Respiratory syncytial virus and other vaccine-preventable infections in multiple myeloma. A population-based study on 8,672 myeloma patients diagnosed 2008-2021 from the Swedish Myeloma Registry

Infections are a major clinical problem in the management of multiple myeloma (MM) due to both disease- and treatment-related factors. Measures to prevent infection, such as vaccinations, are therefore of paramount importance in the clinical care of MM patients. Data on vaccine-preventable infections in MM treated with modern therapy is sparse. Data regarding the burden of Respiratory Syncytial virus (RSV) infection is of particular interest given the recent approval of two immunogenic prefusion F-vaccines against RSV in Europe.

The aim of this study was to estimate the risk of vaccine-preventable infections in myeloma patients compared to a healthy population using real-world data. We used a prospective cohort design with an external comparison population. The study population included all patients with symptomatic MM diagnosed between 2008 and 2021 in Sweden included in the Swedish Myeloma Registry (N=8,672). The coverage in the Swedish Myeloma Registry is high, estimated to be over 95% between 2008-2022. Four controls per MM patient were identified randomly from the Swedish population database matched for age, sex and county of residence (N=34,567). Diagnoses of infectious diseases were retrieved from the Swedish Patient Registry, with good coverage on diagnostic codes for different infections among mainly inpatient but also outpatient visits.[1] Infections must have occurred on separate occasions at least 1 month apart. For COVID-19 this interval was set to 3 months, as prolonged viral replication is common in immunosuppressed patients. Both MM patients and controls were followed until death, permanent emigration or till December 31, 2022. A multi-state Cox proportional hazard model with infection as a time-dependent co-variate was used to estimate the overall risk of infections as well as 1- and 5-year risk of infections compared to controls. All models were adjusted for sex, age and year of diagnosis. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Effects of age, sex and autologous stem cell transplantation (auto-SCT) were evaluated separately. When total number of cases with a specific infectious disease was below 10, no statistical analyses were performed. The study was approved by the Swedish Ethical Review Authority (permit number: 2020-01729).

The majority of patients (73 %) were 65 years or older at diagnosis, 57% were males and 30% were treated with upfront auto-SCT. Patients were treated in accordance with current national MM guidelines at the time,[2] importantly the use of immunomodulatory agents (IMiD) increased during this period from low numbers to over 90% of patients receiving these drugs.[2] Additional clinical details on the included MM patients are shown in the *Online Supplementary Table S1*. The median time of follow-up was 3.1 years for patients and 5.7 years for controls (range, 0-15). The risk of acquiring a vaccine-preventable infection was 8-fold in MM patients compared to matched controls (HR=7.5; 95% CI: 7.0-8.0), see Table 1. The risk of acquiring vaccine-preventable infections was higher in males than females (*P*=0.03) among MM patients. In the group treated with auto-SCT, the risk of vaccine-preventable infections was slightly higher (HR=1.4; 95% CI: 1.2-1.6) compared to patients not treated with auto-SCT. In particular, the risk of herpes zoster was more than two-fold (HR=2.2; 95% CI: 1.7-2.8). The incidence of vaccine-preventable infections was 6-fold higher in MM patients compared to controls in the first year following diagnosis and remained high or increased for certain infections (pneumococcal infection, RSV, influenza and herpes zoster) during follow-up; see Figure 1.

Based on our data, the risk of vaccine-preventable infections was high in MM patients, especially RSV and pneumococcal infection where the risk compared to a healthy population was 16- and 17-fold, respectively. The risk of influenza, herpes zoster and *Haemophilus influenzae* was manyfold in patients with MM and remained high or increased during follow-up. The rates of pneumococcal infection were found to be high in the current study but lower than reported in a Swedish study of invasive pneumococcal disease (IPD) between the years 1996-2008[3] where IPD was shown to be 152-times more common in myeloma patients compared to controls. Pneumococcal vaccination with conjugate vaccines (PCV) was introduced in the Swedish National Vaccination Program in 2008 for children, lowering the mortality rates from IPD in the population,[4] reducing transmission in the community and protecting immunosuppressed populations. A common misconception is that MM patients do not respond to vaccination. However, clinical effectiveness (i.e., reduction in disease severity, hospitalization and

Table 1. Number of infections in multiple myeloma patients and controls.

