BJU Int 2024; **134:** 229–238 doi:10.1111/bju.16303

BJUI
BJU International

Original Article

Cumulative incidence of and risk factors for BCG infection after adjuvant BCG instillations

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Objectives

To investigate the cumulative incidence proportion of disseminated or local Bacillus Calmette-Guérin (BCG) infections after adjuvant BCG instillations in patients with non-muscle-invasive bladder cancer (NMIBC).

Patients and Methods

We analysed the timing and occurrence of BCG infections and absolute and relative risk in relation to patient characteristics available in the Swedish nationwide database 'BladderBaSe 2.0'. The cumulative incidence proportion of a BCG infection was indicated by a reported diagnosis of tuberculosis (TB) in the patient registry or filing a prescription for tuberculostatic drugs.

Results

The cumulative incidence proportion was 1.1% at the 5-year follow-up in 5033 patients exposed to adjuvant BCG instillations. The incidence rate was highest during the first 2 years after start of BCG instillations. Women had a lower risk than men (hazard ratio 0.23, 95% confidence interval 0.07–0.74). Age and calendar time at diagnosis, comorbidity, tumour risk group, previous medication with corticosteroids, immunosuppressive drugs, or time between transurethral resection of the bladder tumour and commencing the adjuvant BCG instillation were not associated with risk.

Conclusions

These data further supports that the overall risk of a BCG infection after BCG-instillation treatment for NMIBC is low. The great majority of infections occur in the first 2 years, calling for an awareness of the diverse symptoms of BCG infection during this period. We provide evidence for male sex as a risk factor; however, the statistical precision is low and with a risk of selection bias, making it difficult to rule out the other suggested risk factors without further studies with different approaches.

Keywords

non-muscle-invasive bladder cancer, BCG instillations, local or systemic BCG infections, cumulative incidence proportion, risk factors

Introduction

Bacillus Calmette-Guérin (BCG) is a live attenuated strain of *Mycobacterium Bovis* belonging to the *Mycobacterium tuberculosis* complex, and disseminated or local BCG infection is a potentially serious complication after adjuvant BCG instillations for non-muscle-invasive bladder cancer (NMIBC). Observational studies in institutional series [1–3], multicentre settings [4] and nationwide observational studies [5,6] have estimated the risk to be between 1% [4,5] and 4.3%

[2]. The Finnish nationwide study [6] found that risk may have increased in 2007–2016 relative to 1996–2006. Randomised controlled trials (RCTs) comparing efficacy of delivering BCG with or without antibiotic prophylaxis [7,8], with different dose and timing [9] or comparing BCG to chemotherapy instillations [10] estimate BCG-related pulmonary infections and disseminated BCG infection to occur at between 0.2% [10] and 11% in a study arm without antibiotic prophylaxis [8].

The variation of the risk estimates has several sources: different definitions of BCG infection; estimation of crude risks only; the majority of studies do not provide the point in time of follow-up for the risk estimate. There is evidence that most serious BCG infections occur early [2,11,12], but none of the studies present a cumulative incidence curve to describe the development of risk over time. To our knowledge, no study has reported the risk of a BCG infection expected in the relevant source population for the cohorts investigated.

Apart from finding male sex to be a risk factor in the nationwide Danish study [5], risk factors have only been studied in smaller cohorts with limited statistical precision [2,3].

We analysed the incidence of BCG infections in a Swedish national cohort of patients with NMIBC, exposed or not exposed to adjuvant BCG instillations, compared to a matched comparison cohort from the background population. The aims were to characterise the timing and occurrence of BCG infections in terms of absolute and relative risk, risk by calendar time of diagnosis and in relation to patient characteristics available in the research database 'BladderBaSe 2.0' [13].

Patients and Methods

Participants

Eligible for the study were patients consecutively reported between 1 January 2008 and 31 December 2019 to the Swedish National Register for Urinary Bladder Cancer (SNRUBC) as having NMIBC without distant or lymph node metastases (M0 and N0 status), requiring that distant and lymph node status was known. Additional exclusion criteria were cystectomy as primary treatment, and tuberculosis (TB) diagnosis or TB medication registered from 30 days before until 60 days after bladder cancer diagnosis.

Data Sources

The SNRUBC is a clinical database for audit and research. All Swedish units treating bladder or upper urinary tract cancers report to the database. The reporting to the SNRUBC is continuously validated by matching to the National Cancer Register, to which reporting of malignant tumours is mandated by law. For 2017–2019, >98% of bladder cancers reported to the National Cancer Register were accounted for in the SNRUBC, which holds detailed information on tumour characteristics and primary treatment.

The BladderBaSe 2.0 is a research database including the patients in the SNRUBC diagnosed 1 January 1997 through to 31 December 2019 individually linked to several Swedish national data sources as described in a cohort profile [13]. For this study we used the linkage to: the Patient Register for information on hospital in- and out-patient diagnoses; the Swedish Prescribed Drug Register holding information on all prescribed drugs dispensed at pharmacies; the Swedish Household Census and the Register of Total Population and Population Changes for vital status and data on immigration and emigration; the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) for information on socioeconomic status.

