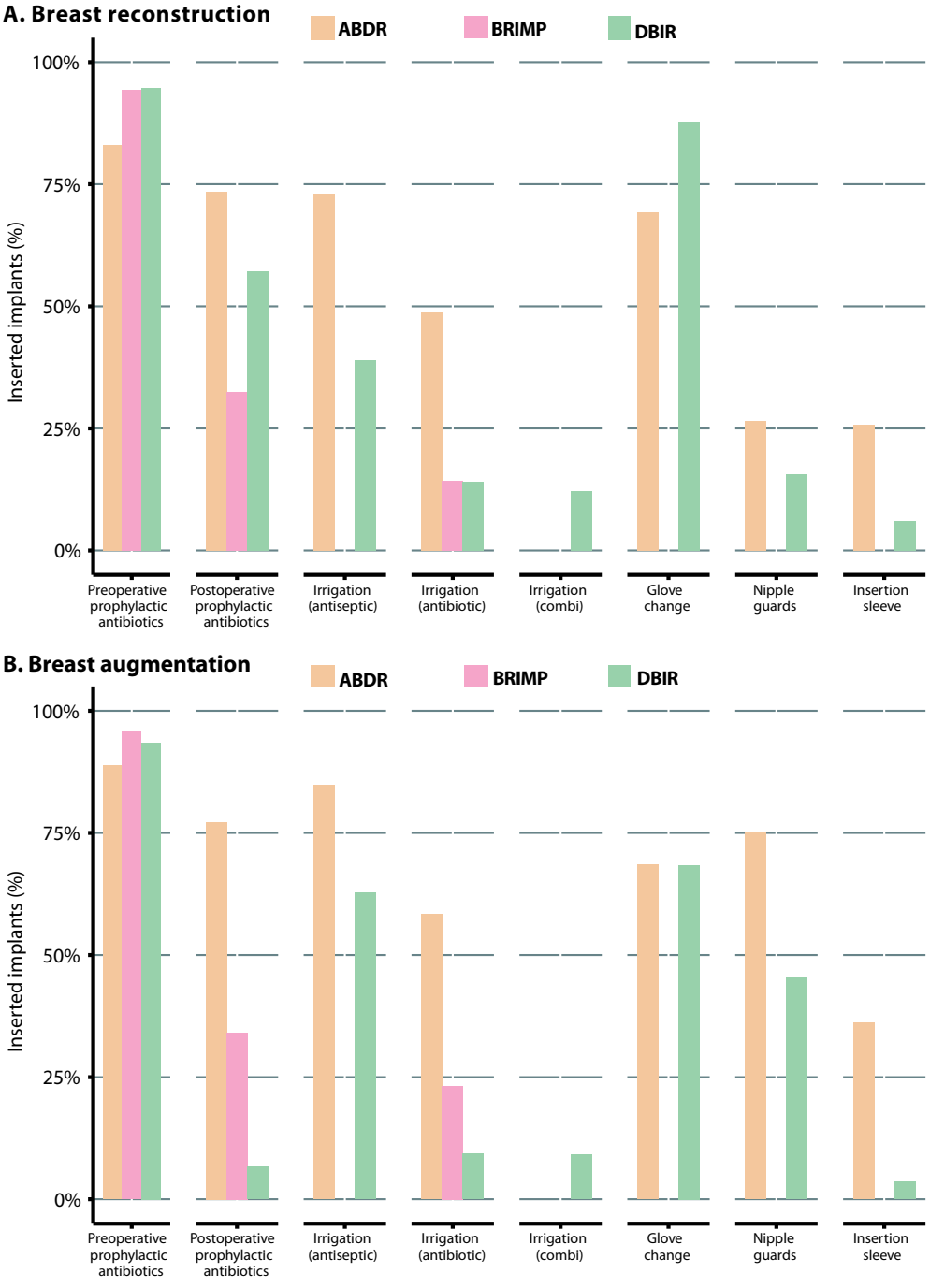
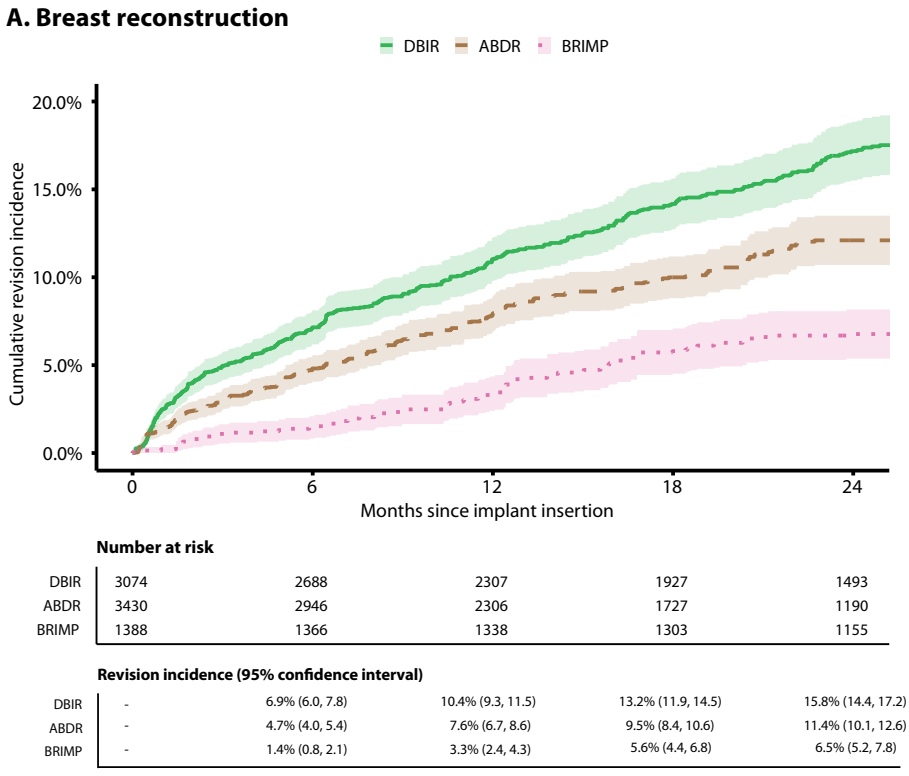


Figure 6. Cumulative all-cause revision incidence of primary inserted permanent breast implants (2015-2018).
(Different scales on y-axis. NBIR did not have enough data to be included in this figure. ABDR, Australian Breast Device Registry; BRIMP, Breast Implant Registry from Sweden; DBIR, Dutch Breast Implant Registry)

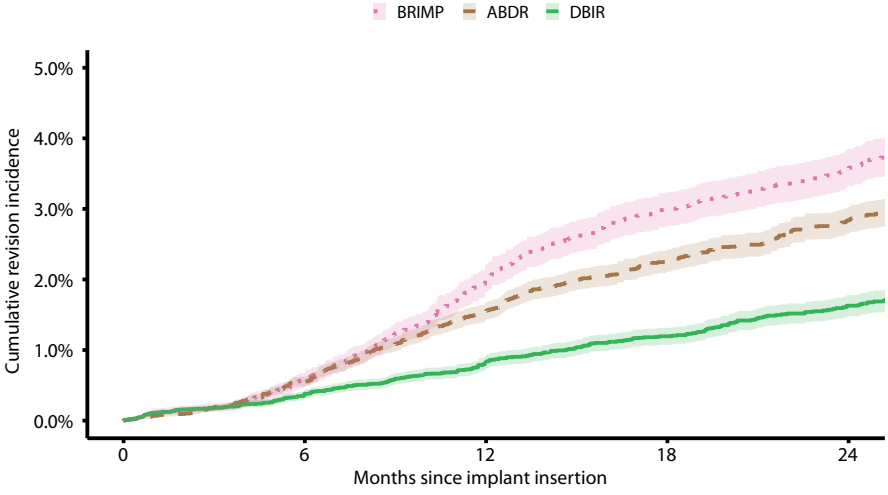


and 97.2 percent (n=37031), respectively. In NBIR, most implants were round (n=1177, 98.0 percent), smooth (n=1183, 99.0 percent), and silicone-filled (n=962, 80.0 percent).

Infection Control Measures *(Figure 5)*

In ABDR, the most frequently registered infection control measure (ICM) for primary breast reconstruction and augmentation was preoperative prophylactic antibiotics (88.8 percent and 83.0 percent, respectively). Additionally, approximately 70 percent of the reconstructions and 75 percent of the augmentations were performed with postoperative prophylactic antibiotics, antiseptic irrigation, and glove change. Antibiotic irrigation was used in approximately 50 percent of all procedures; the combination of antiseptic and antibiotic irrigation was not registered. Nipple guards were used in 26.6 percent of the reconstructions and 75.2 percent of the augmentations. An insertion sleeve was used in 25.8 percent of the reconstructions and 36.1 percent of the augmentations.

B. Breast augmentation



Number at risk

BRIMP	20016	19898	19614	19403	17042
ABDR	44302	40237	32877	24685	16663
DBIR	38100	34810	29539	23213	17289

Revision incidence (95% confidence interval)

DBIR	-	0.6% (0.5, 0.7)	2.0% (1.8, 2.2)	2.9% (2.7, 3.2)	3.5% (3.3, 3.8)
ABDR	-	0.5% (0.4, 0.6)	1.5% (1.4, 1.7)	2.2% (2.1, 2.4)	2.8% (2.6, 3.0)
BRIMP	-	0.4% (0.3, 0.5)	0.8% (0.7, 0.9)	1.2% (1.1, 1.3)	1.2% (1.5, 1.8)

In BRIMP, the most frequently registered ICM was preoperative prophylactic antibiotics (up to 96 percent). Postoperative prophylactic antibiotics and antibiotic irrigation were registered less frequently (reconstruction: 32.4 percent and 14.3 percent, augmentation: 34.1 percent and 23.2 percent, respectively). Glove change, nipple guards, and an insertion sleeve were used in clinical practice, but those ICMs were not captured in the registry.

In DBIR, the most frequently registered ICM was preoperative antibiotics (up to 95 percent). Postoperative antibiotics were used after reconstructions (57.1 percent) but hardly after augmentations (6.7 percent). Glove change was registered in 87.9 percent of all breast reconstructions and 68.4 percent of all augmentations. Implant and/or pocket irrigation was more frequently with antiseptic solutions than antibiotic solutions or both. Nipple guards were used in 15.6 percent of the reconstructions and 45.5 percent of the augmentations. An insertion sleeve was hardly used in both indications (maximum of 6 percent).

Generally, ICMs were registered more extensively in ABDR than in BRIMP and DBIR. This information is not currently captured in NBIR.

Cumulative revision incidence

After primary breast reconstruction, most revisions were registered in DBIR, followed by ABDR and BRIMP (*Figure 6A*). All-cause revision incidence at two years was 15.8 percent (95% CI 14.4-17.2), 11.4 percent (95% CI 10.1-12.6), and 6.5 percent (95% CI 5.2-7.8), respectively. Overall, most revisions were replacement with a new implant or autologous tissue, followed by explantation only and repositioning of the implant.

After primary breast augmentation, most revisions were registered in BRIMP, followed by ABDR and DBIR (*Figure 6B*). All-cause revision incidence at two years was 3.5 percent (95% CI 3.3-3.8), 2.8 percent (95% CI 2.6-3.0), and 1.6 percent (95% CI 1.5-1.8), respectively.
In BRIMP and DBIR, most revisions were replacement with a new implant or autologous tissue, followed by explantation only and repositioning of the implant. In ABDR, most revisions were replacement with a new implant or autologous tissue, followed by a repositioning of the implant and explantation only.

DISCUSSION

This multinational, population-based study combined anonymized aggregate data from breast implant registries in Australia, the Netherlands, Sweden, and USA. By the end of 2018, the registries together captured over 200000 permanent breast implant records. Across the registries, 111590 breast implants and 57574 patients were selected to analyze patient characteristics, implant characteristics, the use of infection control measures, and all-cause revision incidence. These numbers are unprecedented in any publication on breast implants. Moreover, internationally combining breast implant data is considered a major breakthrough in accelerating independent knowledge to patients, surgeons, legislators, and industry.

ABDR, BRIMP, and DBIR had high nationwide coverage and high data completeness (results not shown). The presented results very likely reflect current clinical practice for the selected subpopulation in these countries.[11-13] The NBIR has just started collecting data and covered 3 per cent of the USA. Therefore, the presented results are not yet representative of American clinical practice. On the other hand, their registry structure is robust and it is expected that their case volume will increase exponentially.

