Original research article

Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European Active Surveillance Study on Intrauterine Devices

Klaas Heinemann*, Suzanne Reed, Sabine Moehner, Thai Do Minh

ZEG-Berlin, Chausseestrasse 115, 10115 Berlin, Germany
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Abstract

Objectives: The objectives were to identify and compare the incidence of uterine perforation and other medically adverse events associated with levonorgestrel-releasing intrauterine systems (LNG-IUSs, releasing 20 mcg LNG daily) and copper intrauterine devices (IUDs) under routine conditions of use in a study population representative of typical users.

Methods and materials: This is a multinational, prospective, non-interventional cohort study with new users of LNG-IUSs and copper IUDs. In addition to a baseline questionnaire, women and their treating health care professional completed a single follow-up questionnaire after 12 months. All patient-reported outcomes were validated by the treating physicians.

Results: A total of 61,448 women in six European countries were followed between 2006 and 2013 for more than 68,000 women-years of observation (70% LNG, 30% copper devices). Overall, 81 uterine perforations were reported: 61 for LNG-IUSs [1.4 per 1000 insertions (95% confidence interval {CI}: 1.1–1.8)] and 20 for copper IUDs [1.1 per 1000 insertions (95% CI: 0.7–1.7)], for an adjusted risk ratio (RR_{adj}) of 1.6 (95% CI: 1.0–2.7) when adjusted for age, body mass index, breastfeeding at time of insertion and parity. Breastfeeding at time of insertion was associated with a sixfold increase (RR 6.1, 95% CI: 3.9–9.6), with no differences between LNG and copper IUD users. Sixty-three of the total 81 perforations were associated with previously suspected risk factors (e.g., breastfeeding, time since last delivery ≤36 weeks). No perforations led to serious illness or to injury of intra-abdominal or pelvic structures.

Conclusions: Uterine perforation incidence in this study was low, with a benign clinical course thereafter. The LNG-IUSs and copper IUDs did not have clinically important differences in perforation rates.

Implications: The European Active Surveillance Study on Intrauterine Devices is the first large-scale, prospective, noninterventional study to compare the perforation risk in LNG-IUS and copper IUD users. It is the first to examine the independent roles that breastfeeding status and postpartum status have on perforation risk. Conducted during routine clinical practice, the findings are generalizable to broader populations.

1. Introduction

Uterine perforation is a potentially serious complication of intrauterine device (IUD) use. Reported incidences range from 0.3 to 2.6 per 1000 insertions for levonorgestrel-releasing intrauterine systems (LNG-IUSs) (releasing 20 mcg LNG daily) and 0.3 to 2.2 for copper IUDs [1–6]. Extensive clinical experience with LNG-IUSs suggests that serious outcomes such as peritonitis caused by perforation of the uterine wall after insertion are rare; however, results from large prospective studies with defined diagnostic follow-up procedures are not available. Scientific evidence for the safety of other IUDs — almost exclusively copper IUDs — is also unsatisfactory and not necessarily generalizable to a population of LNG-releasing IUD users.

* Corresponding author at: ZEG - Berlin Center for Epidemiology and Health Research, Invalidenstrasse 115, 10115 Berlin Germany. Tel.: +49 30 945 101 24, +49 1717 554 556 (Mobile); fax: +49 30 945 101 26.
E-mail address: k.heinemann@zeg-berlin.de (K. Heinemann).
URL: http://www.zeg-berlin.de (K. Heinemann).

Several risk factors for uterine perforation have been described. Breastfeeding [5,7] and postpartum state [1,8] have been associated with an increased perforation risk, but these risk factors have previously not been examined independently of each other. Other risk factors include lack of experience of the healthcare professional (HCP) performing the insertion [6,8,9], multiparity [7], nulliparity [1,9] and history of cesarean delivery [1]. These findings, however, are not consistent across studies. The European Active Surveillance Study on Intra-uterine Devices (EURAS IUD) aimed to compare the uterine perforation risk in users of LNG- and copper IUDs in routine clinical practice.