The BladderBaSe 2.0 also includes a comparison cohort from the background population. For each patient with NMIBC, five persons without NMIBC at the date of diagnosis for the patient matched for age, sex and region of residence were randomly selected. The comparison cohort was matched to the same national databases as the cohort of patients with NMIBC not treated with BCG of which some were receiving adjuvant chemotherapy instillations as primary treatment.

Exposure and Outcome

The exposure is treatment of NMIBC with adjuvant BCG instillations. The register holds the starting date for such treatment, although information about which BCG strain, dose and number of instillations are not available.

For the primary outcome we first sought for a diagnosis of mycobacterial infection in the patient register (International Classification of Diseases [ICD]-10 codes A15–A19) after a diagnosis of NMIBC, and after the corresponding index date for the comparison cohort. We used the codes for TB infection, as there is no specified ICD code for BCG infection and such cases will be assigned codes A15–A19 in the registry. We then further sought a date for the first filing of a prescription for the following Anatomical Therapeutic Chemical (ATC) codes: J04AK (Other drugs for treatment of tuberculosis); J04AM (Combinations of drugs for treatment of tuberculosis); J04AB (Group of antibiotics specifically used in tuberculosis, except streptomycin); and J04A (Hydrazides). The primary outcome was defined as the earliest date when either the five sought for events in the patient register or prescribed drug register described above appeared.

In a second analysis to find an outcome indicator for severe mycobacterial infection we sought for patients with an ICD-

10 code A15–A17 (assuming that local infections dominate in code A18) or treated with drugs for mycobacterial infection at ≥6 months, by adding a further criterion of at least 180 defined daily doses (DDD) in a 210-day time frame. For the combination of J04AB and J04AC drugs the 28-day window was replaced by a requirement of at least 180 DDD for either of the two drugs and a further requirement of at least 90 DDD in a 210-day look-back window.

In a sensitivity analysis we aimed to also capture cases that may have had only one drug prescribed, and the other drugs in a combined treatment delivered in an out-patient clinic, which is not captured in the Prescribed Drug Register. For this purpose, we relaxed the condition regarding the combination of the J04AB and J04AC drugs within a 28-day window and considered the outcome to be the first date when an ICD-10 codes A15–A19 was found in the patient registry or when a prescription code of either J04AK, J04AM, J04AB, or J04AK was found in the prescribed drug registry.

Co-Variates of Interest

Besides age at diagnosis and sex, we extracted tumour risk group, treatment with serial adjuvant chemotherapy instillations and calendar period of diagnosis from the SNRUBC. Educational level (mandatory school, high school, or university) and civil status from the LISA database were used as indicators of socioeconomic status. Country of birth was stratified as follows: Sweden, Nordic countries except Sweden, Europe, and outside Europe. A previous diagnosis of TB, recent (within 18 months before diagnosis) exposure to corticosteroids or immunosuppressive drugs (ATC-codes H02AB and L04A, respectively), and time between transurethral resection of bladder tumour (TURBT) and start of BCG instillation were also considered to be potentially influential factors.

The Charlson Comorbidity Index (CCI) [14] was calculated based on diagnoses reported to the Patient Register from 10 years before diagnosis or the index date of the case for the members of the comparison cohort. We used the adaptation of CCI to Swedish registries made by Ludvigsson et al. [15] based on ICD-9 and ICD-10 codes, in which the CCI is a sum of points given for the following diagnoses (with points in parenthesis): Cerebrovascular disease (1), Congestive heart failure (1), Chronic obstructive pulmonary disease (1), Dementia (1), Diabetes (1), Mild liver disease (1), Myocardial infarction (1), Other chronic pulmonary diseases (1), Peripheral vascular (1), Rheumatic disease(1), Ulcer (1), Hemiplegia (2), Severe kidney disease (2), Severe liver disease (3), AIDS (6), Malignancy (except bladder cancer) (2), Metastatic cancer (6).

We further assessed a Drug Comorbidity Index (DCI) using the Prescribed Drug Register. The DCI is based on the prescription of 106 drugs in a 1-year interval preceding start of follow-up and has a better discrimination for overall mortality than the CCI [16,17].

The WHO 1999 grading system is applied in Sweden, and tumour risk groups were stratified as low risk (low malignant potential [LMP]/G1 and Ta), intermediate risk (TaG2), and high risk (TaG3 or T1 [any grade] or carcinoma *in situ* [CIS]), respectively.

Statistical Methods

Only adjuvant BCG instillations performed less than a 1 year from diagnosis were included. Follow-up started on date of BCG instillation, and this date was inherited by the five matched persons without NMIBC. Follow-up ended at the date of event, date of death or 31 December 2019, whichever came first. In case a matched person was diagnosed with bladder cancer during follow up, that person was censored at the day of bladder cancer diagnosis. Cumulative incidence proportions with 95% (CIs) were used to account for death without a prior event [18]. Incidence was calculated as the ratio between number of events and sum of person-years in follow-up time. In the Cox-regression models, death without a prior event was considered a censoring event. A series of sensitivity analyses were performed according to the outcome definitions above. Calendar time trends were compared by log-rank test.

Ethical Statement

The study was approved by the Research Ethics Board of Uppsala University, Sweden (EPN 2015/277 and 2022-01747-02).