Across the registries, mean patient age varied between 41-51 years for breast reconstruction and 31-36 years for augmentation. Compared to the general female population in each

country, breast reconstruction patients were 5-10 years older in our subpopulation and augmentation patients 5-10 years younger.[19-22] Median patient BMI was higher in BRIMP than in DBIR and NBIR (25-30 kg/m2 versus 18.5-25 kg/m^2). The BMI in BRIMP was higher than the BMI of the general female population; in DBIR and NBIR, the BMI was slightly lower.[23-25] BMI was not yet collected in ABDR but will be after a registry update.

In Australia, Sweden, and the Netherlands, breast reconstruction was most frequently performed with anatomically shaped, textured, silicone-filled implants and augmentation with round, textured, silicone-filled implants. Interestingly, an increase in the proportion of round, smooth implants was observed over time, which could be explained by the increasing concern about BIA-ALCL and its association with textured implants rather than smooth implants.[26,27] In NBIR, round, smooth, silicone-filled implants were mostly registered, regardless of the indication.

The most frequently registered ICM was preoperative prophylactic antibiotics. The registration of other ICMs varied between and within the countries, which most likely reflects the lack of epidemiologically sound evidence for these interventions, and resultant variation in national guidelines. For example, Swedish guidelines advise against using an antiseptic solution for pocket and/or implant irrigation.[28] In the Netherlands, the use of antiseptic irrigation, glove change, and nipple shields are left to the surgeons' discretion because of their low costs and no real drawbacks.[29,30] In Australia, there is high usage of intraoperative and postoperative antibiotics, with substantial regional variation in the use of other ICMs.[31,32] NBIR does not capture ICM data at this time.

Cumulative revision incidence ranged from 6-16 percent after breast reconstruction and 1-4 percent after augmentation. Depending on each registry's maturity, these revision rates reflect *registered* revisions rather than *actual* revisions. Furthermore, no adjustment for confounding factors was performed. Revision incidence could have been affected by specific patient and treatment characteristics not included in this study. Additionally, underreporting of revisions might be present, especially in the registries' earliest years. Finally, differences between the countries in patients' attitudes towards cosmetic reoperation could have affected revision incidence. Therefore, more research is needed to provide insight into the underlying reasons for the observed variation.

Future perspectives

By presenting combined results from different breast implant registries, this study confirms three crucial findings: 1) data can be combined using the ICOBRA harmonized dataset, 2) differences and similarities between countries can be identified, and 3) trends over time can be recognized. This is just the start, and it portends a whole new spectrum of future collaborative projects. For example, when focusing on BIA-ALCL, several theories on

etiology have arisen, such as the impact of implant texture, particle shedding, or chronic infection. However, as the search for evidence has been challenged by differences in implant preference, surgical techniques, and patient characteristics, combining data from different national registries can be key to an earlier clarification of etiology.

Furthermore, this study addresses the importance of sharing data safely and considering the FAIR principles of data (findability, accessibility, interoperability, and reusability).[16] The General Data Protection Regulation (GDPR) does not allow sharing de-identified patient-level data. Therefore, this study used anonymous aggregated analyses. However, to properly conduct high-quality research on breast implant safety and early detection of malfunctioning breast devices, de-identified patient-level data is required. Therefore, the impact of the current GDPR on (breast implant) registries, its impact on future research, and the options to safely share data need to remain serious topics of discussion. Especially because the British, German, and French breast implant registries are ready to join in soon.

Strengths and limitations

This is the first study combining real-world data from four breast implant registries, including breast reconstructions and breast augmentations. Comparing data from different registries can be difficult because of limited overlapping variables.[33] However, the ICOBRA harmonized dataset makes comparisons more manageable and reliable. Additionally, the scripts for the analyses have been made collaboratively by data analysts from each registry, which prevents differences in interpretation and data selection.

However, this study is not exempt from limitations. Data from tissue expanders could not be included because BRIMP and NBIR do not capture these implant types. Second, due to the recent SARS-CoV-2 pandemic, registry data from 2019 was not finished in time to be included in this report and will be included in future studies.

CONCLUSION

Growing awareness about breast implant-related adverse events has resulted in the demand for independent data resources by patients, surgeons, legislators, and industry. This is the first study combining objective, population-based data from four breast implant registries with over 200000 breast implants. The possibility of internationally combining data and revealing similarities and variation between countries is a powerful and essential step forward in breast implant monitoring. It lays the foundation for evidence-based decision-making and optimizes patient safety in the current debates on breast implant surgery.

REFERENCES

1. Hopper I, Ahern S, Nguyen TQ, Mulvany C, McNeil JJ, Deva AK, et al. Breast Implant Registries: A Call to Action. Aesthet Surg J. 2018;38(7):807-10.
2. Hopper I, Ahern S, Best RL, McNeil J, Cooter RD. Australian Breast Device Registry: breast device safety transformed. ANZ J Surg. 2017;87(1-2):9-10.
3. Rakhorst HA, Mureau MAM, Cooter RD, McNeil J, van Hooff M, van der Hulst R, et al. The new opt-out Dutch National Breast Implant Registry–Lessons learnt from the road to implementation. J Plast Reconstr Aesthet Surg. 2017;70(10):1354-60.
4. Prantl L, von Fritschen U, Liebau J, von Hassel J, Baur EM, Vogt PM, et al. [Concept for a National Implant Registry to Improve Patient Safety]. Handchir Mikrochir Plast Chir. 2016;48(6):320-9.
5. NHS Digital. Breast and Cosmetic Implant Registry 2016 [updated 29 September 2020]. Available from: https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/breast-and-cosmetic-implant-registry#top.
6. The Plastic Surgery Foundation. The National Breast Implant Registry (NBIR) 2018 [updated 2020]. Available from: https://www.thepsf.org/research/registries/nbir.
7. Registercentrum Västa Götaland. BRIMP Bröstimplantatregistret 2014 [updated 2020]. Available from: https://brimp.registercentrum.se/om-brimp/om-broestimplantatregistret/p/BkuO2oSQS.
8. Cooter RD, Barker S, Carroll SM, Evans GR, von Fritschen U, Hoflehner H, et al. International importance of robust breast device registries. Plast Reconstr Surg. 2015;135(2):330-6.
9. Cooter R, Barnett R, Deva A, Magnusson MR, McNeil J, Perks G, et al. In Defense of the International Collaboration of Breast Registry Activities (ICOBRA). Aesthet Surg J. 2016;36(7):NP225-7.
10. Spronk PE, Begum H, Vishwanath S, Crosby A, Earnest A, Elder E, et al. Toward International Harmonization of Breast Implant Registries: ICOBRA global common dataset. Plastic and Reconstructive Surgery. 2020;146(2):255-67.
11. Hopper I, Parker E, Pellegrini B, Mulvany C, Pase M, Ahern S, et al. The Australian Breast Device Registry 2018 Annual Report. Monash University, Department of Epidemiology and Preventive Medicine; October 2019.
12. BRIMP. Breast Implant Register Annual Report 2018. Sweden: Register Centrum Västra Götaland; 2019.
13. Becherer BE, Rakhorst HA, Mureau MAM, Hommes JE, van Bommel ACM, Hoornweg MJ, et al. Dutch Breast Implant Registry (DBIR)–Annual Report 2018. Dutch Institute for Clinical Auditing (DICA); November 2019.
14. Clinical Audit and Registries Management Service. Breast and Cosmetic Implant Registry: July 2018 to June 2019–Report v1.1. NHS Digital; October 2019.
15. The Plastic Surgery Foundation. The National Breast Implant Registry Annual Report 2019. 2020.
16 Bargon CA, Becherer BE, Young-Afat DA, van Bommel A, Hommes J, Hoornweg MJ, et al. Moving breast implant registries forward: Are they FAIR and Functional? J Plast Reconstr Aesthet Surg. 2020;74(1):4-12.

17. Hopper I, Best RL, McNeil JJ, Mulvany CM, Moor CCM, Elder E, et al. Pilot for the Australian Breast Device Registry (ABDR): a national opt-out clinical quality registry for breast device surgery. BMJ Open. 2017;7(12):e017778.
18. BRIMP. Breast Implant Register Annual Report 2019. Sweden: Register Centrum Västra Götaland; 2020.
19. Australian Institute of Health and Welfare. Australia's health 2018. Canberra: AIHW; 2018. Australia's health series no.16(AUS221):570 pages.
20. Statistics Sweden. Average age of the population by sex and year 2018. [updated 20 Februari 2020]. Available from: http://www.statistikdatabasen.scb.se/pxweb/en/ssd/START__BE__BE0101__BE0101B/BefolkMedianAlder/table/tableViewLayout1/.
21. Centraal Bureau voor de Statistiek. Bevolking; kerncijfers 2018. Available from: https://opendata.cbs.nl/#/CBS/nl/dataset/37296ned/table.
22. United States Census Bureau. Age and Sex Composition in the United States: 2018. Table 1: Population by Age and Sex 2018. [July 11, 2019]. Available from: https://www.census.gov/data/tables/2018/demo/age-and-sex/2018-age-sex-composition.html.
23. Statistics Sweden. BMI 2010-2011, Andelar i procent samt felmarginal (95-procentigt konfindensintervall). Available from: https://www.scb.se/en/.
24. Centraal Bureau voor de Statistiek. Lenge en gewicht van personen, ondergewicht en overgewicht; vanaf 1981. 2018 [updated 31 Maart 2020]. Available from: https://opendata.cbs.nl/#/CBS/nl/dataset/81565NED/table?defaultview&dl=E311.
25. United States Census Bureau. Statistical Abstract of the United States: 2012. Section 3: Health and Nutrition, 211–Age-adjusted Percent Distributions of Body Mass Index (BMI) Among Persons 18 Years Old and Over, by Selected Characteristics. [updated February 9, 2018]. Available from: https://www.census.gov/library/publications/2011/compendia/statab/131ed/health-nutrition.html.
26. U.S. Food and Drug Administration. Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses: US Food and Drug Administration (FDA); 2011 [updated 21 March 2017]. Available from: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239996.htm.
27. U.S. Food and Drug Administration. Questions and Answers about Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL); 2019 [updated 23 October 2019]. Available from: https://www.fda.gov/medical-devices/breast-implants/questions-and-answers-about-breast-implant-associated-anaplastic-large-cell-lymphoma-bia-alcl.
28. Livsmedelsverket, Swedish Food Agency. November 2020. Available from: www.livsmedelsverket.se/bestall-ladda-ner-material/2020.
29. Nederlandse Vereniging voor Plastische Chirurgie. Richtlijn Borstprothesechirurgie. 2020.
30. Mureau MAM on behalf of the Breast Reconstruction Guideline Working Group. Dutch breast reconstruction guideline. J Plast Reconstr Aesthet Surg. 2018;71(3):290-304.

31. Hopper I, Pellegrini B, Gartoulla P, Kalbasi S, Ahern S, Earnest A, et al. The Australian Breast Device Registry 2019 Annual Report. Monash University, Department of Epidemiology and Preventive Medicine; November 2020.
32. Vishwanath S, Pellegrini B, Parker E, et al. Breast Device Surgery in Australia: Early Results from the Australian Breast Device Registry. J Plast Reconstr Aesthet Surg. 2020;in press.
33. Kamali P, van Bommel A, Becherer B, Cooter RD, Mureau MAM, Pusic A, et al. Immediate Breast Reconstruction in The Netherlands and the United States: a proof-of-concept to internationally compare quality of care using cancer registry data. Plastic and Reconstructive Surgery. 2019;144(4):565e-74e.

SUPPLEMENTARY DATA

Supplementary table 1. Definitions of the variables used for this study, derived from the ICOBRA harmonized dataset.