Infection	MM patients, N total N=8,672	Controls, N total N=34,567	HR (95% CI)	*P*
All vaccine-preventable infections	1,969	1,608	7.5 (7.0-8.0)	<0.001
Respiratory syncytial	199	71	16.1(12.9-22.1)	<0.001
Pneumococcus	452	143	16.8 (13.9-20.4)	<0.001
Influenza	486	333	9.4 (8.2-10.8)	<0.001
Herpes zoster	574	376	9.3 (8.2-10.6)	<0.001
COVID-19	271	651	2.5 (2.1-2.9)	<0.001
Haemophilus influenzae (HiB)	71	30	13.0 (8.6-19.7)	<0.001
Varicella	24	14	10.1 (5.3-19.6)	<0.001
Tick-borne encephalitis	6	9	1.9 (0.6-5.9)	<0.001
Pertussis	4	2	-	-
Meningococcus	4	0	-	-
Human papilloma	4	5	-	-
Hepatitis A/B	0/5	1/1	-	-
Tetanus/ diphtheria/ polio/ yellow fever/ measles/ rubella/ hepatitis C	0	0	-	-

MM: multiple myelpoma; HR: Hazard ratio; CI: confidence interval.

death) has been shown for pneumococcal-, influenza- and COVID-19 mRNA vaccines in MM.[5,6] As evaluating the occurrence of clinical infection as an endpoint requires large numbers of patients, serological response is instead frequently reported in vaccine studies. In MM, serological responses are often somewhat inferior compared to a healthy population. There are, however, several studies that demonstrate good serological responses following pneumococcal vaccination.[7,8] One study even showed a similar response to PCV13 in healthy controls as compared to MM patients[8] many of whom were receiving active treatment at the time of the study. Treatment with IMiD has been shown to act as a vaccine adjuvant in patients with MM and thus augment vaccine responses.[9] Despite this, according to recently published data, only about 30% of MM patients receive pneumococcal vaccination.[5] IgG-responses to pneumococcal vaccination in patients treated with daratumumab, that targets CD-38 positive plasma cells, are similar to those seen in daratumumab naïve patients, suggesting that B cells can differentiate into plasma cells even during treatment.[10] Altogether, these data imply that there is no need to suspend vaccination in patients receiving active myeloma treatment including IMID and daratumumab. There is, however, insufficient data on vaccine responses in patients treated with bispecific antibodies and chimeric antigen recepetor (CAR) T cells are needed. Poor responses to COVID-19 mRNA vaccines in myeloma patients after CAR T have been documented.[11] The current study has some strengths, including its large sample size and the robust statistical methods. Furthermore, the registries used in the study have a high coverage rate. However, a major limitation is the lack of vaccination data. There is, unfortunately, no reliable registry in Sweden on administered vaccinations. Since 2002, national vaccination guidelines recommend that everyone above 65 years old in Sweden should be offered a free pneumococcal polysaccharide vaccine (PSV) and a yearly influenza vaccination. According to the Public Health Agency of Sweden, around 70% of the Swedish population above 65 years old received influenza vaccination in 2021-2022. The coverage of pneumococcal vaccination in this population, however, remains largely unknown. In 2022, a pneumococcal conjugate vaccine (PCV) covering 20 serotypes, was recommended to all patients at risk of severe pneumococcal infection, including patients with MM. However, this was not a general recommendation at the time of our study. International guidelines recommend PCV followed by PSV23, Hib-vaccination and yearly flu vaccine to all patients with MM.[12,13] Recent studies have shown an underuse of vaccinations in MM patients[5] which is also in accordance with our clinical experience. The reasons for this are likely manyfold, lack of infrastructure for vaccination, a paucity of data to inform clinical decision-making regarding the timing of vaccination in conjunction to treatment, and the relatively low priority given to supportive measures in national myeloma guidelines. All patients who have undergone auto-SCT, 30% in our study, have most likely been vaccinated after transplant with three doses of PCV (starting at 3 or 6 months after auto-SCT) followed by one dose of PSV23 and influenza before season. The vaccine