Results

Baseline Characteristics

Table 1 show the baseline characteristics for 5033 patients exposed to adjuvant BCG-instillations and 15 391 patients with NMIBC not exposed to BCG as primary treatment and the corresponding data for their respective, matched comparison cohorts. There were 54 primary outcomes among patients with NMIBC exposed to adjuvant BCG, 27 among patients with NMIBC not exposed, and 17 and 10 in their respective comparison cohorts.

Those exposed were on an average slightly younger and more often males than the unexposed patients with NMIBC while both groups had the same age and sex as their respective comparison cohorts due to the matching. The exposed had somewhat lower CCI and DCI scores than the unexposed patients with NMIBC, but both had more comorbidities than their comparison cohort referents.

Table 1 Baseline characteristics of the patients with NMIBC exposed to BCG instillations, patients with NMIBC not exposed to BCG as primary treatment, and their respective matched comparison cohorts.

Characteristic	BCG treated NMIBC (*n* = 5033)	Matched comparison cohort (*n* = 23 144)	NMIBC without primary BCG treatment (*n* = 15 391)	Matched comparison cohort (*n* = 69 966)	All (*n* = 113 534)
Calendar year, *n* (%)					
2008–2010	923 (18.3)	4196 (18.1)	3409 (22.1)	15 366 (22.0)	23 894 (21.0)
2011–2013	1125 (22.4)	5149 (22.2)	3644 (23.7)	16 523 (23.6)	26 441 (23.3)
2014–2016	1327 (26.4)	6102 (26.4)	4085 (26.5)	18 614 (26.6)	30 128 (26.5)
2017–2019	1658 (32.9)	7697 (33.3)	4253 (27.6)	19 463 (27.8)	33 071 (29.1)
Sex, *n* (%)					
Male	4028 (80.0)	18 432 (79.6)	11 313 (73.5)	51 253 (73.3)	85 026 (74.9)
Female	1005 (20.0)	4712 (20.4)	4078 (26.5)	18 713 (26.7)	28 508 (25.1)
Age (years), *n* (%)					
≤64	871 (17.3)	3571 (15.4)	2853 (18.5)	11 392 (16.3)	18 687 (16.5)
65–69	795 (15.8)	3600 (15.6)	2236 (14.5)	9860 (14.1)	16 491 (14.5)
70–74	1152 (22.9)	5318 (23.0)	2839 (18.4)	13 064 (18.7)	22 373 (19.7)
75–79	1047 (20.8)	4969 (21.5)	2791 (18.1)	13 026 (18.6)	21 833 (19.2)
80–84	752 (14.9)	3640 (15.7)	2391 (15.5)	11 589 (16.6)	18 372 (16.2)
≥85	416 (8.3)	2046 (8.8)	2281 (14.8)	11 035 (15.8)	15 778 (13.9)
CCI score, *n* (%)					
0	2568 (51.0)	13 072 (56.5)	7110 (46.2)	39 028 (55.8)	61 778 (54.4)
1	883 (17.5)	3655 (15.8)	2687 (17.5)	11 355 (16.2)	18 580 (16.4)
2	934 (18.6)	3616 (15.6)	2988 (19.4)	11 067 (15.8)	18 605 (16.4)
3	379 (7.5)	1550 (6.7)	1345 (8.7)	4673 (6.7)	7947 (7.0)
3+	269 (5.3)	1251 (5.4)	1261 (8.2)	3843 (5.5)	6624 (5.8)
DCI score, *n* (%)					
<0.4	1059 (21.0)	6065 (26.2)	2829 (18.4)	18 097 (25.9)	28 050 (24.7)
0.4–1.15	1275 (25.3)	6037 (26.1)	3740 (24.3)	17 623 (25.2)	28 675 (25.3)
1.15–2.5	1408 (28.0)	5556 (24.0)	4063 (26.4)	16 805 (24.0)	27 832 (24.5)
≥2.5	1291 (25.7)	5486 (23.7)	4759 (30.9)	17 441 (24.9)	28 977 (25.5)
Educational level, *n* (%)					
Low	1766 (35.1)	8463 (36.6)	5986 (38.9)	26 473 (37.8)	42 688 (37.6)
Middle	2116 (42.0)	9030 (39.0)	6003 (39.0)	26 589 (38.0)	43 738 (38.5)
High	1086 (21.6)	5368 (23.2)	3203 (20.8)	15 982 (22.8)	25 639 (22.6)
Missing	65 (1.3)	283 (1.2)	199 (1.3)	922 (1.3)	1469 (1.3)
Civil status, *n* (%)					
Unmarried/single	523 (10.4)	2592 (11.2)	1621 (10.5)	7629 (10.9)	12 365 (10.9)
Married/registered partners	3100 (61.6)	13 875 (60.0)	8676 (56.4)	39 914 (57.0)	65 565 (57.7)
Divorced/widowed	1408 (28.0)	6671 (28.8)	5087 (33.1)	22 406 (32.0)	35 572 (31.3)
Missing	2 (0.0)	6 (0.0)	7 (0.0)	17 (0.0)	32 (0.0)
Country of birth, *n* (%)					
Sweden	4335 (86.1)	20 286 (87.7)	13 096 (85.1)	61 480 (87.9)	99 197 (87.4)
Other Nordic countries	209 (4.2)	1078 (4.7)	681 (4.4)	3272 (4.7)	5240 (4.6)
Europe	336 (6.7)	1121 (4.8)	1078 (7.0)	3256 (4.7)	5791 (5.1)
Other	153 (3.0)	659 (2.8)	536 (3.5)	1958 (2.8)	3306 (2.9)
History of TB, *n* (%)					
No	5031 (100.0)	23 134 (100.0)	15 379 (99.9)	69 917 (99.9)	113 461 (99.9)
Yes	2 (0.0)	10 (0.0)	12 (0.1)	49 (0.1)	73 (0.1)
History of previous immunosuppressants (code L04A)					
6 months, *n* (%)					
No	4963 (98.6)	22 710 (98.1)	15 079 (98.0)	68 737 (98.2)	111 489 (98.2)
Yes	70 (1.4)	434 (1.9)	312 (2.0)	1229 (1.8)	2045 (1.8)
6–18 months prior, *n* (%)					
No	4946 (98.3)	22 657 (97.9)	15 041 (97.7)	68 632 (98.1)	111 276 (98.0)
Yes	87 (1.7)	487 (2.1)	350 (2.3)	1334 (1.9)	2258 (2.0)
History of previous glucocorticoids (code H02AB)					
6 months, *n* (%)					
No	4715 (93.7)	21 545 (93.1)	14 022 (91.1)	65 271 (93.3)	105 553 (93.0)
Yes	318 (6.3)	1599 (6.9)	1369 (8.9)	4695 (6.7)	7981 (7.0)
6–18 months prior, *n* (%)					
No	4571 (90.8)	20 921 (90.4)	13 834 (89.9)	63 807 (91.2)	103 133 (90.8)
Yes	462 (9.2)	2223 (9.6)	1557 (10.1)	6159 (8.8)	10 401 (9.2)