Variable	Definition	ICOBRA harmonized dataset
Implant insertion	A procedure in which a new breast implant is placed, either in a breast without an implant or as replacement of an in-situ device.	Yes
Primary implant surgery	The first operation recorded in the registry in which a new breast implant is inserted in a patient without any previous breast implant or tissue expander in their medical history.	Yes
Revision surgery	The first reoperation after insertion, in which an implant is repositioned, explanted or replaced with a new implant or autologous tissue, regardless of the revision indication.	Yes
Breast reconstruction	A reconstructive procedure to recreate, restore or create a breast in patients with loss or absence of all or some breast tissue due to (risk reducing) mastectomy, benign conditions, congenital deformity, tuberous breasts, or gender affirming surgery.	Yes
Breast augmentation	A cosmetic procedure for enlarging the breast(s).	Yes
Age of patient	As identified in the medical record, at timing of surgery.	Yes
Body mass index	Calculated using the ICOBRA variables height (in meters) and weight (in kilograms) of a person. Expressed in kg/m^2. In categories according to the World Health Organization: <18·5 (underweight), 18·5-24·9 (normal weight), 25-29·9 (overweight), and ≥30 (obese).	Yes
Implant shape	The shape of the implant being inserted into or explanted from the breast; where the shape of the device is either round (implant is shaped like a flattened sphere) or shaped (a contoured shape that recreates the more teardrop outline of a mature breast).	Yes
Implant shell	The surface texture of the implant being inserted or explanted. Could be textured, smooth or polyurethane coated.	Yes
Implant fill	The material used to fill the breast implant: saline solution, silicone gel or other. Other includes hydrogel or a combination of silicone and saline.	Yes
Preoperative prophylactic antibiotics	Use of prophylactic antibiotics provided IV, orally or IM before incision.	Yes
Postoperative prophylactic antibiotics	Use of prophylactic antibiotics provided IV, orally or IM at any time after 3 hours post-surgery.	Yes
Implant and/or pocket irrigation	Rinse of breast implant and/or the surgically created pocket before implant insertion. Intraoperative wash could be performed with an antiseptic solution such as povidone-iodine, antibiotics, or both.	Yes
Glove change	Change of gloves immediately prior to insertion of the implant.	Yes
Nipple guards	The use of adhesive film dressing covering the nipple-areola complex to prevent perioperative expression of bacteria from nipple ducts contaminating the operative field.	Yes
Insertion sleeve	A skin barrier protector such as a Keller funnel, used during insertion of the implant.	No

Supplementary table 2. Patient body mass index per primary inserted permanent breast implant.

	Breast Reconstruction				Breast Augmentation			
	ABDRa n=3430	BRIMP n=1393	DBIRb n=3074	NBIR n=10	ABDRa n=44302	BRIMP n=20084	DBIRb n=38100	NBIR n=1197
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Body Mass Index, kg/m2								
<18.5 (underweight)	-	45 (3.2)	24 (3.6)	0 (0)	-	1 366 (6.8)	641 (5.8)	34 (3.0)
18.5-24.9 (normal weight)	-	52 (3.7)	375 (56.0)	1 (10.0)	-	181 (0.9)	8 335 (74.9)	714 (60.0)
25-29.9 (overweight)	-	862 (61.9)	171 (25.5)	0 (0)	-	15 806 (78.7)	1 112 (10.0)	232 (19.0)
≥30 (obese)	-	260 (18.7)	72 (10.7)	0 (0)	-	2 229 (11.1)	136 (1.2)	59 (5.0)
Not stated	-	174 (12.5)	28 (4.2)	9 (90.0)	-	502 (2.5)	908 (8.1)	158 (13.0)

Difference in BMI distribution between registries: breast reconstruction P-value = 0.007, breast augmentation P-value = 0.080. aABDR does not register BMI. bDBIR registers BMI since September 2017, therefore the percentages are from the first full registration year 2018 (n=670 reconstructions, n=11132 augmentations).
Abbreviations: ABDR, Australian Breast Device Registry; BRIMP, Breast Implant Register from Sweden; DBIR, Dutch Breast Implant Registry; NBIR, National Breast Implant Registry from the United States of America.

DISCUSSION & CONCLUSION

CHAPTER 8

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION

Parts derived from "Moving breast implant registries forward: are they FAIR and functional?" (2020)(1)

Breast implant registries are essential for optimizing the quality and safety of breast implant surgery, by evaluating the performance of registered devices, providing healthcare institutions with continuous feedback, and facilitating a track-and-trace system for potential recalls. Following dr. Pauline Spronk's thesis (2019) which described the start of DBIR,(2) the present thesis used DBIR to provide insight into breast implant surgery practice in the Netherlands (part I), to investigate variation in surgical practices and outcomes (part II), and to assess the potential of combining DBIR data with other registries (part III).

BREAST IMPLANT SURGERY IN PERSPECTIVE

Implant-based breast reconstruction is the most common type of postmastectomy breast reconstruction, and breast augmentation is one of the most performed cosmetic surgical procedures worldwide.(3-6) In 2017, the estimated prevalence of breast implants in the Netherlands was 1 in 30 women, based on routine chest radiographs.(7) However, no objective, detailed epidemiological data were present about the patient population and different implant types used. Worldwide, DBIR is one of the first up-and-running, opt-out breast implant registries with nationwide coverage and a sustainable funding structure (*Chapter 2*). By using DBIR, a minimum breast implant incidence of 1 per 1,691 women could be defined (*Chapter 3*). Insight into breast implant prevalence and incidence provides essential information on numerators and denominators for risk assessment of breast implant-related adverse events.

Additionally, preferences for the use of different breast implants became clear in the period between 2015 and 2018. In the Netherlands, breast reconstruction was most frequently performed with anatomically shaped, textured, silicone-filled implants, and breast augmentation with round, textured, silicone-filled implants. However, for both indications, an increase in the proportion of round, smooth implants was observed over time, which may be explained by the increasing concern about BIA-ALCL and its presumed association with textured implants rather than smooth implants (*Chapters 3 and 7*).(8-10)

VARIATION IN SURGICAL PRACTICE AND OUTCOMES

Variation between healthcare institutions in daily surgical practice is usually more than the reflection of different patient characteristics. Institution specific customs, differences in surgical training, the extent of shared decision making, or a lack of high-quality evidence can result in different treatment strategies. Insight into variation, the underlying reasons,

and the impact on patient outcomes opens discussions among clinicians and helps to further improve guidelines and the quality of care provided.

In this thesis, variation in the use of infection control measures was observed on a national (*Chapters 3 and 4*) and international level (*Chapter 7*). Furthermore, differences were found in the use of direct-to-implant versus two-stage immediate implant-based breast reconstruction techniques (*Chapter 5*). To study variation, the use of national, opt-out quality registries is very efficient, rather than setting up a nationwide clinical trial. On the other hand, to study the effect of different perioperative protocols on surgical outcomes, a randomized controlled trial (RCT) is generally considered the gold standard. However, if the outcome of interest has a low-event-rate (e.g., breast implant revision incidence), RCTs are not always feasible, and clinical registries such as DBIR can be a good alternative.(11) Moreover, observational studies based on real-world data from clinical quality registries can complement RCTs by assessing outcomes in larger and more diverse patient populations and using longer follow-up periods.(12, 13) Of course, bias related to database research, such as confounding by indication, selection bias, missing data, or residual confounding always has to be kept in mind.(14-17)

JOINING FORCES WITH OTHER REGISTRIES

In *Chapter 6*, a proof of concept was performed, retrieving complementary data on patient, implant, and pathology details from DBIR and the Dutch pathology registry PALGA. In *Chapter 7*, data from the Australian, Dutch, Swedish, and American breast implant registries were combined for the first time in history. Although these two projects were successful, matching DBIR to PALGA had to be executed manually, and analyses between the four countries had to be performed on an aggregated level to comply with the General Data Protection Regulation (GDPR). However, to properly conduct high-quality research on breast implant safety or factors associated with BIA-ALCL, de-identified patient-level data is required, and a more automatic matching process would be beneficial.

FUTURE PERSPECTIVES

Based on the early results and experiences described in this thesis, recommendations for future research and improvements regarding DBIR could be outlined.

REGISTRY VALIDATION

The value of a clinical quality registry depends on its data quality. DICA, which facilitates DBIR, has incorporated several methods for data quality assurance in their registries. (18) Data quality can be evaluated and promoted on three levels: nationwide coverage, completeness, and accuracy of the registered data.

Nationwide coverage

DBIR's nationwide coverage is checked annually by comparing the participating healthcare institutions to all eligible institutions known by the Dutch Health and Youth Care Inspectorate. Meanwhile, DBIR has matured into a registry including 100% of the hospitals and 94% of the private clinics.(19) Additionally, "participation in DBIR" has become an external quality indicator for healthcare institutions where breast implant surgery is performed.

Data completeness

DBIR uses an opt-out structure, which means that patients are automatically enrolled in the registry unless they object. To further improve data completeness, surgeons are provided with immediate feedback on missing, erroneous, or unlikely data during the online registration process. Additionally, surgeons receive a list of remaining patients with missing or erroneous data to rectify these records.

Despite these attempts to optimize data quality, validation of the registered implant procedures versus the actually performed procedures remains difficult. The number of newly *inserted* implants could be verified using DBIR-SUPPLIERS. However, DBIR-SUPPLIERS does not yet contain enough adequate data. Currently, to get an impression of the capture rate and data completeness of DBIR, healthcare institutions are obligated by the Dutch Health and Youth Care Inspectorate to provide their performance on the two external quality indicators: "percentage of registered implants in DBIR" and the "percentage of complete implant records".

Even a bigger challenge is validating *revision* surgery data. Health insurance data could be a reliable validation source, however, more than 80% of the implant surgery is performed for breast augmentation and remains outside the medical insurance system. An external data verification project would be the best option to validate the data quality by comparing registered records with Electronic Patient Records (EPRs). In 2020, such an

external verification project should have taken place. However, the SARS-CoV-2 pandemic, unfortunately, has caused a delay.

Data accuracy
In addition to the above-mentioned activities to optimize data quality, DBIR data undergo extensive data cleaning before they are used for analyses. To further improve data accuracy, three initiatives have been started, which also decrease the registration burden.

First, DBIR has incorporated barcode scanning technology for data entry. By scanning the standardized GS1-barcode of an implant, characteristics, such as the serial number, batch number, and expiration date are automatically registered.(20) For automatically registering implant type, manufacturer, shape, texture, fill, and volume, this first requires all implant characteristics to be included in an international product data network, like the Global Data Synchronization Network (GDSN).(21) GDSN enables manufacturers, distributors, healthcare institutions, and registries to access up-to-date product information, all based on one unique device identifier (UDI).

Until this system is available for breast implants, DBIR will keep using the GS1-barcode scanning technology together with a newly developed implant catalog which will be incorporated in 2021. This catalog was built manually and automatically connects the implant reference number to the implant type, manufacturer, shape, texture, fill, and volume during registration.

Finally, the extent to which DBIR can be integrated in the EPR has to be improved. For this, Detailed Clinical Models, such as Health and Care Information Models (HCIM) or Clinical Building Blocks (CBB's) (zorginformatiebouwstenen in Dutch) are used.(22, 23) These models describe a care-based concept in terms of data elements, data types, data structure, data relationships, etc. Subsequently, data from the EPR may be reused to automatically fill clinical quality registries, among others.

CLINICAL AUDITING

In the Dutch Upper gastrointestinal Cancer Audit (DUCA), a more mature DICA registry, audit data are used to organize meetings for upper gastrointestinal surgeons to evaluate outcomes and discuss how outcomes might be improved.(24) In an open but safe setting, surgeons are asked to present their outcomes, focusing on two particular topics: anastomotic leakage and lymph node retrieval. By sharing experiences and insights, surgeons have become more involved, and future improvement points could be identified. Such meetings are of interest to DBIR-users as well. For example, by discussing the use of a direct-to-implant versus two-stage technique in immediate implant-based breast

reconstruction, or the use of infection control measures, variation in current practice could be explained better, and perhaps more consensus could be reached (*Chapters 4 and 5)*.

IMPLANT PERFORMANCE

Monitoring and comparing the performance of different breast implant types has its difficulties. First, classifying breast implant types may be based on endless combinations of different implant characteristics, of which some even lack an international consensus.(25) Second, event rates might be too low to gain enough statistical power to reliably identify implant performance problems.

To increase statistical power, data from different ICOBRA-registries can be combined (*Chapter 7*). However, to identify implant outliers, patient-level analyses are required. One way to share anonymous patient-level data in accordance with the privacy law is the use of different data files per analysis. For each analysis, only the variables necessary for that specific analysis are selected per registry and exported in a .csv file. Next, the .csv files are merged and used for analysis. This process has to be repeated for each separate analysis, and each data export file may never contain a record ID or other unique variables making records identifiably across different data export files.

Another approach to increase statistical power is to focus on other outcome measures that occur more frequently than revision surgery or to use indirect measures of quality, such as patient-reported outcome measures (PROMS).(26)

Lastly, breast implant registries have to reach consensus on how implant underperforming is defined, which methods will be incorporated to identify underperformers, and how *chance cause variation* will be distinguished from *assignable cause variation*. Change cause variation, often referred to as common cause variation, is present in all processes and remains within the control limits. Assignable cause variation, also called special cause variation, is present in some processes and exceeds the control limits. Experiences from cardiac and orthopedic implant registries might be helpful for this.(27-29)

COMPLEMENTARY DATA

In clinical quality registries, a minimum of data points must be collected to execute its main tasks. Including unnecessary data points has to be avoided, as they could become "nails in the coffin" of the registry by unnecessarily increasing the registration burden. Therefore, combining data from different data sources is an interesting opportunity when specific research questions are studied using data not solely captured in DBIR.