2. Methods

2.1. Study design

EURAS IUD was a prospective cohort study with recruitment in six European countries from 2006 to 2012. Its two cohorts consisted of new users of levonorgestrel-releasing IUDs (releasing 20 mcg LNG daily) and all copper IUDs currently used in the participating countries. A non-interference approach was chosen to avoid influencing the health care professionals' prescribing behavior and to provide standard-ized, comprehensive and reliable information on these IUDs under routine medical conditions. The study was approved by the ethical committee of the physicians' association in Berlin, Germany, and the Ethics Committee of Hospital District of Southwest Finland.

2.2. Study objectives

The primary outcome of interest was the incidence of uterine perforation. This included an estimate of the perforation incidence associated with IUD insertion, the proportion of uterine perforations associated with serious clinical complications, the interval between IUD insertion and diagnosis of uterine perforation and the impact of postpartum IUD insertion on the uterine perforation rate. For each of these outcome measures, comparisons were made between LNG and copper IUDs. For the analysis, the most conservative approach was used to define perforation. All events reported by the participating HCPs and/or patients where any part of the device was considered to have crossed the endometrium and entered the myometrium were considered a perforation.

The secondary objective of this study was to compare the contraceptive effectiveness and pregnancy-related outcomes (including ectopic pregnancies) for users of LNG and copper IUDs, and also the incidence of other medically relevant adverse events. This report focuses on only the primary objective; the secondary outcome will be described in another report.

2.3. Study population

Study participants were recruited via a network of 1200 HCPs (e.g., gynecologists, midwifes, specialized clinics) who regularly insert IUDs. All women with a newly inserted IUD were eligible for enrollment. Study participants consisted of first-ever IUD users and consecutive users (previous IUD use). After a patient decided to use an IUD, participating HCPs invited the patient to participate in the study. Because of the non-interference approach, eligibility criteria were minimal: these included a willingness to sign an informed consent form and data privacy form, and an absence of a language barrier that could prevent the patient from completing the questionnaires.

2.4. Baseline and follow-up questionnaires

At the time of IUD insertion, study participants completed a baseline questionnaire designed to collect information relating to their medical and gynecological history (including medication and contraceptive use), age, body mass index (BMI), lifestyle factors (smoking, alcohol consumption, exercise, heavy lifting) and level of education. Breastfeeding status and time since last delivery were of particular interest. On a separate form, the women provided their contact details (postal and email addresses and telephone numbers) and those of an additional contact, such as a relative or friend, and also those of their gynecologist or primary care physician. Contact data were documented separately in compliance with data protection regulations.

The follow-up questionnaire was sent to study participants 12 months after the IUD insertion. It contained questions about the insertion procedure, its aftermath, complications, medical checkups, illnesses, hospitalization and pregnancy, along with changes in physician contact information.

All patient-reported events of interest were validated by direct contact with the study participants and the diagnosing and/or treating physicians. Participating HCPs followed their participating patients in accordance with customary proce-dures for newly inserted IUDs. To capture information relating to the routinely conducted post-insertion examina-tion during the first year, follow-up questionnaires were sent 1 year after insertion to the clinician. The clinician was asked to record information on checkup dates, IUD position, diagnosed perforations and patients' medical conditions for those patients who had returned to the respective clinician during the first year post-insertion. The clinician was not required to actively follow-up patients who did not come back for a postinsertion checkup.

In order to minimize loss to follow-up, a multifaceted, four-level follow-up process was used. The first level consists of mailing the follow-up questionnaire, as well as two reminder letters in case of no response. If these actions did not reinstate contact with the women, multiple level 2 attempts are made to contact the women by phone or, if necessary, their friends/relatives who were listed as additional contacts, in addition to the gynecologists/primary care physicians. Parallel level 3 activities consist of searches in national and international telephone and address directories. If they are not successful, an official address search via the respective governmental

administration is conducted. This level 4 activity can provide information on new addresses (or emigration or death).

2.5. Study size and evaluation

The study was powered to test noninferiority of LNG-IUSs regarding the perforation risk in comparison to copper IUDs. The null hypothesis to be tested was: risk ratio $(RR)_{Perf} \geq 2$ (i.e., the perforation incidence ratio for LNG-IUD vs. copper IUD is higher than or equal to 2). The alternative hypothesis was: $RR_{Perf} < 2$. Sample size calculations for a two-group test of equivalence in proportions showed that a total of approximately 60,000 insertions would be needed. These calculations were based on a perforation rate of 0.5 per 1000 insertions, a 1-to-1 ratio between LNG and copper IUD users, a one-sided α of 0.025 and a power of 0.80.