It was more common for the exposed patients with NMIBC to cohabitate with a partner than for the unexposed, with both having similar civil status as their comparison cohorts. Only a very few individuals with NMIBC exposed (two) and not exposed to BCG (12) had a history of TB.

We divided the window of exposure for glucocorticoids and immunosuppressive drugs into 6 months and 6–18 months prior to diagnosis to detect if a policy of modifying such treatments to optimise the effect of the adjuvant BCG instillations had been applied. A smaller proportion of patients were on corticosteroids 6 months prior to diagnosis and adjuvant BCG instillations compared to 6–18 months prior, but the same was observed in the comparison cohort in relation to the index date for the NMIBC diagnosis and to some degree also in patients with NMIBC not exposed to BCG (Table 1).

Cumulative Incidence Proportion and Incidence Rate

Figure 1 shows the cumulative incidence proportion of the primary outcome BCG infection. For those exposed to adjuvant BCG instillations, the cumulative incidence proportion increased rapidly during the first 2 years but then less quickly, corresponding to an incidence rate of 515 events/100 000 person years during the 0–2-year period and of 37 events/100 000 person years during the 3–6-year period (Table 2). The cumulative incidence proportion at

Fig. 1 Cumulative incidence proportion of the primary outcome BCG infection in patients with NMIBC exposed to BCG instillations, patients with NMIBC not exposed, and their respective matched comparison cohorts.