As illustrated in *Chapters 6 and 7*, DBIR data can be combined with Dutch pathology data and international breast implant data. Three other interesting sources for combining data are

the Dutch NABON Breast Cancer Audit (NBCA), the Netherlands Institute for Health Services Research (NIVEL), and the hotline and expertise center for implant-related adverse events (MEBI) from the Dutch National Institute for Public Health and the Environment (Meldpunt en Expertisecentrum Bijwerkingen Implantaten van het RIVM in Dutch). With the NBCA, complementary data could be obtained about breast cancer treatment characteristics, such as radiotherapy and tumor characteristics. Through NIVEL, DBIR data could be combined with primary care data, which is particularly interesting for studying the possible association between silicone-exposure and non-specific health complaints. Using MEBI, the reported adverse events in DBIR could be compared with the adverse events reported by patients and health care professionals to the hotline of the Dutch National Institute for Public Health and the Environment.

Relevant to sharing and reusing data are the FAIR principles. The FAIR principles were introduced by Wilkinson and colleagues in 2016 and are an acronym for Findable, Accessible, Interoperable, and Reusable.(30, 31) They support data reusability, i.e., for future research or data verification, focusing on data, metadata, and infrastructure. 'Findable' means that the data and metadata should be easy to find for both humans and computers. 'Accessible' describes how data can be retrieved, including the required authorization and authentication. 'Interoperable' indicates that data should have a formal, accessible, and shared language understandable for both machines and humans. Finally, 'Reusable' implies that data and metadata should be well-described to be reused and linked to other data sources.

PATIENT-REPORTED OUTCOMES (PROs)

In addition to www.implantaatcheck.nl, where patients can check whether their implant has been registered in DBIR, there are other ways to involve patients in their care process. Patient-reported outcomes (PROs) are frequently used to monitor outcomes meaningful to patients and to improve communication between patients and their caregivers.(32, 33) Additionally, PROs could be used to screen for early symptoms of device issues and serve as an outcome measure for clinical auditing.(34)

The Breast-Q Implant Surveillance module (BREAST-Q IS), based on the BREAST-Q, was developed explicitly for breast implant surgery.(35-37) The PRO-module contains five questions most sensitive for predicting adverse events and the need for revision surgery. Two questions are about pain and tightness, and three about satisfaction with shape, feel, and rippling.

In the Australian and Swedish breast implant registry, PROs are already being collected, and the American breast implant registry will start piloting.(37-39) However, before implementing PROs in DBIR, some barriers have to be broken down first. For example,

better digital infrastructure is required, which allows combining PRO-data with clinical data. Additionally, it has to be decided which method will be used to collect PROs during routine care, at which time intervals, how to engage patients, and how to provide patients with feedback.

SAFETY OF BREAST IMPLANTS

As in all medical treatments, the discussion on medical devices is not just about safe versus not safe. It is about weighing the benefits against the risks. No medical device is without risks; its insertion procedure to start with. Compared to neurological, cardiovascular, and orthopedic devices, breast implants are used for improving the quality of life rather than saving lives. This results in a different benefit-risk balance. Even between different patients, the benefit-risk balance may differ. For example, breast reconstruction patients generally have a higher-risk profile for surgery, but breast implants are sometimes the only reconstructive option. Therefore, informing patients properly and stimulating shared decision making is crucial in breast implant surgery practice. However, information needs to be based on epidemiologically sound evidence rather than subjective information from social media platforms. Research into breast implant safety and potential alternatives remain important future steps, and national breast implant registries play an invaluable part in this.

CONCLUSION

Clinical breast implant registries are important and valuable for monitoring breast implant performance, evaluating the quality of care, and ultimately optimizing patient safety. Breast implant registries provide evidence that supports clinical decision-making, and they have value for many stakeholders, including patients, clinicians, manufacturers, and regulators. The main points of improvement of DBIR are to incorporate methods to identify implant outliers, to increase data accuracy, to decrease registration burden, to stimulate inter-surgeon discussions using audit information, and to join forces with other registries. By continually improving the registry's effectiveness and sustainability, we can keep providing the best evidence-based care to our patients.

REFERENCES

1. Bargon CA, Becherer BE, Young-Afat DA, van Bommel A, Hommes J, Hoornweg MJ, et al. Moving breast implant registries forward: Are they FAIR and Functional? J Plast Reconstr Aesthet Surg. 2020;74(1):4-12.
2. Spronk PER. Thesis: Quality assurance in breast cancer care and breast implant surgery. Department of Surgery, Leiden University, the Netherlands; 2019.
3. Dutch Institute for Clinical Auditing (DICA). Jaarrapportage 2017 Nabon Breast Cancer Audit (NBCA), indicatorentabel indicator 13 en 14 [Available from: http://dica.nl/jaarrapportage-2017/nbca.
4. Ilonzo N, Tsang A, Tsantes S, Estabrook A, Thu Ma AM. Breast reconstruction after mastectomy: A ten-year analysis of trends and immediate postoperative outcomes. Breast. 2017;32:7-12.
5. American Society of Plastic Surgeons. Plastic surgery statistics report 2019. ASPS National Clearinghouse of Plastic Surgery Procedural Statistics. Jun 2020.
6. International Society of Aesthetic Plastic Surgery (ISAPS). ISAPS Global Survey Results 2018. 2019.
7. de Boer M, van Middelkoop M, Hauptmann M, van der Bijl N, Bosmans JAW, Hendriks-Brouwer N, et al. Breast Implant Prevalence in the Dutch Female Population Assessed by Chest Radiographs. Aesthet Surg J. 2019;40(2):156-64.
8. U.S. Food and Drug Administration (FDA). Questions and Answers about Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) 2019 [updated 23 October 2019. Available from: https://www.fda.gov/medical-devices/breast-implants/questions-and-answers-about-breast-implant-associated-anaplastic-large-cell-lymphoma-bia-alcl.
9. Loch-Wilkinson A, Beath KJ, Knight RJW, Wessels WLF, Magnusson M, Papadopoulos T, et al. Breast Implant-Associated Anaplastic Large Cell Lymphoma in Australia and New Zealand: High-Surface-Area Textured Implants Are Associated with Increased Risk. Plast Reconstr Surg. 2017;140(4):645-54.
10. Doren EL, Miranda RN, Selber JC, Garvey PB, Liu J, Medeiros LJ, et al. U.S. Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Plast Reconstr Surg. 2017;139(5):1042-50.
11. Franklin JM, Schneeweiss S. When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials? Clin Pharmacol Ther. 2017;102(6):924-33.
12. Silverman SL. From randomized controlled trials to observational studies. Am J Med. 2009;122(2):114-20.
13. Garrison LP, Jr., Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. Value Health. 2007;10(5):326-35.
14. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
15. Olmos A, Govindasamy P. Propensity Scores: A Practical Introduction Using R. Journal of MultiDisciplinary Evaluation. 2015;11(25):68-88.

16. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.
17. Osborne JW. Dealing With Missing or Incomplete Data. Data Cleaning: A Complete Guide to Everything You Need to Do Before and After Collecting Your Data. United States of America: SAGE Publications, Inc.; 2013.
18. Hoeijmakers F, Beck N, Wouters M, Prins HA, Steup WH. National quality registries: how to improve the quality of data? J Thorac Dis. 2018;10(Suppl 29):S3490-S9.
19. Vrolijk JJ, Rakhorst HA, Mureau MAM, Hommes JE, Becherer BE, van Bommel ACM, et al. Dutch Breast Implant Registry (DBIR)–Annual Report 2019. Dutch Institute for Clinical Auditing (DICA); October 2020.
20. GS1. UDI (Unique Device Identification) 2020 [Available from: https://www.gs1.org/industries/healthcare/udi.
21. GS1. Global Data Synchronisation Network (GDSN) 2020 [Available from: https://www.gs1.org/services/gdsn.
22. International Organisation of Stadardization (ISO). ISO/TS 13972:2015: Health informatics — Detailed clinical models, characteristics and processes. Geneva, Switzerland. 2015;p.56.
23. Nictiz. Health and Care information models 2020 [updated October 2020. Available from: https://zibs.nl/wiki/HCIM_Mainpage.
24. van der Werf LR. Thesis: Quality Measurement in Oesophagogastric Cancer Surgery. Chapter 12. Erasmus University Rotterdam, the Netherlands; 2020.
25. Munhoz AM, Clemens MW, Nahabedian MY. Breast Implant Surfaces and Their Impact on Current Practices: Where We Are Now and Where Are We Going? Plast Reconstr Surg Glob Open. 2019;7(10):e2466.
26. Dimick JB, Welch HG, Birkmeyer JD. Surgical mortality as an indicator of hospital quality: the problem with small sample size. JAMA. 2004;292(7):847-51.
27. Cecil E, Bottle A, Esmail A, Wilkinson S, Vincent C, Aylin PP. Investigating the association of alerts from a national mortality surveillance system with subsequent hospital mortality in England: an interrupted time series analysis. BMJ Qual Saf. 2018;27(12):965-73.
28. Anhoj J, Hellesoe AB. The problem with red, amber, green: the need to avoid distraction by random variation in organisational performance measures. BMJ Qual Saf. 2017;26(1):81-4.
29. Marshall T, Mohammed MA. Case-mix and the use of control charts in monitoring mortality rates after coronary artery bypass. BMC Health Serv Res. 2007;7:63.
30. Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data. 2016;3:160018.
31. GO FAIR International Support & Coordination Office. FAIR Principles [Available from: https://www.go-fair.org/fair-principles/.
32. Pusic AL, Chen CM, Cano S, Klassen A, McCarthy C, Collins ED, et al. Measuring quality of life in cosmetic and reconstructive breast surgery: a systematic review of patient-reported outcomes instruments. Plast Reconstr Surg. 2007;120(4):823-37; discussion 38-9.

33. Frank L, Basch E, Selby JV, Patient-Centered Outcomes Research I. The PCORI perspective on patient-centered outcomes research. JAMA. 2014;312(15):1513-4.
34. Banerjee AK, Okun S, Edwards IR, Wicks P, Smith MY, Mayall SJ, et al. Patient-Reported Outcome Measures in Safety Event Reporting: PROSPER Consortium guidance. Drug Saf. 2013;36(12):1129-49.
35. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. Plast Reconstr Surg. 2009;124(2):345-53.
36. Ng S, Pusic A, Parker E, Vishwanath S, Cooter RD, Elder E, et al. Patient-Reported Outcome Measures for Breast Implant Surgery: A Pilot Study. Aesthet Surg J. 2019;39(8):NP314-NP21.
37. Merenda M, Vishwanath S, Ng S, Parker E, Ernest A, Klassen A, et al. Test-retest Reliability of the BREAST-Q IS in the Australian Breast Device Registry. Aesthet Surg J. 2020;41(4):NP177-84.
38. Register Centrum Västra Götaland. BRIMP Breast Implant Register Annual Report 2019. Sweden; 2020.
39. The Plastic Surgery Foundation. The National Breast Implant Registry Annual Report 2019. 2019.

CHAPTER 9

SUMMARY IN ENGLISH AND DUTCH

SUMMARY IN ENGLISH

The female breasts play an essential role in physical and mental well-being throughout different stages of a woman's life. Since the early 1960s, breast implants have been routinely used to (re)create the shape and look of a breast or to enlarge a breast. Although breast implants have been shown to increase women's physical and mental well-being, they are not without complications.(1-3) In addition to surgery-related and implant-related complications, manufacturing problems may negatively impact patient safety. Additionally, before the start of the studies in this thesis, it was still unknown how many women carry a breast implant. Therefore, national breast implant registries play an important role.

In response to the Poly Implant Prothèses crisis in 2010, when breast implants appeared to be manufactured with non-medical-grade silicone, several countries developed a new generation of independent, national breast implant registries.(4-14) To share best practices and facilitate international collaboration, these registries united in the International Collaboration of Breast Registry Activities (ICOBRA).(5, 15)

One of these new registries was the Dutch Breast Implant Registry (DBIR), initiated by the Netherlands Society of Plastic Surgery. DBIR is an opt-out registry that registers patient, implant, and surgery characteristics since April 2015. It captures implanted and explanted temporary tissue expanders and "permanent" breast implants. DBIR has three primary purposes: 1) to monitor and evaluate the quality of care using clinical auditing, 2) to monitor and evaluate the quality of inserted breast implants, and 3) to serve as a track-and-trace system in case of a recall. Registration in DBIR is mandatory for all board-certified plastic surgeons in the Netherlands, and a certified Trusted Third Party securely manages the data in compliance with the General Data Protection Regulation.