Crude as well as adjusted relative risks were calculated using a logistic regression model. The appropriate confounding variables (see Section 3.2.) were included in the model. Based on the expectation of a small absolute number of perforations, the number of confounding variables was limited to a small number of predefined risk factors as recommended by the independent Safety Monitoring and Advisory Council. In addition, a sensitivity analysis was performed with other potential baseline risk factors to check the appropriateness and robustness of the primary analysis. A backward stepwise approach was used in which all prognostic factors that did not change the point estimate of the RR by more than 10% or that had no statistically significant impact (p>0.10) were removed. This approach was taken solely for exploratory reasons. All analyses were performed using STATA 11.0 and SAS 9.1. This report complies with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies [10].

3. Results

Recruitment started in Germany and Austria in 2006, the United Kingdom and Finland in 2008, Sweden in early 2009 and Poland in November 2009. Recruitment stopped at the end of 2012.

A total of 63,194 women at 1230 study centers agreed to participate in the study. Overall, 1746 (2.8%) were excluded because of protocol violations (e.g., no newly inserted IUD, age under 18 years, no informed consent, duplication). The remaining 61,448 quality-controlled computerized data sets (one per woman) with baseline information were analyzed.

Table 1
Baseline characteristics of the study population by cohorts

Baseline characteristics	LNG IUS		Copper IUD	
	%	95% CI	%	95% CI
Age (years)				
<20	0.9	(0.8–1.0)	2.0	(1.8–2.2)
20–29	15.9	(15.5–16.2)	32.0	(31.3–32.7)
30–39	39.6	(39.1–40.0)	42.4	(41.7–43.1)
40–49	40.9	(40.5–41.4)	22.7	(22.1–23.3)
≥50	2.7	(2.5–2.9)	0.9	(0.8–1.0)
BMI <20	5.7	(5.5–5.9)	6.9	(6.6–7.3)
BMI≥20 & <25	46.8	(46.3–47.2)	49.5	(48.7–50.2)
BMI≥25 & <30	30.1	(29.7–30.6)	28.3	(27.6–28.9)
BMI≥30 & <35	11.1	(10.8–11.4)	10.2	(9.8–10.7)
BMI≥35	6.1	(5.9–6.3)	4.8	(4.5–5.1)
Current smoker	23.2	(22.9–23.6)	24.2	(23.6–24.8)
Heavy smoker (>15 cigarettes per day)	4.0	(3.8–4.1)	4.0	(3.7–4.2)
Ex-smoker	21.0	(20.6–21.4)	18.8	(18.2–19.4)
Low (no university entrance level)	48.7	(48.2–49.2)	41.6	(40.9–42.3)
Mid (university entrance level)	23.0	(22.6–23.4)	26.0	(25.4–26.6)
High (university)	26.7	(26.2–27.1)	29.6	(28.9–30.2)
Ever cesarean delivery	19.6	(19.2–20.0)	17.6	(17.0–18.1)
Cesarean delivery at most recent pregnancy	14.3	(13.9–14.6)	12.9	(12.4–13.4)
Ever pregnant	93.0	(92.7–93.2)	88.0	(87.5–88.4)
Delivery 36 weeks or less before IUD insertion	17.3	(16.9–17.6)	24.7	(24.1–25.4)
Delivery 1 year or less before IUD insertion	19.8	(19.5–20.2)	28.7	(28.1-29.4)
Currently breastfeeding	9.2	(8.9–9.5)	14.6	(14.1–15.1)
Ever hormonal contraception use	91.8	(91.6–92.1)	81.6	(81.0–82.2)
Self-reported history of				
Inflammation of ovaries/fallopian tubes	3.0	(2.8–3.2)	2.2	(2.0–2.4)
Endometriosis	2.2	(2.1–2.4)	0.7	(0.6–0.8)
Benign uterus tumor	6.8	(6.6–7.1)	2.8	(2.6–3.1)
Inflammation of intestine	1.8	(1.7–1.9)	1.3	(1.1–1.5)

This was sufficient to perform the a priori planned analyses. At study entry, 43,078 women received an LNG-IUS (70.1%); and 18,370, a copper IUD (29.9%). More than 30 types of copper IUDs were included in the copper IUD cohort, the most frequent ones being NovaT (200 or 380) with 37%, T Safe Cu 380 with 18% and Multiload CU (250 or 375) with 14%. The percentage of first-time users was 46.3% and 52.0% for LNG and copper, respectively.