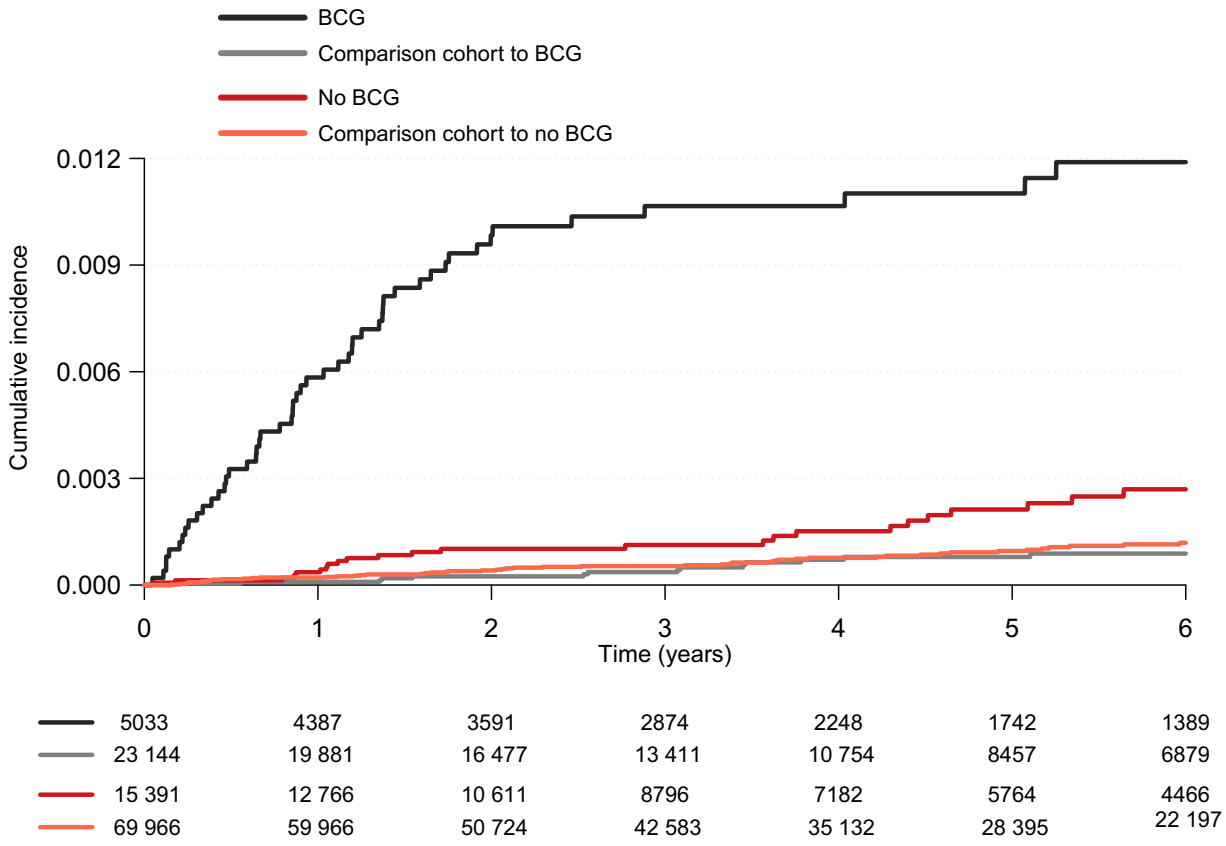

Table 2 Incidence rate (*n*/100 000 person-years) in different time intervals of follow-up and cumulative incidence proportion (95% CI) at 5 years of medication for a diagnosis in the Patient Register of BCG infection by exposure to BCG due to NMIBC, NMIBC without primary BCG exposure, and in their respective comparison cohorts.

Exposure	Incidence rate 0–2 years, *n*/100 000 person-years	Incidence rate 3–6 years, *n*/100 000 person-years	Cumulative incidence at 5 years, % (95% CI)
NMIBC, exposed to adjuvant BCG	515	37.1	11.0 (8.3–14.6
Comparison cohort	12.6	16.2	0.8 (0.5–1.4)
NMIBC, not exposed	50.6	25.1	1.8 (1.1–2.7)
Comparison cohort to NMIBC, not exposed	20.8	13.8	0.8 (0.6–1.1)

5 years was for those exposed 1.1%, 0.18% for those with NMIBC but unexposed, and 0.08% for their respective comparison cohorts (Table 2).

In the analysis to find instances of severe BCG infection (medical treatment over 6 months or a reported diagnosis of ICD-10-codes A15–A17), the cumulative incidence proportion at 5 years was for those exposed 0.38% (95% CI 0.23–0.61%), and 0.11% (95% CI 0.06–0.19%) for the patients with NMIBC not exposed with 0.05% and 0.04% for their corresponding comparison cohorts. The cumulative incidence curve rose rapidly during the first 2 years, but then levelled off (Fig. S1).

The sensitivity analysis with the broadest criteria for an event, showed a cumulative incidence proportion at 5 years for those exposed 2.09% (95% CI 1.7–2.57%) and 0.17% (95% CI 0.12–0.24%) for their comparison cohort. The corresponding estimates for the NMIBC cohort not exposed and their comparison cohort was 0.46% (95% CI 0.35–0.6%) and 0.21% (95% CI 0.18–0.25%), respectively. The incidence rate and risk pattern in relation to follow-up time was similar to the main analysis (Fig. 2 and Table S1).

We explored if unexposed patients with NMIBC receiving chemotherapy instillations differed from unexposed to BCG not receiving adjuvant chemotherapy instillations, but their outcome was very similar (data not shown).

Calendar Time of Treatment

The cumulative incidence proportion in those exposed to adjuvant BCG instillations by calendar period of treatment stratified by 3-year strata were similar (data not shown).

Risk Factors

Table 3 shows the hazard ratios (HRs) from a univariable and a multivariable Cox regression for patients with NMIBC exposed to adjuvant BCG instillations, analysing the risk of experiencing a BCG infection. In the multivariable model, we used educational level and DCI as proxies for socioeconomic status and comorbidity, respectively. For the primary outcome BCG infection, women had a statistically significant lower risk (HR 0.23, 95% CI 0.07–0.74). Age group or time between TURBT and start of instillations did not have an association

Fig. 2 Cumulative incidence proportion of the primary outcome as defined in the sensitivity analysis with the broadest criteria for an event in patients with NMIBC exposed to BCG instillations, patients with NMIBC not exposed, and their respective matched comparison cohorts.