The studies in this thesis aimed to provide insight into breast implant surgery practice in the Netherlands (part I), to investigate nationwide variation in surgical practice and outcomes (part II), and to assess the potential of combining DBIR data with other registries on a national and international level (part III).

PART I – BREAST IMPLANT SURGERY IN PERSPECTIVE

Although some breast implant registries did exist in the past, most are no longer operational due to low capture rates and insufficient funding. ***Chapter 2*** compared the recently initiated breast implant registries to more mature orthopedic and cardiac device registries to evaluate registries' costs and value, governance and stakeholders, and funding and sustainability. Worldwide, DBIR is one of the first up-and-running, opt-out breast implant registries with nationwide coverage and a sustainable funding structure.

In ***chapter 3***, the first outcomes and experiences of DBIR are described. Between 2015 and 2017, a total of 15,049 patients and 30,541 implants were captured. Subsequently, a minimum breast implant incidence of 1 per 1,691 women could be determined for 2017. Approximately 80% of the implants were inserted for breast augmentation and 20% for reconstruction. Additionally, preferences for the use of different breast implants became clear. In the Netherlands, breast reconstruction is most frequently performed with anatomically shaped, textured, silicone-filled implants, and breast augmentation with round, textured, silicone-filled implants. Finally, substantial variation in the use of infection control measures was observed. These insights into the patient population, implant types, and nationwide variation are essential for future research on breast implant performance, adverse events, and quality improvement initiatives.

PART II – VARIATION IN SURGICAL PRACTICE AND OUTCOMES

Insight into variation in daily surgical practice, the underlying reasons, and the impact on patient outcomes opens up discussions among clinicians and helps to further improve guidelines and the quality of care provided. Following the observed variation in the use of infection control measures in ***chapter 3***, seven different infection control measures were further evaluated in ***chapter 4***. The study showed that most surgeons use three infection control measures for breast augmentation and four for reconstruction. Perioperative systemic antibiotics, implant and/or pocket irrigation, and glove change were most frequently used. Within three years, the infection-related revision incidence was low: 2.1% after reconstruction and 0.1% after augmentation. Due to this low event rate, the impact of using fewer or more infection control measures on the infection-related revision incidence remained unclear.

In current practice, variation was also observed between the two most common immediate implant-based breast reconstruction techniques after mastectomy: the direct-to-implant and two-stage techniques. Therefore, ***chapter 5*** aimed to compare the incidence of unplanned revision surgery between these two techniques. Proper adjustment for confounding factors and variation among centers was performed, and confounding by indication was limited. It was found that the direct-to-implant technique was associated with a lower short-term and long-term unplanned revision incidence compared to the two-stage technique. Furthermore, more breasts were reconstructed within the planned number of operations in the direct-to-implant group than in the two-stage group.

PART III – JOINING FORCES WITH OTHER REGISTRIES

The last two chapters evaluated the ability to combine DBIR data with other registries. First, in ***chapter 6***, a proof of concept was performed using two full years of DBIR-data and data from the Dutch Pathology Registry PALGA, using PALGA as the gold standard. Between the registries, an overlap of 100% of the BIA-ALCL cases was found in 2016 and 70% in 2017.

In total, 17 patients were identified in PALGA, of which 14 patients were also identified in DBIR; three patients were not registered, and ten patients were registered false-positive. For all confirmed BIA-ALCL cases present in both registries, complementary (anonymous) data on patient, implant, and pathology characteristics could successfully be retrieved. It became clear that both registration systems remain essential tools to study BIA-ALCL.

The aim of ***chapter 7*** was to assess whether data from different national breast implant registries could be combined to improve breast implant monitoring on an international level. The study included 85,254 patients and 207,189 permanent breast implants (7% breast reconstruction, 93% breast augmentation) from the American, Australian, Dutch, and Swedish breast implant registries. Across the registries, mean patient age varied between 41-51 years for breast reconstruction and 31-36 years for breast augmentation. Median BMI differed between the registries for breast reconstruction but not for breast augmentation. Variation was observed in the use of infection control measures and implant preferences across the countries and over the years. Between the registries, cumulative revision incidence at two years ranged from 6-16% after breast reconstruction and 1-4% after breast augmentation. For the first time in history, data of four active breast implant registries could successfully be combined and compared using the ICOBRA harmonized dataset. This is a powerful step forward in international breast implant monitoring, evidence-based decision making, and optimizing patient safety.

CONCLUSION & FUTURE PERSPECTIVES

Clinical breast implant registries are important and valuable for monitoring breast implant performance, evaluating the quality of care, and ultimately optimizing patient safety. Breast implant registries provide evidence that supports clinical decision-making and creates value for many stakeholders, including patients, clinicians, manufacturers, and regulators.

The main points of improvement of DBIR are to incorporate methods to identify implant outliers, increase data accuracy, decrease registration burden, stimulate inter-surgeon discussions using audit information, and join forces with other registries. By continually improving the registry's effectiveness and sustainability, we can keep providing the best evidence-based care to our patients.

SUMMARY IN DUTCH

Nederlandse samenvatting

Borsten spelen een essentiële rol in het mentale en fysieke welzijn van een vrouw. Sinds het begin van de jaren 60 worden borstimplantaten regelmatig gebruikt om (opnieuw) een borst te creëren of om een borst te vergroten. Hoewel is aangetoond dat borstimplantaten het mentale en fysieke welzijn van vrouwen kunnen verbeteren, zijn borstimplantaten niet zonder risico's.(1-3) Naast operatie-gerelateerde en implantaat-gerelateerde complicaties, kunnen ook problemen tijdens het productieproces de patiëntveiligheid negatief beïnvloeden. Bovendien was het voor de start van dit proefschrift nog niet bekend hoeveel vrouwen in Nederland een borstimplantaat hebben. Goed functionerende, landelijke borstimplantaatregistraties spelen daarom een belangrijke rol.

Naar aanleiding van de Poly Implant Prothèses crisis in 2010, toen borstimplantaten van niet-medische siliconen bleken te zijn gemaakt, hebben verschillende landen een nieuwe generatie, onafhankelijke borstimplantaatregistraties ontwikkeld.(4-14) Om internationale samenwerking te stimuleren en kennis en ervaring met elkaar te kunnen delen, hebben deze registraties zich verenigd in the International Collaboration of Breast Registry Activities (ICOBRA).(5, 15)

Een van deze nieuwe borstimplantaatregistraties was de Dutch Breast Implant Registry (DBIR), destijds geïnitieerd door de Nederlandse Vereniging voor Plastische Chirurgie. DBIR is een opt-out registratie dat sinds april 2015 patiënt-, implantaat- en operatiekenmerken registreert. Het registreert zowel geïmplanteerde als geëxplanteerde implantaten, waaronder tijdelijke tissue expanders en "permanente" borstimplantaten. DBIR heeft drie hoofddoelen: 1) het bewaken en evalueren van de kwaliteit van zorg door middel van clinical auditing, 2) het bewaken en evalueren van de kwaliteit van de geregistreerde borstimplantaten, en 3) het dienen als een track-and-trace systeem in het geval van een terugroepactie. Het registreren van borstimplantaten in DBIR is verplicht voor alle gecertificeerde plastisch chirurgen in Nederland en de data worden veilig beheerd door een gecertificeerde Trusted Third Party conform de Algemene Verordening Gegevensbescherming.

In dit proefschrift wordt inzicht gegeven in de Nederlandse borstimplantaatchirurgie (deel I), wordt onderzoek gedaan naar landelijke variatie in operatietechnieken en resultaten (deel II), en wordt gekeken naar de mogelijkheden om DBIR-data te combineren met andere registraties op nationale en internationale schaal (deel III).

DEEL I – BORSTIMPLANTAATCHIRURGIE IN PERSPECTIEF

Ondanks dat er in het verleden enkele borstimplantaatregistraties bestonden, zijn de meesten niet meer operationeel vanwege een te lage landelijke dekkingsgraad en onvoldoende financiering. In ***hoofdstuk 2*** werden de relatief jonge borstimplantaatregistraties vergeleken met de langer bestaande orthopedische en cardiovasculaire implantaatregistraties. Het hoofdstuk evalueert de kosten en baten van de registraties, de managementstructuur en financieringsstructuur. Wereldwijd is DBIR een van de eerste up-and-running, opt-out borstimplantatenregistraties met een landelijke dekkingsgraad en een duurzame financieringsstructuur.

In ***hoofdstuk 3*** worden de eerste resultaten van de DBIR beschreven. Tussen 2015 en 2017 werden in totaal 15.049 patiënten en 30.541 implantaten geregistreerd. De minimale incidentie van borstimplantaten bleek in 2017 1 per 1.691 vrouwen te zijn. Ongeveer 80% van de borstimplantaten werd geplaatst voor een borstvergroting en 20% voor een borstreconstructie. Het bleek dat in Nederland bij een borstreconstructie de voorkeur uitgaat naar anatomisch gevormde, getextureerde, siliconen borstimplantaten en bij een borstvergroting naar ronde, getextureerde, siliconen borstimplantaten. Als laatste werd een opvallende variatie gezien in de toepassing van verschillende infectiepreventiemaatregelen. Deze inzichten vormen een belangrijk startpunt voor toekomstig onderzoek naar de kwaliteit van borstimplantaten, bijwerkingen en initiatieven voor kwaliteitsverbetering.

DEEL II – VARIATIE IN OPERATIETECHNIEKEN EN RESULTATEN

Het verkrijgen van inzicht in de landelijke variatie van toegepaste operatietechnieken, de onderliggende redenen hiervoor en de impact op de kwaliteit van zorg is interessante informatie voor open gesprekken tussen clinici. Onder andere kan het leiden tot minder ongewenste praktijkvariatie, het verder verbeteren van richtlijnen en onze kwaliteit van zorg. In aanvulling op de gevonden landelijke variatie in het gebruik van infectiepreventiemaatregelen in ***hoofdstuk 3***, werden daarom in ***hoofdstuk 4*** zeven verschillende infectiepreventiemaatregelen verder geëvalueerd. Het werd duidelijk dat de meeste chirurgen drie infectiepreventiemaatregelen gebruikten bij een borstvergroting en vier bij een borstreconstructie. Perioperatieve systemische antibiotica, het spoelen van het implantaat en/of de implantaatholte en handschoenenwissel werden het meest toegepast. De infectie-gerelateerde revisie-incidentie binnen drie jaar was laag: 2,1% na een borst reconstructie en 0,1% na een borstvergroting. Vanwege deze lage revisie-incidentie bleef de impact van het gebruik van meer of minder infectiepreventiemaatregelen op de infectie-gerelateerde revisie-incidentie echter onbekend.

In ***hoofdstuk 5*** werd de landelijke variatie in het gebruik van de twee meest voorkomende directe borstreconstructietechnieken met een implantaat geëvalueerd: de een-fase versus de twee-fase reconstructie. Er werd zorgvuldig rekening gehouden met confounders,

indicatiebias en variatie tussen en binnen zorginstellingen. Vervolgens bleek dat de een-fase techniek geassocieerd was met een lagere ongeplande revisie-incidentie op zowel de korte- als langere termijn in vergelijking met de twee-fase techniek. Bovendien werden meer borsten gereconstrueerd binnen het geplande aantal operaties in de een-fase groep dan in de twee-fase groep.

DEEL III – KRACHTEN BUNDELEN MET ANDERE REGISTRATIES

De laatste twee hoofdstukken, ***hoofdstuk 6 en 7***, evalueerden de mogelijkheid om DBIR-data te combineren met andere registraties. Eerst werd op nationale schaal (***hoofdstuk 6***) een *proof of concept* uitgevoerd met DBIR-data en data uit de Nederlandse pathologiedatabase PALGA, waarbij PALGA gold als gouden standaard. In 2016 bevatten beide registers alle bekende BIA-ALCL casus (100% overlap), in 2017 miste DBIR enkele casus (70% overlap). In totaal konden van de 17 BIA-ALCL casus in PALGA, 14 casus ook gevonden worden in DBIR; 3 casus waren niet geregistreerd in DBIR en 10 casus waren vals-positief geregistreerd in DBIR. Van alle bewezen BIA-ALCL casus die aanwezig waren in beide registraties konden (anonieme) patiënt-, implantaat- en pathologiegegevens succesvol worden gecombineerd. Het werd duidelijk dat zowel PALGA als DBIR essentiële en elkaar aanvullende registraties zijn voor het verder onderzoeken van BIA-ALCL.