Validated follow-up information was collected on 60,213 women: 42,353 users of LNG-IUSs and 17,860 users of copper IUDs who contributed 68,372 women-years of observation. In total, 1235 women, or 2.0% (1.7% for LNG-IUS, 2.8% for copper IUD), were lost to follow-up during the 1-year follow-up period.

3.1. Baseline characteristics

The LNG-IUD cohort had a higher mean age (37.4 years) than the copper IUD cohort (33.3 years) and contained a higher proportion of women over the age of 40 (Table 1). For example, LNG-IUS users were less likely than copper IUD users to have never been pregnant (7.0% and 12.0%, respectively) and to have delivered in the 12 months before insertion (19.8% and 28.7%, respectively). The age difference between the cohorts also partially explains the smaller percentage of LNG-IUS users (9.2%) who were breastfeeding at the time of insertion in comparison to copper IUD users (14.6%).

3.2. Follow-up data

Overall, 81 perforations were identified during the 1-year follow-up after insertion, of which 61 occurred during LNG-IUS use and 20 during copper IUD use. Eighty percent of these perforations were complete perforations. The proportion per 1000 insertions was 1.4 [95% confidence interval (CI): 1.1–1.8] for LNG-IUSs and 1.1 (95% CI: 0.7–1.7) for copper IUDs. The crude relative risk for LNG-IUSs versus copper IUDs was 1.3 (95% CI: 0.8–2.2).

A model containing the predefined prognostic factors of age, BMI, breastfeeding at time of insertion and parity (referred to as 'Model 1') yielded an adjusted RR of 1.6 (95% CI: 1.0–2.7). A second model containing the variables age, BMI, time since last delivery and HCP experience (referred to as 'Model 2') did not substantially change the RR (1.7; 95% CI: 1.0–2.8). Therefore, a twofold higher risk of uterine perforation with LNG-IUS use compared to copper IUD use cannot be excluded. Alternative analyses using a backward stepwise procedure to select prognostic factors yielded almost identical results.

Only a small proportion of the perforations in both cohorts (9% of LNG-IUS and 20% of copper IUD perforation cases) were diagnosed during or immediately after insertion; most perforations were reported only at follow-up. The perforation risk was significantly higher in women who were using an IUD for the first time compared to women who had used an IUD previously. After adjusting for time since last delivery and breastfeeding status at time of insertion, the higher risk among first-ever users remained statistically significant (hazard ratio: 2.6; 95% CI: 1.5–4.4).

3.3. Breastfeeding/time since last delivery

Thirty-five of the total 81 perforations occurred in women who were breastfeeding: the incidence was 6.3 (95% CI: 4.1–9.3) for LNG-IUSs and 3.7 (95% CI: 1.8–6.8) for copper IUDs per 1000 insertions among breastfeeding women. The incidence in parous women who were not breastfeeding was 1.0 (95% CI: 0.7–1.4) for LNG-IUSs and 0.5 (95% CI: 0.2–1.0) for copper IUDs (Fig. 1). The relative perforation risk for women breastfeeding versus not breastfeeding was 6.1 (95% CI: 3.9–9.6); the respective relative risks for LNG-IUS and copper IUD users were 6.3 (95% CI: 3.8–10.5) and 7.8 (95% CI: 2.8–21.4).

Women who were breastfeeding at the time of insertion were also more likely to have delivered in closer temporal proximity to IUD insertion. Therefore, further stratified analyses using time intervals of ≤36 weeks and >36 weeks were conducted to assess the independent effects of these factors on perforation risk (Table 2). The decision to dichotomize the data at 36 weeks since delivery was made following inspection of the data and was not governed by clinical guidelines or a priori hypotheses.

Among breastfeeding women, the perforation incidence was 5.6 (95% CI: 3.9–7.9) and 1.6 (95% CI: 0.0–9.1) per 1000 women who had delivered ≤36 weeks and >36 weeks prior to insertion, respectively. Among women who were not breastfeeding at the time of insertion, the corresponding figures were 1.7 (95% CI: 0.8–3.1) and 0.7 (95% CI: 0.5–1.1), respectively, for the two interval strata (≤36 and >36 weeks).