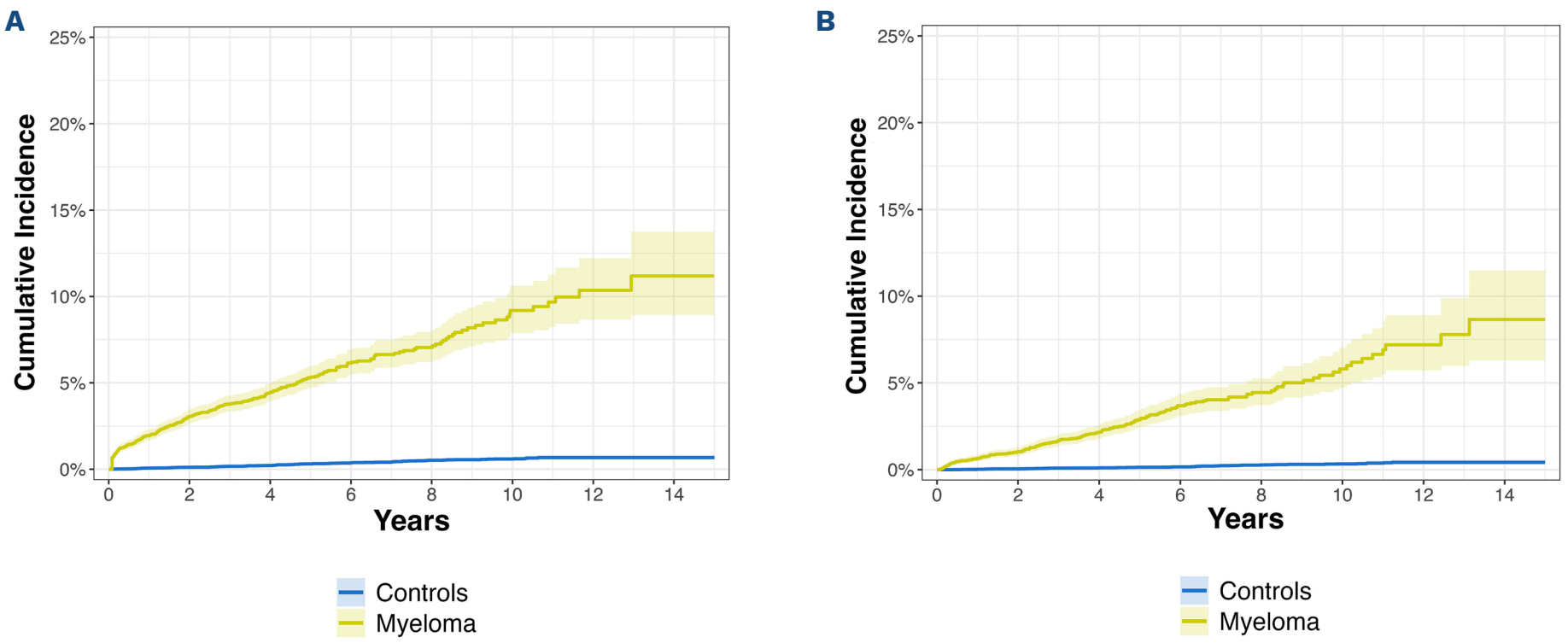

Figure 1. Cumulative incidence of infections in multiple myeloma patients and controls. (A) Cumulative incidence of Respiratory Syncytial virus infection in multiple myeloma patients and controls. (B) Cumulative incidence of pneumococcal infection in multiple myeloma patients and controls.

status among the other 70% is unknown.

Another limitation is the possibility that some of the infections might be underreported. This might be even more pronounced among MM patients compared to healthy controls. Further, we are lacking severity data. Most of the diagnoses on infectious disease are retrieved from the inpatient registry. But we do not know whether MM patients in the study were hospitalized for longer periods of time than controls or needed more ventilatory support. There is however extensive data in the literature showing that MM patients have a greater infectious morbidity and mortality compared to the healthy population.[14,15]

We conclude that most vaccine-preventable infections, including RSV and pneumococcal infection, are heavily overrepresented in MM patients compared to healthy controls. Their incidence was found to increase over time. Some of the RSV infections can potentially be prevented or more importantly, their severity mitigated, by the newly introduced RSV vaccines. From the data in our study, it seems important not to exclude older patients and patients in later lines of treatment from vaccination and vaccine efficacy studies. Vaccinations are in recent studies underused in MM, despite their proven efficacy. Our data suggest that they should be encouraged along with other measures, to prevent infections. Prospective vaccine trials in MM patients receiving modern therapy with bi-specific antibodies and CAR T cells are urgently needed.

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Contributions

CB designed the trial, sought the ethical approval, wrote the project plan and participated in analyzing data and writing of the

manuscript. SE designed this sub-study, analyzed data, made the table and wrote the first draft of the manuscript. IS and GL analyzed the data, made the figures and the table. CD, MV, IT, GJ, MH participated in designing the trial and participated in analyzing data. All authors critically reviewed, edited and approved the manuscript.

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Data-sharing statement

For original data, please contact the corresponding author. As per Swedish law, individual participant data will not be shared.

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