In ***hoofdstuk 7*** werd vervolgens onderzocht of data van meerdere nationale borstimplantaatregistraties gecombineerd konden worden om borstimplantaatmonitoring op internationaal niveau verder te verbeteren. Deze internationale studie bevatte in totaal 85.254 patiënten en 207.189 permanente borstimplantaten (7% borstreconstructie, 93% borstvergroting) uit de Amerikaanse, Australische, Nederlandse en Zweedse borstimplantaatregistraties. Tussen de registraties varieerde de gemiddelde patiëntleeftijd voor een borstreconstructie tussen 41-51 jaar en voor een borstvergroting tussen 31-36 jaar. De mediane BMI van patiënten was in de registraties verschillend in het geval van een borstreconstructie, maar niet in het geval van een borstvergroting. Tevens werd er variatie gezien in het toepassen van infectiepreventiemaatregelen en welke borstimplantaattypes de voorkeur hadden. Tussen de registraties varieerde de cumulatieve revisie-incidentie na 2 jaar tussen 6-16% in het geval van een borstreconstructie en 1-4% in het geval van een borstvergroting. Voor het eerst in de geschiedenis konden gegevens van vier borstimplantaatregistraties met succes worden gecombineerd en vergeleken met behulp van de geharmoniseerde ICOBRA-dataset. Deze studie is een belangrijke stap vooruit om op internationaal niveau borstimplantaatmonitoring, *evidence-based* besluitvorming en de patiëntveiligheid nog verder te verbeteren.

CONCLUSIE & TOEKOMSTPERSPECTIEVEN

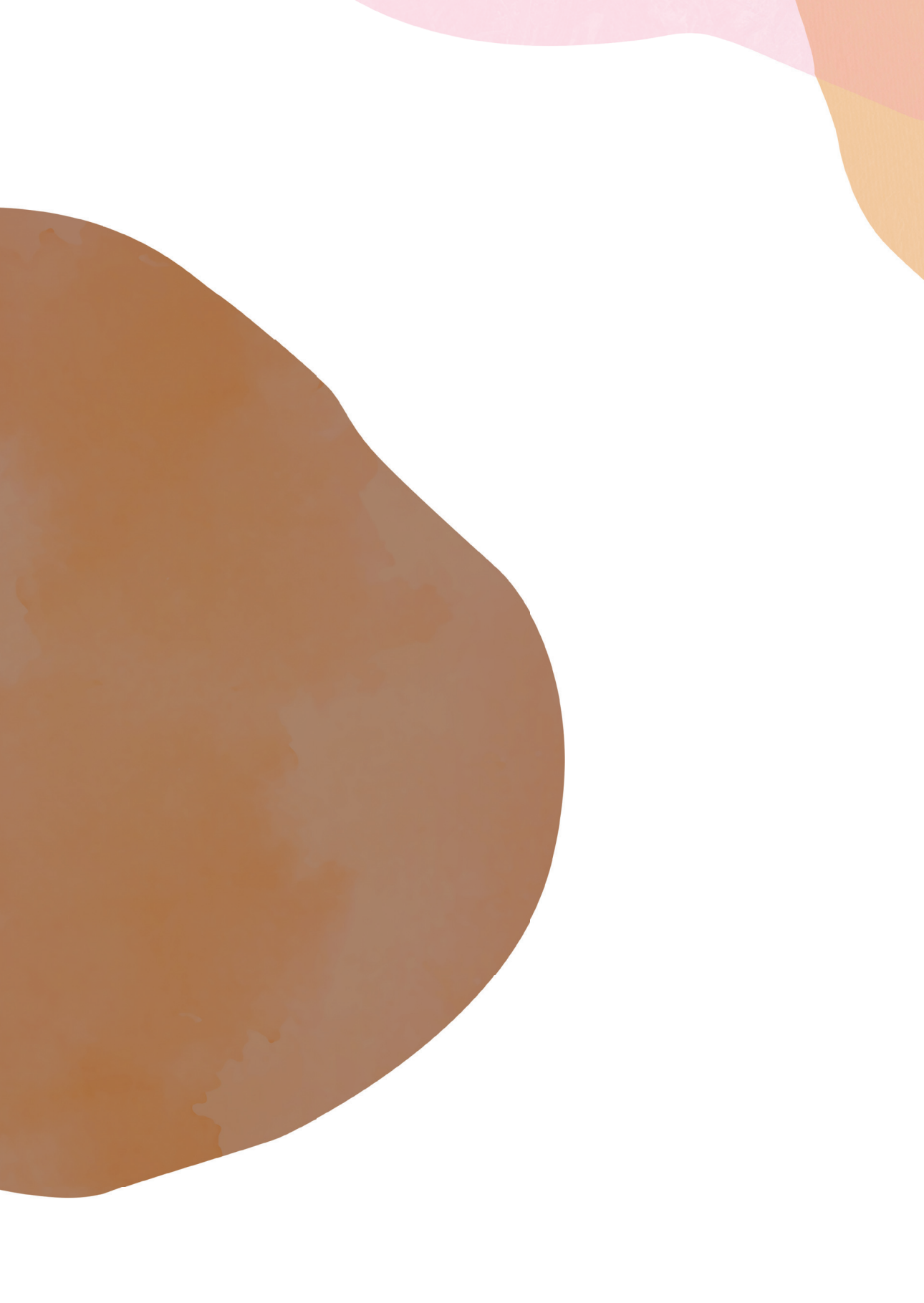
Borstimplantaatregistraties spelen een belangrijke rol in het monitoren van de kwaliteit van borstimplantaten, het evalueren van de kwaliteit van de zorg en uiteindelijk

het optimaliseren van de patiëntveiligheid. Door middel van de geregistreerde data bieden borstimplantaatregistraties inzicht in verschillende aspecten van de borstimplantaatchirurgie, wat de klinische besluitvorming ondersteund en van grote waarde is voor alle betrokken partijen, zoals de patiënten, artsen, fabrikanten en toezichthouders.

De belangrijkste verbeterpunten van DBIR zijn het implementeren van methoden om onvoldoende functionerende borstimplantaten te identificeren, de datakwaliteit te verbeteren, de registratielast te verminderen, open gesprekken tussen chirurgen te stimuleren en de krachten te bundelen met andere registraties. Want door de registratie voortdurend te blijven verbeteren, kunnen we nu en in de toekomst onze patiënten de beste borstimplantaatzorg blijven bieden.

REFERENCES

1. Kouwenberg CAE, de Ligt KM, Kranenburg LW, Rakhorst H, de Leeuw D, Siesling S, et al. Long-Term Health-Related Quality of Life after Four Common Surgical Treatment Options for Breast Cancer and the Effect of Complications: A Retrospective Patient-Reported Survey among 1871 Patients. Plast Reconstr Surg. 2020;146(1):1-13.
2. Alderman AK, Bauer J, Fardo D, Abrahamse P, Pusic A. Understanding the effect of breast augmentation on quality of life: prospective analysis using the BREAST-Q. Plast Reconstr Surg. 2014;133(4):787-95.
3. Cordeiro PG. Breast reconstruction after surgery for breast cancer. N Engl J Med. 2008;359(15):1590-601.
4. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Scientific opinion on the safety of Poly Implant Prothèse (PIP) Silicone Breast Implants (2013 update).12 May 2014.
5. Cooter RD, Barker S, Carroll SM, Evans GR, von Fritschen U, Hoflehner H, et al. International importance of robust breast device registries. Plast Reconstr Surg. 2015;135(2):330-6.
6. James S, Daubert JC, Van de Werf F. Commentary: Use of registries to investigate the past and develop the future. BMJ. 2011;342:d2826.
7. Nahabedian MY. Discussion: International importance of robust breast device registries. Plast Reconstr Surg. 2015;135(2):337-8.
8. Hopper I, Ahern S, Nguyen TQ, Mulvany C, McNeil JJ, Deva AK, et al. Breast Implant Registries: A Call to Action. Aesthet Surg J. 2018;38(7):807-10.
9. Hopper I, Ahern S, Best RL, McNeil J, Cooter RD. Australian Breast Device Registry: breast device safety transformed. ANZ J Surg. 2017;87(1-2):9-10.
10. Rakhorst HA, Mureau MAM, Cooter RD, McNeil J, van Hooff M, van der Hulst R, et al. The new opt-out Dutch National Breast Implant Registry–Lessons learnt from the road to implementation. J Plast Reconstr Aesthet Surg. 2017;70(10):1354-60.
11. Registercentrum Västa Götaland. BRIMP Bröstimplantatregistret 2014 [updated 2020]. Available from: https://brimp.registercentrum.se/om-brimp/om-broestimplantatregistret/p/BkuO2oSQS.
12. NHS Digital. Breast and Cosmetic Implant Registry 2016 [updated 29 September 2020]. Available from: https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/breast-and-cosmetic-implant-registry#top.
13. Prantl L, von Fritschen U, Liebau J, von Hassel J, Baur EM, Vogt PM, et al. [Concept for a National Implant Registry to Improve Patient Safety]. Handchir Mikrochir Plast Chir. 2016;48(6):320-9.
14. The Plastic Surgery Foundation. The National Breast Implant Registry (NBIR) 2018 [updated 2020]. Available from: https://www.thepsf.org/research/registries/nbir.
15. Cooter R, Barnett R, Deva A, Magnusson MR, McNeil J, Perks G, et al. In Defense of the International Collaboration of Breast Registry Activities (ICOBRA). Aesthet Surg J. 2016;36(7):NP225-7.



APPENDICES

CONTRIBUTING AUTHORS
AUTHOR'S LIST OF PUBLICATIONS
PHD PORTFOLIO
DANKWOORD
ABOUT THE AUTHOR

CONTRIBUTING AUTHORS

Listed in alphabetical order.
Affiliations at the time that research was conducted.

Jan Paul de Boer
Department of Medical Oncology
Netherlands Cancer Institute/Antoni van Leeuwenhoek
Amsterdam, the Netherlands

Mintsje de Boer
Department of Plastic, Reconstructive and Hand Surgery
Maastricht University Medical Center
Maastricht, the Netherlands

Annette H. Bruggink
Dutch Nationwide Network and Registry of Histo- and Cytopathology (PALGA)
Houten, the Netherlands

Rodney D. Cooter
Australian Society for Plastic Surgeons
Sydney, NSW, Australia

Benoît Couturaud
Department of Plastic and Reconstructive Surgery
Curie Institute
Paris, France

Uwe von Fritschen
Department of Plastic, Aesthetic and Hand Surgery
Helios Clinic Emil von Behring
Berlin, Germany

Erik Heeg
Department of Surgery
Leiden University Medical Center
Leiden, the Netherlands

Juliëtte Hommes
Department of Plastic, Reconstructive and Hand Surgery
Maastricht University Medical Center
Maastricht, the Netherlands

Marije J. Hoornweg
Department of Plastic and Reconstructive Surgery
Netherlands Cancer Institute/Antoni van Leeuwenhoek
Amsterdam, the Netherlands

Ingrid Hopper
Department of Epidemiology and Preventive Medicine
Monash University
Melbourne, VIC, Australia

René R.W.J. van der Hulst
Department of Plastic, Reconstructive and Hand Surgery
Maastricht University Medical Center
Maastricht, the Netherlands

Daphne de Jong
Department of Pathology
Amsterdam University Medical Centers, VU University Medical Center
Amsterdam, the Netherlands

Xavier H.A. Keuter
Department of Plastic, Reconstructive and Hand Surgery
Maastricht University Medical Center & VieCuri Medical Center
Maastricht & Venray, the Netherlands

Flora E. van Leeuwen
Department of Epidemiology and Biostatistics
Netherlands Cancer Institute/Antoni van Leeuwenhoek
Amsterdam, the Netherlands

David B. Lumenta
Division of Plastic, Aesthetic and Reconstructive Surgery
Department of Surgery
Medical University of Graz
Graz, Austria

Perla J. Marang-van de Mheen
Department of Medical Decision making
Leiden University Medical Center
Leiden, the Netherlands

Stephen Mulgrew
Department of Plastic surgery
Lister Hospital NHS Trust
Stevenage, United Kingdom

Erin Mullen
The Plastic Surgery Foundation
American Society of Plastic Surgeons
Arlington Heights, IL, United States of America

Marc A.M. Mureau
Department of Plastic and Reconstructive Surgery
Erasmus MC Cancer Institute, University Medical Center Rotterdam
Rotterdam, the Netherlands

A. Graeme Perks
Department of Plastic, Reconstructive and Burns surgery
Nottingham University Hospitals NHS Trust
Nottingham, United Kingdom

Andrea L. Pusic
Division of Plastic Surgery
Brigham and Women's Hospital
Boston, MA, United States of America

Hinne A. Rakhorst
Department of Plastic, Reconstructive and Hand Surgery
Medisch Spectrum Twente & ZGT
Enschede, Almelo & Hengelo, the Netherlands

Pauline E.R. Spronk
Department of Surgery
Leiden University Medical Center
Leiden, the Netherlands

Birgit Stark
Department of Plastic and Reconstructive Surgery
Department of Molecular Medicine and Surgery
Karolinska University Hospital
Stockholm, Sweden

Marie-Jeanne T.F.D. Vrancken Peeters
Department of Surgery
Netherlands Cancer Institute/Antoni van Leeuwenhoek
Amsterdam, the Netherlands

Michel W.J.M. Wouters
Department of Surgical Oncology
Netherlands Cancer Institute/Antoni van Leeuwenhoek
Amsterdam, the Netherlands

Danny A. Young-Afat
Department of Plastic and Reconstructive Surgery
Amsterdam University Medical Centers, VU University Medical Center
Amsterdam, the Netherlands

AUTHOR'S LIST OF PUBLICATIONS

Listed in chronological order.