Breastfeeding and time since last delivery were independently associated with perforation risk. In summary, risk estimates showed an important increase for breastfeeding versus non-breastfeeding women at ≤36 weeks since last delivery and for non-breastfeeding women at ≤36 weeks versus >36 weeks since last delivery.

3.4. Other prognostic factors

A stratified analysis was performed to assess potential differences in perforation risk for patients with clinicians who inserted fewer than 50 IUDs per year versus those who inserted 50 or more IUDs per year for each user cohort. The results suggest that patients of more experienced clinicians were less likely to suffer perforation, regardless of IUD type (Table 3). Other potential confounding variables such as dilatation and the use of anesthesia were assessed in univariate analyses, but no significant associations with perforation risk were identified. In both cohorts, the RRs comparing users with and without previous cesarean sections (ever and at last delivery) were neither statistically significantly decreased nor increased (data not shown).

3.5. Sequelae

For both cohorts, more than 50% of perforations were diagnosed within the first 2 months of IUD insertion. The time interval between insertion and diagnosis did not differ substantially between cohorts.

In most cases of perforation in our study, the IUDs were removed laparoscopically (72% of LNG and 58% of copper cases). Laparotomy was rare in both cohorts (3% and 5%, respectively). A substantial number of perforated IUDs could be removed transvaginally via the strings (12% and 21%, respectively), most commonly in cases of partial perforation.

None of the perforations resulted in serious sequelae, such as bowel or bladder injury, septicemia or peritonitis.

4. Discussion

Perforation rates for the more than 60,000 participating women were low (1.4 per 1000 insertions in LNG-IUS users/ 1.1 per 1000 insertions in copper IUD users), and no serious complications were associated with any of the 81 perforations observed. Besides a few partial perforations and embedded IUDs, the vast majority of these perforations were complete perforations.

The risk of perforation reported here is within the range previously observed (0.3 to 2.6 per 1000 insertions). Using prescription event monitoring (PEM) data, Harrison-Woolrych found 0.3 per 1000 insertions for LNG-IUS and 0.6 for copper IUD users at time of insertion [2]. Kaislasuo et al. found 0.4 per 1000 insertions for both types of IUD in a retrospective population-based registry study [4]. Another study of copper IUD users reported a perforation risk of 2.2 per 1000 insertions [1]. Zhou et al. found an LNG-IUS perforation incidence of 0.9 per 1000 insertions in a New Zealand population using PEM data [6], and van Houdenhoven et al. reported 2.6 for a Dutch population [5]. Because our study had a large patient base, used prospective sampling directly from the population and had the greatest depth of information regarding potential confounding factors, the risk estimates found here may be regarded as a more robust and current estimate.

The strongest risk factors for uterine perforation were breastfeeding at time of insertion and a time since last delivery of less than 36 weeks. These two factors were associated with a similar risk increase. Heartwell et al. found a 10-fold increase in perforation risk for women breastfeeding at the time of insertion but could find no risk differences for lactating women who had delivered less than 2 months before IUD insertion compared to more than 2 months. The authors concluded that breastfeeding rather than time since last delivery is associated with perforation risk [7].

In most cases of perforation in our study, the IUDs were removed by laparoscope. This finding corresponds with the results of other studies. For example, Van Grootheest reports

that laparoscopy was used in 70% of perforation cases with known IUD removal methods [11].

Relative risk estimates in observational studies that are close to unity do not allow differentiation between causation, bias and confounding [12,13]. In general, it is very difficult to interpret a relative risk of two or less in such research [14–18].

In seeking to address these difficulties, the EURAS-IUD study combines several methodological strengths that contribute to the validity of the results: (a) a prospective, comparative cohort design; (b) detailed information on potentially important confounders relevant for the final statistical models (e.g., breastfeeding status, date of last delivery); (c) validation of outcomes of interest; (d) comprehensive follow-up procedure and very low loss to follow-up to minimize underreporting; (e) a study population representative for IUD users under routine clinical conditions and (f) supervision by an independent Safety Monitoring and Advisory Council as well as scientific independence from the study funder.