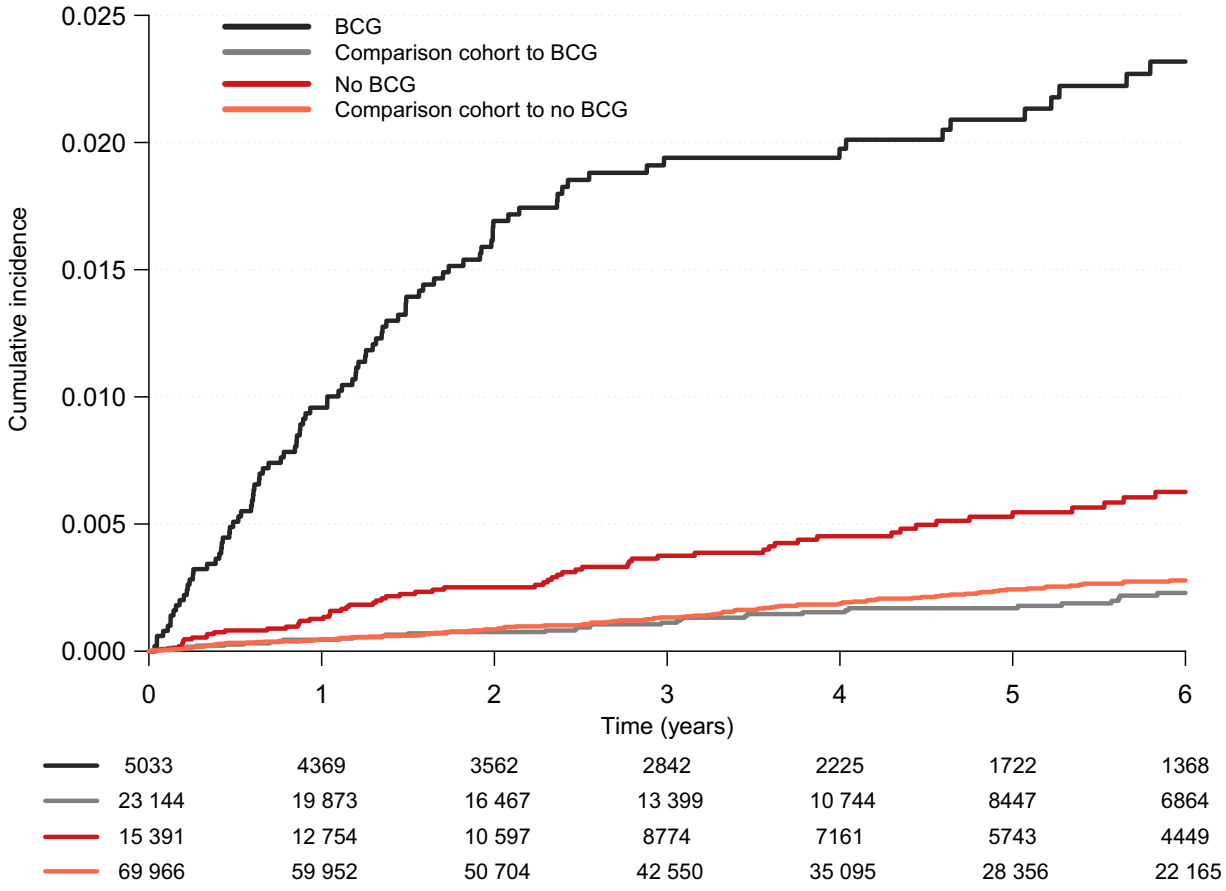

Table 3 The HRs with 95% CIs from uni- and multivariable Cox regression models for a BCG infection in relation to sex, age, DCI, time from TURBT to BCG-instillations, tumour risk group (low, LMP/TaG1; intermediate, TaG2; and high, CIS/TaG3/T1), DCI and medication with corticosteroids or immunosuppressive drugs (immunosuppressants [LO4A] or glucocorticoids [H02AB]), and educational level (mandatory school, high school or university) in patients with NMIBC exposed to BCG-instillations.

	N events	Univariable model HR (95% CI)	Multivariable model HR* (95% CI)
Sex			
Male	51	1.00 (Ref.)	1.00 (Ref.)
Female	3	0.23 (0.07–0.72)	0.23 (0.07–0.74)
Age (years)			
≤64	7	1.00 (Ref.)	1.00 (Ref.)
65–69	12	1.94 (0.77–4.94)	1.96 (0.77–5.00)
70–74	16	1.89 (0.78–4.60)	1.84 (0.75–4.50)
75–79	11	1.51 (0.58–3.90)	1.45 (0.56–3.78)
80–84	7	1.36 (0.48–3.89)	1.31 (0.45–3.79)
≥85	1	0.35 (0.04–2.87)	0.35 (0.04–2.84)
Time from TURBT to BCG instillations			
Q1: 1–35 days	18	1.00 (Ref.)	1.00 (Ref.)
Q2: 36–45 days	10	0.65 (0.30–1.41)	0.63 (0.29–1.36)
Q3: 46–62 days	11	0.68 (0.32–1.43)	0.63 (0.30–1.34)
Q4: 63–305 days	15	0.93 (0.47–1.85)	0.89 (0.45–1.76)
Tumour risk group			
Low	2	1.00 (Ref.)	1.00 (Ref.)
Intermediate	4	0.51 (0.09–2.78)	0.49 (0.09–2.70)
High	48	0.86 (0.21–3.54)	0.83 (0.20–3.45)
DCI			
Per unit increase	54	1.02 (0.87–1.21)	1.04 (0.87–1.23)
History of immunosuppressive medications			
No	49	1.00 (Ref.)	1.00 (Ref.)
Yes	5	0.74 (0.29–1.85)	0.73 (0.28–1.88)

**Adjusted for sex, age, time from TURB to BCG instillations, tumour risk group, DCI (continuous variable), History of immunosuppressive medications, and educational level. Ref. reference.*

with BCG infection or showed signs of having a regular trend with e.g., increasing age or increasing interval between TURBT and start of instillations; however, the CIs were wide and some of the point-estimates were far from unity as e.g., 1.94 for the age group 65–69 years or 0.65 for time interval of 36–45 days after TURBT. The estimates obtained in the uni- and multivariable models were similar. The same pattern emerged when a Cox model was applied using the wider criteria for an event in the sensitivity analysis (data not shown).