THIS THESIS

1. BE Becherer, PER Spronk, MAM Mureau, S Mulgrew, AGB Perks, B Stark, AL Pusic, DB Lumenta, I Hopper, RD Cooter, HA Rakhorst. High-risk device registries: Global value, costs and sustainable funding. J Plast Reconstr Aesthet Surg. 2018;71(9):1362-80.
2. PER Spronk*, BE Becherer*, J Hommes, XHA Keuter, DA Young-Afat, MJ Hoornweg, MWJM Wouters, MAM Mureau, HA Rakhorst. How to improve patient safety and quality of care in breast implant surgery? First outcomes from the Dutch Breast Implant Registry (2015–2017). J Plast Reconstr Aesthet Surg. 2019;72(10):1607-15. **contributed equally as first author*
3. BE Becherer*, M de Boer*, PER Spronk, AH Bruggink, JP de Boer, FE van Leeuwen, MAM Mureau, RRWJ van der Hulst, D de Jong*, HA Rakhorst*. The Dutch Breast Implant Registry (DBIR): Registration of Breast Implant – Associated Anaplastic Large Cell Lymphoma (BIA-ALCL), a proof of concept. Plast Reconstr Surg. 2019;143(5):1298-1306. **contributed equally as first and last author*
4. BE Becherer, PJ Marang-van de Mheen, DA Young-Afat, RRWJ van der Hulst, XHA Keuter, HA Rakhorst, MAM Mureau, Dutch Breast Implant Registry (DBIR) group. Variation in the use of infection control measures and infection-related revision incidence after breast implant surgery. Submitted.
5. BE Becherer, E Heeg, DA Young-Afat, MTFD Vrancken Peeters, HA Rakhorst, MAM Mureau, Dutch Breast Implant Registry (DBIR) group. Revision incidence after immediate direct-to-implant versus two-stage implant-based breast reconstruction: results from a nationwide breast implant registry. Submitted.
6. BE Becherer, I Hopper, RD Cooter, B Couturaud, U von Fritschen, E Mullen, AGB Perks, AL Pusic, B Stark, MAM Mureau, HA Rakhorst. Improving breast implant safety through international collaboration of national registries – A review of over 85,000 patients and 200,000 implants from four countries. Submitted.

OTHER PUBLICATIONS

1. JJ Vrolijk, Becherer BE, ACM van Bommel, MJ Hoornweg, J Hommes, XHA Keuter, PLT Liem, MAM Mureau, HM Verkooijen, DA Young-Afat, HA Rakhorst. Dutch Breast Implant Registry (DBIR) – Annual Report 2019. Dutch Institute for Clinical Auditing (DICA); 2020.
2. CA Bargon, BE Becherer, DA Young-Afat, ACM van Bommel, J Hommes, MJ Hoornweg, XHA Keuter, S de Fazio, D Melnikov, J Monton Echeverria, AGB Perks, DB Lumenta, B Couturaud, U von Fritschen, B Stark, LR Hölmich, A Crosbie, L Lispi, A Campanale, RD

Cooter, AL Pusic, I Hopper, MAM Mureau, HA Rakhorst. Moving breast implant registries forward: are they FAIR and functional? J Plast Reconstr Aesthet Surg. 2020;S1748-6815(20)30498-8.

3. E Heeg, JX Harmeling, BE Becherer, PJ Marang-van de Mheen, MTFD Vrancken Peeters, MAM Mureau. Nationwide population-based study of the impact of immediate breast reconstruction after mastectomy on the timing of adjuvant chemotherapy. Br J Surg. 2019;106(12):1540-8.
4. Becherer BE, MJ Hoornweg, J Hommes, XHA Keuter, PLT Liem, MAM Mureau, PER Spronk, DA Young-Afat, HA Rakhorst. Dutch Breast Implant Registry (DBIR) – Annual Report 2018. Dutch Institute for Clinical Auditing (DICA); 2019.
5. P Kamali, ACM van Bommel, BE Becherer, RD Cooter, MAM Mureau, AL Pusic, S Siesling, RRWJ van der Hulst, SJ Lin, HA Rakhorst. Immediate Breast Reconstruction in The Netherlands and the United States: A Proof-of-Concept to Internationally Compare Quality of Care Using Cancer Registry Data. Plast Reconstr Surg. 2019;144(4):565e-47e.
6. Becherer BE, ACM van Bommel, MJ Hoornweg, J Hommes, XHA Keuter, PLT Liem, MAM Mureau, DA Young-Afat, HA Rakhorst. Dutch Breast Implant Registry (DBIR) – Annual Report 2017. Dutch Institute for Clinical Auditing (DICA); 2018.
7. MA Paul, P Kamali, AD Chen, AMS Ibrahim, W Wu, BE Becherer, C Medin, SJ Lin. Assessment of functional rhinoplasty with spreader grafting using acoustic rhinomanometry and validated outcome measurements. Plast Reconstr Surg Glob Open. 2018;6(3);e1615
8. CL van Veldhuisen, P Kamali, W Wu, BE Becherer, H Sinno, AA Ashraf, AMS Ibrahim, AM Tobias, BT Lee, SJ Lin. Prospective, double-blind evaluation of umbilicoplasty techniques using conventional and crowdsourcing methods. Plast Reconstr Surg. 2017;140(6):1151-62.
9. BE Becherer, P Kamali, MA Paul, W Wu, DA Curiel, HA Rakhorst, BT Lee, SJ Lin, KJ Kansal. Prevalence of psychiatric comorbidities among women undergoing autologous breast reconstruction. J Surg Oncol. 2017;116(7):803-10.
10. JA Ricci, P Kamali, BE Becherer, DA Curiel, W Wu, AM Tobias, SJ Lin, BT Lee. Umbilical Necrosis Rates After Abdominal Based Microsurgical Breast Reconstruction. J Surg Res. 2017;215:257-63.
11. P Kamali, M Lee, BE Becherer, W Wu, DA Curiel, AM Tobias, SJ Lin, BT Lee. Medial row perforators are associated with higher rates of fat necrosis in bilateral DIEP flap breast reconstruction. Plast Reconstr Surg. 2017;140(1):19-24.
12. BE Becherer, J Roelink, J van Baal. Case report: Two patients with Fournier's gangrene (fasciitis necroticans). Tijdschr Urol 2015;5(6):155.

PHD PORTFOLIO

COURSES		ECTS
2020	Entrepreneurship awakening *Erasmus University, Rotterdam*	1.0
2019	Analytics translator *Xebia Academy, Amsterdam*	0.6
2019	Joint models for longitudinal and survival data ESP72 *Erasmus University MC, Rotterdam*	0.7
2019	Clinical epidemiology *Leiden University Medical Center, Schiermonnikoog*	2.1
2019	Personal effectiveness *Astrid Paalvast coaching, Leiden*	0.3
2019	eBROK *Erasmus University MC, Rotterdam*	1.5
2019	Scientific integrity *Erasmus University MC, Rotterdam*	0.3
2018-2020	Microsurgical training (104 hours) *Microsurgical skillslab Erasmus University MC, Rotterdam*	3.7
2018	Statistics in Medicine *Stanford University (online)*	2.1
2018	R-course *Dutch Institute for Clinical Auditing, Leiden*	1.1
2018	Scientific writing course *British Journal of Surgery, Birmingham, United Kingdom*	1.0

ORAL & POSTER PRESENTATIONS		ECTS
2020	Fall meeting Netherlands Society of Plastic Surgery (NVPC) *Immediate breast reconstruction: direct-to-implant vs. two-stage*	1.0
2020	Local meeting Plastic Surgery dept. Erasmus University MC *Immediate breast reconstruction: direct-to-implant vs. two-stage*	1.0
2019	Fall meeting Netherlands Society of Plastic Surgery (NVPC) *The second Dutch Breast Implant Registry Annual Report*	1.0
2019	DICA conference *Clinical auditing in breast implant surgery*	1.0
2018	Fall meeting Netherlands Society of Plastic Surgery (NVPC) *The first Dutch Breast Implant Registry Annual Report*	1.0
2018	GS1 Traceability in healthcare *The Dutch Breast Implant Registry and the importance of UDI*	1.0

2018	DICA conference *Oral presentation: Results of the first three years of DBIR* *Poster presentation: registration of BIA-ALCL in DBIR – a proof of concept*	1.0
2018	Spring meeting Netherlands Society of Plastic Surgery (NVPC) *Registration of BIA-ALCL in DBIR – a proof of concept*	1.0
2017	Spring meeting Netherlands Society of Plastic Surgery (NVPC) *High risk device registries: value, costs, and sustainable funding*	1.0

ATTENDED CONFERENCES & SEMINARS		**ECTS**
2021	Local Plastic Surgery meeting (refereeravond) *Erasmus University MC, Rotterdam*	0.2
2020	Fall meeting Netherlands Society of Plastic Surgery (NVPC) *Amsterdam*	1.0
2020	Local Plastic Surgery meeting (refereeravond) *Erasmus University MC, Rotterdam*	0.2
2020	Medical Business Masterclass *3 online webinars*	1.0
2019	De Jonge Specialist conference *Tiel*	0.5
2019	Meet Up Artificial Intelligence in the current healthcare *Netherlands Cancer Institute, Amsterdam*	0.2
2019	Young Bilderberg Conference *Nyenrode, Breukelen*	1.0
2019	International meeting on breast implants (Ministry of Health, Welfare and Sport) *Amsterdam*	1.0
2019	DICA conference *Amsterdam*	1.0
2019	Meeting Netherlands Society of Plastic Surgery (NVPC) 2x *Amsterdam and Leeuwarden*	2.0
2019	Medical Business Labs *Rotterdam*	0.2
2019	Medical Business Masterclass *Leiden, Rotterdam, Amsterdam*	1.0
2019	WKNVPC Scientific day *Utrecht*	1.0
2019	Local and regional Plastic Surgery meeting (refereeravond) 3x *Erasmus University MC, Rotterdam*	0.6
2018	International expert meeting on BIA-ALCL (RIVM) *Amsterdam*	1.0

2018	Local Plastic Surgery meeting (refereeravond) *Erasmus University MC, Rotterdam*	0.2
2018	Kortjakje Sunday school for plastic surgery *Zeist*	1.0
2018	DICA conference *Amsterdam*	1.0
2018	Meeting Netherlands Society of Plastic Surgery (NVPC) 2x *Amsterdam and Ede*	2.0
2017	DICA conference *Amsterdam*	1.0
2017	Meeting Netherlands Society of Plastic Surgery (NVPC) 2x *Amsterdam and Hengelo*	2.0

TEACHING		**ECTS**
2020	Supervising master thesis of a medical student	2.0
2018-2020	Monthly journal club	1.5
2017-2020	Education methodology and plastic surgery at DICA	4.0

EXPERIENCE ABROAD		**ECTS**
2020	Collaborative research project with the Australian Breast Device Registry (ABDR) and Dutch Breast Implant Registry (DBIR) at Monash University, Department of Epidemiology and Preventive Medicine, in Melbourne, Australia	4.0

AWARDS

2020	Best oral presentation NVPC *Immediate breast reconstruction: direct-to-implant vs. two-stage*
2019	Travel grant NVPC *Collaborative research project with ABDR and DBIR at Monash University in Melbourne, Australia in 2020*

DANKWOORD

Dit proefschrift is het resultaat van 4 unieke jaren. Een unieke combinatie van tegelijkertijd onderzoek leren doen en leren over kwaliteit van zorg, van werken in een academisch ziekenhuis en op kantoor, op landelijke en internationale schaal. Deze afwisseling maakte het nooit saai en heeft ervoor gezorgd dat de jaren voorbij zijn gevlogen.