In addition to these methodological strengths, special attention was paid to typical biases. The approach used in the EURAS-IUD study probably means that selection bias was not a major issue. Participation by gynecologists, midwives and specialized clinics yielded a representative mix of those who prescribe and insert IUDs. Enrollment bias is also unlikely to have substantially affected the results. Sites consecutively enrolled patients who were willing to participate and who fulfilled the other eligibility criteria.

In order to reduce channeling (referral) bias, factors associated with the selection of LNG versus copper IUDs, and also with any of the study outcomes of interest, were measured at baseline and accounted for in multivariate analyses.

A low overall loss to follow-up rate of 2% was achieved, in part due to the advantageous study design that enabled follow-up with the study participants to be maintained even if they did not return to the center that enrolled them. In
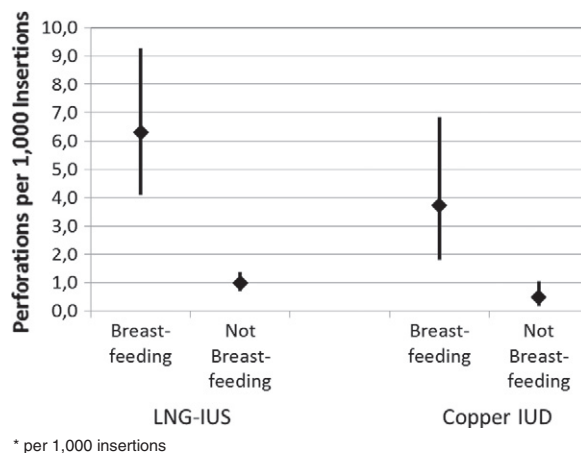

Fig. 1. Perforation incidence* with 95% CI stratified by IUD and breastfeeding at time of insertion.

Table 2
Perforation incidence[a] and RRs stratified by breastfeeding status and time since last delivery interval

Time since last delivery	Breastfeeding		
	Yes	No	RR (95% CI)
≤36 weeks	5.6 (3.9–7.9)	1.7 (0.8–3.1)	3.3 (1.6–6.7)
>36 weeks	1.6 (0.0–9.1)	0.7 (0.5–1.1)	2.2 (0.3–16.3)
RR (95% CI)	3.4 (0.5–24.8)	2.3 (1.1–4.7)	

[a] Per 1000 insertions.

theory, a disproportionately high percentage of serious adverse events (SAEs) could have occurred in those patients who were lost to follow-up because significant events (e.g., pregnancy) could have been the reason for the break in contact with the investigators.

Misclassification bias probably had no substantial impact on the results given that precise information on the exposure and the outcomes of interest was available. By contrast, it is impossible to exclude diagnostic bias. Clinical symptoms of perforations cover the spectrum from complete absence or unspecific, slight symptoms to prominent symptoms [1,5,7,11]. Increased awareness of perforation risks among LNG-IUS users, especially after a warning letter was issued in Germany during the early recruitment phase, might have led to more intensive diagnostic scrutiny and therefore to more detected perforations, especially asymptomatic ones. This potential bias could have led to an overestimation of the relative risk for the LNG-IUS cohort compared to the copper cohort.

During the study period, no LNG-medicated IUDs releasing less than 20 mcg LNG daily were on the market in the participating countries. Therefore, only limited inferences to LNG containing IUDs with a daily release rate of less than 20 mcg LNG can be made based on these study results.

5. Conclusion

No substantial difference in uterine perforation risk was evident between LNG-IUSs and copper IUDs during routine clinical use. Breastfeeding and proximity to a recent delivery (up to 36 weeks) were both independently associated with an increased risk of uterine perforation. The presence of these two factors in combination was associated with an additive increase; however, even among women with both of these risk factors, perforation remains rare. From a public health perspective, the most important finding may be the rarity of perforation and the absence of serious sequelae if perforation occurred.

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Table 3
Perforation incidence stratified by experience of inserting clinician

IUD insertions per year	LNG IUS			Copper IUD		
	N	Incidence[a]	95% CI	N	Incidence[a]	95% CI
<50	36	1.9	(1.3–2.56)	15	1.5	(0.8–2.5)
≥50/year	21	1.1	(0.7–1.7)	3	0.6	(0.1–1.7)
Unknown	4	0.8	(0.2–2.1)	2	0.6	(0.1–2.3)

[a] Per 1000 insertions.