Discussion

Main Findings

The cumulative incidence proportion of a BCG infection as indicated by a reported diagnosis of TB in the ICD registry or filing a prescription for tuberculostatic drugs was 1.1% in a 5-year perspective in patients exposed to adjuvant BCG instillations. This is five to 10 times more common than in other patients with NMIBC or in a comparison cohort from the background population. The incidence rate was highest during the first 2 years of follow-up in those undergoing treatment with adjuvant BCG-instillations. There was no consistent time trend for a change of risk by calendar year of diagnosis. With the exception for a lower risk for women, we could not find a consistent pattern for risk associated with age at diagnosis, comorbidity, tumour risk group, previous medication with glucocorticoids, immunosuppressive drugs, or time between TURBT and commencing the adjuvant BCG instillation.

Strengths and Weaknesses

We included virtually all patients diagnosed with NMIBC in Sweden 2008–2019, with a complete follow-up through nationwide registers with high capture rates. This enabled us to calculate absolute risk and a cumulative risk pattern of BCG infection with stable 5-year estimates, accounting for censoring. The available data allowed for a multivariable regression analysis of risk factors, and the background population allowed us to estimate the baseline risk of TB in the population from which the NMIBC cohort arises.

Our outcome variables may have under-estimated the absolute risk: reporting of BCG infections to the Patient Register may be less strict from urological clinics where focus is on tumour control; in some institutions TB medication is delivered directly from a hospital out-patient unit to the patient to optimise compliance, and such an occasion goes undetected in the Prescribed Drug Register. Some instances of BCG infection may have been coded under ICD code A31

(other mycobacterial infections), which is not included in the database. We did not have access to bacteriological laboratory data or the mandatory reporting of TB infection to health authorities. However, BCG infections are not mandatory to report in Sweden and this register probably catches only few BCG infections. The lack of data on which BCG strain, dose, and number of instillations precludes an analysis of the influence of these components of the exposure. Our endpoints do not allow for a detailed analysis of which organs the BCG infection engaged, as we lacked information from the subdivisions of ICD-10 codes A15–A19. We also lacked data on the use of subsequent BCG instillations as second-line treatment for recurrent disease in the comparison cohort, which likely explain the occurrence of BCG - infections at follow-up in in this comparison cohort (Fig. 1).

Occurrence

The absolute risk of BCG infection after exposure to adjuvant BCG-instillations at 5 years in our study was 1.1%, which is similar to the estimates in the nationwide Danish and Finnish studies, which report a risk of 1% and 1.9%, respectively [5,6]. It is not clear to which timepoint of follow-up these estimates refer, and they are crude risks, but nevertheless in the same range as our estimates. An early observational study in 2602 patients from multiple centres reported a crude risk of 1.1% summing up pneumonitis and sepsis [4]. Two RCTs also reported low risks of what most probably are BCG infections (pulmonary infections and sepsis): 0.7% [9] and only one infection in 519 patients [10], both at a 3-year follow up.

Some studies report higher risks, but with data that are more difficult to compare to the other studies. Pérez-Jacoiste Asín et al. [2] estimated a crude risk of 4.3% in their institutional series of 256 patients but applied broader criteria of BCG infections such as early fever. Two small RCTs (72 and 115 patients, respectively), testing prophylactic treatment with quinolones to decrease side-effects of BCG instillations and increase compliance, reported the need for tuberculostatic drug treatment within 3 months of follow-up at a level of 11% [8] and 8.6% [7]. Thus, with our study accumulating evidence from larger cohorts indicate a lower overall risk.

The unexposed patients with NMIBC also had an increased risk compared to their comparison cohort. This is expected as some of these patients may have had adjuvant BCG instillations later during the disease course for recurrences after failing intravesical chemotherapy instillations, where BCG frequently is applied as a second-line treatment, although not caught by the SNRUBC clinical database. The low risk in the comparison cohort indicates that about nine out 10 instances of need for tuberculostatic drugs or reported with a mycobacterial infection to the Patient Register is due to the treatment in patients exposed to adjuvant BCG instillations.

Development of Risk over Follow Up Time

Our data corroborate earlier indications that the risk of BCG infection is highest in the first years of follow-up, but then occurs also—but seldom—during at least 5 years after BCG treatment. It is interesting that the incidence changes so abruptly after 2 years of follow-up. This was true for the primary outcome, as well as for the wider definition of an event, and especially so for the indicator for a more serious infection where there were no events beyond 2 years. The pattern indirectly supports the notion that more serious lung and liver BCG infections tend to occur early whereas testicular, vascular, muscular and osteoarticular BCG infections occur at a median of 12–22 months after the last BCG-instillation [11].