Dat ik zo positief terugkijk op mijn promotietijd heeft allereerst te maken met het beste promotieteam dat ik me kon wensen. Het team waarin iedereen open en eerlijk was. Van wie ik leerde om kritisch te blijven op mijn eigen werk en ook buiten de academische kaders te durven denken.

Beste **Marc**, professor Mureau, als reactie op mijn plan om zo snel mogelijk te willen solliciteren voor de opleiding tot plastisch chirurg opperde jij een andere idee, namelijk, promoveren. Mijn eigen enthousiasme was destijds wat minder, maar nogmaals bedankt. Bedankt voor dit bijzondere traject dat achteraf precies bij mij bleek te passen. Tevens bedankt voor de autoritjes terug naar Rotterdam met eerlijke gesprekken. En voor de cappuccino's aan jullie keukentafel, voorzien van de no-nonsense peptalks van Rachel. Het is een eer 1 van jouw eerste promovendi te zijn.

Beste **Rene**, professor van der Hulst, voor het realiseren van een eerste DBIR-promotieplek moesten meerdere hobbels overwonnen worden. Ondanks dat wij elkaar niet kenden, was jij bereid op te treden als mijn promotor. Bedankt voor wat je hebt betekend in het opzetten en voltooien van mijn promotietraject, je enthousiasme gaandeweg en natuurlijk de Maastrichtse gezelligheid.

Beste **Hinne**, dr. Rakhorst, onze samenwerking begon in 2014. Sindsdien gaat mijn dank uit naar jouw rotsvaste vertrouwen en support. Naar de inspirerende mensen met wie je me in contact hebt gebracht en de ondersteuning voor mijn buitenlandavonturen waarin jij een onmisbare rol hebt gespeeld. Ik kan je voor nog veel meer bedanken, maar ik sluit graag af met een dankjewel voor jouw vele Twentse of vaak zelfbedachte, vermakelijke afkortingen. Want met het oog op de toekomst gaan we k.w.w.* maar blijven we altijd m.b.b.o.d.g.**!

Uiteraard is dit proefschrift niet door mij alleen geschreven. Dank aan alle **coauteurs** voor de samenwerking en jullie kritische feedback.

Geachte leden van de **promotiecommissie,** veel dank voor jullie bereidheid om mijn proefschrift te beoordelen en zitting te nemen in de promotiecommissie.

Voor dit proefschrift had ik het geluk samen te kunnen werken met de **wetenschappelijke commissie van de DBIR**. Dank voor jullie steun, vertrouwen en inspiratie, maar ook voor de talloze uitdagingen. Want naast de gezelligheid in de groep, lag de lat bij jullie nooit te laag. Daarnaast specifiek **Patricia Liem** bedankt, mijn steun en toeverlaat binnen de NVPC. En **Juliët Vrolijk**, aan wie ik de DBIR met mijn volle vertrouwen heb kunnen overgedragen.

Beste **DICA-collega's**, door al jullie verschillende achtergronden en specialismes waren chaos en feest gegarandeerd. Bedankt voor de nieuwe invalshoeken, het delen van "ICT"-frustraties, de promovendi-uurtjes, heidagen en alle spontane strandmiddagen. Dames van het **secretariaat**, bedankt voor jullie luisterend oor en de altijd goedgevulde koekjestrommel. Jullie zijn onmisbaar. Tot slot, **directie en managementteam**, bedankt voor de samenwerking bij het laten uitgroeien van de DBIR tot een volwaardige registratie. Ik ben trots om te zien wat er is bereikt.

Lieve **Erik, Fieke** en **Michael**, maar voornamelijk **Anna, Arthur en Karlijn**: bedankt voor alle highs en lows die we met elkaar hebben gedeeld. Ik had me geen leukere kamergenoten kunnen wensen. Dat we nog veel grappen en verhalen met elkaar mogen delen die regelmatig binnenskamers moeten blijven.

Beste **promovendi van de 15e, dames van het skills lab** en de **afdeling plastische chirurgie van het Erasmus MC**, ondanks dat ik niet fulltime in het EMC werkte, hebben jullie me altijd fulltime welkom laten voelen. Bedankt!

Dear **ICOBRA key members**, thank you for welcoming me into your group, for the inspiring collaboration, and for the conference calls at the most interesting times of the day (in pajamas or scrubs). I am looking forward to what our work brings in the future.

Also, many thanks to the **Australian Breast Device Registry team**, particularly **Ingrid Hopper**, for making me feel so welcome Down Under. Thank you for teaching me about the ABDR, introducing me to your lovely family, taking me on trips, laughing at my bike (eventually buying my bike), and taking care of me during the start of the turbulent Covid19 pandemic.

En dan natuurlijk mijn paranimfen, **Erik en Xavier**.
Erik, wie had gedacht dat we elkaar na al die avonturen in Groningen (2011, ja ja) en ieders omzwervingen weer zouden treffen in het Poortgebouw in Leiden?! Ik ben blij dat onze paden blijven kruisen en ik ben apetrots dat onze promotietrajecten er nu op zitten en dat we elkaar onze paranimf mogen noemen!

Xavier, mijn mamma-recon maatje van de 15e. Tevens ook mijn mannelijke equivalent in perfectionisme en bepaalde levensopvattingen. Bedankt voor de goede en eerlijke gesprekken, je mede-kitesurfenthousiasme, het levendig delen van je bergwandelavonturen en de altijd goeie beats tijdens het schrijven.
Beste mannen, ik hoop me gauw jullie plastische collega te kunnen noemen!

De steun van de volgende mensen begon ruim voor de start van mijn promotietijd. Ondanks dat ze niet hebben bijgedragen aan de exacte inhoud van dit proefschrift, hebben ze een onmisbare rol gespeeld. Het is lastig om de work-life balance te verliezen met zulke fijne mensen om je heen.

Lieve **dames van Fatelle**, wat begon als een roze hertenclub is inmiddels een groep vrouwen met unieke persoonlijkheden en geweldige talenten. Ik ben onwijs dankbaar voor jullie vriendschap, oprechtheid, gekheid en ontstane tradities.

Daarnaast **de Sjorsies**: Marly, Mary en Jos (en tegenwoordig ook Lou, San en Val). Als ik van tevoren had geweten wat een jaar samen aan de Esgang ons had gebracht, dan had ik Almelo zonder twijfel op nummer 1 t/m 7 gezet. Bedankt voor de bijzondere band die we als huisgenoten hebben opgebouwd. Met jullie is het altijd feest!

Ook de **takkenwijven** bedankt voor jullie altijd nuchtere adviezen en gezelligheid.

En natuurlijk de **"Kubb club"**, dank voor jullie fanatisme op het speelveld, maar bovenal voor de vriendschap, sportieve vakanties en nieuwe avonturen in het Goudse.

Dan de leukste schoonfamilie: **John en Gerda, Thijs, Ines en Fenna,** jullie weten wat het is om zelf de slingers op te hangen en dragen deze kunst met veel enthousiasme op mij over. *Poh!* Ik ben *onmeunig* dankbaar dat ik al meer dan 10 jaar met liefde door jullie word omarmd.

Mijn broertje **Bas**, wij zijn gerust uitersten te noemen. Je daagt me (soms ongewenst) uit, staat altijd open voor impulsieve plannen, maar bovenal leer je me dat niet alles uitgesproken hoeft te worden. Sommige dingen zijn er gewoon en woorden maken dat voor jou niet sterker. Daden wel. Toch kan ik het niet laten om deze woorden aan je te schrijven: dankjewel dat je er voor me bent, ik ben trots op jou.

Mijn liefste ouders, **Max en Sjoukje**, jullie hebben mij letterlijk in alle vrijheid en ruimte laten opgroeien. Jullie laten me voelen wat onvoorwaardelijke liefde en steun betekent, altijd met een gezonde dosis nuchterheid. Ik zal straks zelf gaan ervaren hoe het is om je kind los te leren laten, maar daarbij hoop ik in jullie voetsporen te kunnen treden. Hoe jullie

mij altijd gesteund hebben bij mijn (buitenland)plannen, meegegeven hebben dat afstand relatief is en mij geleerd hebben om mijn eigen pad te durven bewandelen, betekent alles voor mij. Ik hou van jullie, bedankt voor ALLES!

Lieve **Sjoerd** (na al die jaren heb ik nog steeds niet de juiste bijnaam voor je gevonden), bedankt voor de stabiliteit en rust die je me geeft. En tegelijkertijd voor de onvermoeibare eigenschap om niet alleen je eigen, maar ook mijn grenzen uit te dagen. Bedankt voor alle avonturen die we al samen hebben beleefd, maar ook voor de ruimte en het vertrouwen dat we elkaar gunnen en geven. We staan nu samen voor een van onze grootste avonturen ooit en ik zou dat met niemand liever willen doen. Dankjewel, ik hou van ons.

**k.w.w. = kiek'n wat 't wot*

***m.b.b.o.d.g. = met beide benen op de grond*

About the author

Babette Becherer was born on October 22nd, 1990, in Drouwen, the Netherlands. She attended pre-university education at the Ubbo Emmius College in Stadskanaal, from which she graduated in 2008. For her studies, she moved from the countryside to the city of Groningen. Before starting medical school at the University of Groningen in 2009, she obtained a foundation degree in pharmacy.

Halfway through medical school, Babette developed a specific interest in plastic and reconstructive surgery. Therefore, in 2015, she spent seven months in Boston (U.S.A.) performing a research project on autologous breast reconstruction and mental health problems at the Department of Plastic and Reconstructive Surgery in the Beth Israel Deaconess Medical Center, supervised by Associate Professor S.J. Lin, Dr. H.A. Rakhorst and Prof. dr. M.A.M. Mureau. For this project, she was accepted for the Groningen International Program of Science in Medicine and supported by several student grants. Shortly afterward, Babette performed her final rotation at the Department of Anatomy and the Department of Plastic and Reconstructive surgery of the Erasmus MC, University Medical Center Rotterdam.

After graduating from medical school in December 2016, she obtained clinical experience as a resident not in training at the Department of Surgery of the Sint Franciscus Gasthuis in Rotterdam. In the summer of 2017, she started a full-time PhD program in plastic and reconstructive surgery under the supervision of Prof. dr. M.A.M. Mureau, Prof. dr. R.R.W.J. van der Hulst and Dr. H.A. Rakhorst, leading to this thesis.

Her PhD program was a collaboration between the Department of Plastic and Reconstructive Surgery of the Erasmus MC and the Dutch Institute for Clinical Auditing (DICA). Besides conducting research into optimizing the quality and safety of breast implant surgery, she coordinated the Dutch Breast Implant Registry (DBIR) and the registry for breast implant suppliers. As part of her PhD program, in 2019, Babette performed a collaborative research project between the DBIR and the Australian Breast Device Registry, for which she spent a few months in Melbourne, Australia. Under the daily supervision of Associate Professor I. Hopper, she studied the options to safely combine data from two nationwide registries to accelerate research into breast implant safety on an international scale. For this project, she was supported by several funds, including the travel fund from the Netherlands Society of Plastic Surgery.

Next to her PhD activities, Babette was given the opportunity to start training her microsurgery skills at the Erasmus MC Skills Lab. She was actively involved in the

International Collaboration of Breast Device Activities (ICOBRA), and she enriched herself with courses about entrepreneurship and artificial intelligence to apply this in her future medical career.

In her spare time, her heart starts beating faster for kitesurfing and sailing. She gets refueled from being outdoors, at the beach, in the woods, the mountains, or just a garden, preferably with friends or family. She balances this all out during a regular yoga practice.

Currently, Babette is temporarily working for the Dutch COVID19-vaccination program. Together with her love Sjoerd, she expects their first baby girl at the end of this Summer. Next, she will start working as a resident not in training at the Department of Plastic and Reconstructive Surgery of the Erasmus MC. She will remain active in research projects, the DBIR committee, and ICOBRA and aims to become a plastic surgeon ultimately.