Time Trend

We could not corroborate an increasing risk associated with more recent years of diagnosis seen in a Finnish report reporting an increased risk after 2006 [6]. However, our investigation starts well after the Finnish study, and we may not have captured a trend break that occurred before 2008. We could not investigate if the number of doses or BCG strain affected the risk of BCG infection, as the SNRUBC do not hold these data, although as a general trend, the TICE strain and induction series only were more frequently used during earlier years whereas the RIVM strain and 1-year maintenance have been the dominating standards during later years. Suggestions that the TICE strain is mainly associated with milder local side-effects and that RIVM are associated with systemic BCG infections have been reported [19], albeit no differences in side-effects were detected in a randomised three-armed trial comparing intravesical instillations with mitomycin, BCG (RIVM strain), and BCG (TICE strain) [20].

Risk Factors

Male sex, older age, tumour size, comorbidity, traumatic catheterisation before instillation, immunosuppression, previous TB, short time between TURBT and start of adjuvant BCG instillations, and number of instillations have all been implicated as possible risk factors [2,3,6,21]. However, empirical evidence to verify them as clinically relevant are sparse. In this context, male sex stands out as implicated in our study and in the Danish nationwide study [5]; however, not in the single-centre studies by Pérez-Jacoiste Asín et al. [2] and Nummi et al. [3]. The higher risk might be explained by the anatomical propensity for BCG to spread intraductally through the prostate, especially if resection biopsies have been obtained at the time of TURBT, or along the vas deferens to the epididymis and testis. Also, male anatomy per se increases the risk of traumatic catheterisation.

Older age might theoretically cause the effectiveness of the immune system to decline. This has not been substantiated in our data or in the studies investigating age [2,5]. On the contrary, a single-centre study [3] found an inverse association between risk and age. However, the analysis did not account for censoring, which may have biased the results.

We could not corroborate comorbidity, tumour risk group, previous medication with corticosteroids, immunosuppressive drugs, or time between TURBT and BCG instillation as risk factors. This was also true for the other studies with access to data on risk factors [2,3,5]. However, all the available studies—also the nationwide studies—have a low statistical precision and modest but clinically important risk factors may go undetected. The issue with statistical precision may for instance explain the different findings for male sex, a risk being seen in the large cohorts, but not the single-institution series. Also, the notion among clinicians that these previously publicly discussed risk factors may play a role may have led to selection of patients to undergo or not undergo BCG treatment, introducing a bias.

The risk for a selection bias is especially true for the only tentative risk factor that have entered clinical guidelines: time between TURBT and start of BCG instillations [21]. A short time between TURBT and BCG instillations is thought to increase risk of local BCG infection and also possible haematogenous spread of mycobacteria. Current recommendations to postpone BCG-instillations until 2 or 3 weeks after TURBT may have led clinicians to postpone BCG instillations in patients with large tumours and more extensive TURBTs and/or resection biopsies from the prostatic urethra, so that those in our study with a short time between TURBT and BCG instillations is a selected 'low-risk' group.

Conclusions

By estimating a 5-year cumulative incidence proportion accounting for censoring, we have substantiated that the overall risk of a BCG infection after BCG installation for NMIBC is low. Virtually all mycobacterial infections in this NMIBC population derived from BCG infections and were thus due to BCG exposure and the majority of infections—especially the more severe—occur within 2 years after start of BCG treatment calling for a high awareness during this timeframe. We have contributed to evidence for male sex as a risk factor, but the overall statistical precision and risk of selection bias makes it difficult to rule out the other risk factors discussed in the literature. The search for risk factors should continue to guide clinical practice, where also mechanistic studies may have to contribute.

Acknowledgements

This work was supported by the Swedish Cancer Society (grant numbers CAN 2022/1971 and CAN 2023/2807) and the Swedish Research Council (2021-00859).

Disclosure of Interests

None declared.

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Abbreviations: ATC, Anatomical Therapeutic Chemical (codes); CCI, Charlson Comorbidity Index; CIS, carcinoma *in situ*; DCI, Drug Comorbidity Index; DDD, defined daily doses; HR, hazard ratio; ICD, International Classification of Diseases; LISA, Longitudinal Integration Database for Health Insurance and Labour Market Studies; LMP, low malignant potential; NMIBC, non-muscle-invasive bladder cancer; RCT, randomised controlled trial; SNRUBC, Swedish National Register for Urinary Bladder Cancer; TB, tuberculosis; TURBT, transurethral resection of bladder tumour.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Cumulative incidence proportion of the indicator for severe BCG infection (i.e., ICD-10 codes A15–A17 and a minimum of 6 months treatment) in patients with NMIBC exposed to BCG instillations, patients with NMIBC not exposed and their respective matched comparison cohorts.

Table S1 Incidence rate (*n*/100 000 person-years) in different time intervals of follow-up and cumulative incidence proportion (95% CI) at 5 years of medication for a diagnosis of BCG infection by exposure to BCG due to NMIBC, NMIBC without primary BCG exposure and in their respective comparison cohorts: definition of the outcome according to the sensitivity analysis.