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An Overlooked Risk Group in Adult Immunization: Vaccination Awareness and Knowledge in Patients with Cushing's Syndrome: A Cross-sectional Study

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ABSTRACT

Objective: The aim was to quantify registry-documented adult vaccine uptake among patients with Cushing's syndrome and to assess vaccine awareness in a voluntary survey subgroup.

Materials and Methods: We conducted a record-based, retrospective, cross-sectional analysis of adults with confirmed Cushing's syndrome who were followed at a tertiary endocrinology clinic in Türkiye between January 1, 2017, and May 31, 2023. Vaccine histories were obtained from the national vaccination registry. In addition, a structured telephone questionnaire assessed awareness of vaccines for hepatitis A–D, pneumococcal disease, herpes zoster, influenza, and COVID-19 in a convenience sample of reachable, consenting patients. Analyses were descriptive; subgroup comparisons were exploratory.

Results: The registry cohort included 119 patients (83.2% female; median age 51 years). Beyond SARS-CoV-2 vaccination, uptake of routinely indicated adult vaccines was low: tetanus–diphtheria vaccine (38.7%), pneumococcal conjugate vaccine (23.5%), hepatitis B vaccine (18.5%), influenza vaccine (2.5%), and meningococcal vaccine (1.7%). In the survey subgroup (n=35), awareness of hepatitis B infection was high (80.0%), but knowledge of hepatitis A (28.6%) and hepatitis B (51.4%)vaccines was limited. Although 80.0% reported awareness of pneumococcal vaccination, only 20.0% reported having received it; the most common reason cited was that it was perceived as unnecessary.

Conclusion: Adults with Cushing's syndrome had high SARS-CoV-2 vaccine uptake but substantial gaps in uptake and awareness of other recommended vaccines. Routine immunization assessment and proactive counseling in endocrinology clinics may help close preventable vaccination gaps.

Keywords: Adult immunization, Cushing's syndrome, influenza vaccine, pneumococcal vaccine, vaccine awareness, vaccine uptake.

INTRODUCTION

Cushing's syndrome is an endocrine disorder resulting from chronic exposure to elevated glucocorticoids, either due to endogenous overproduction or exogenous corticosteroid therapy.[1–4] Cortisol excess exerts systemic effects across many organs, most critically impairing the immune system.[5,6]

Glucocorticoids disrupt both innate and adaptive immunity by suppressing cytokine signaling altering T-cell differentiation, inhibiting lymphocyte proliferation, and promoting lymphocyte apoptosis.[7,8] These effects lead to lymphopenia, reductions in CD4+ T-helper cells, alterations in CD4/CD8 ratios, and diminished natural killer (NK) cell cytotoxicity.[9] B-cell function may also be compromised, attenuating humoral immune responses even after natural infections or vaccination.[10] Neutrophil numbers paradoxically rise via demargination, while their functional activity (chemotaxis, phagocytosis, reactive oxygen species production) declines.[11] Macrophage cytokine secretion and dendritic cell maturation are suppressed, reducing antigen presentation and downstream T-cell activation.[12,13] The combined consequence is impaired pathogen clearance and weakened antiviral defense.[14]

Cushing's syndrome patients exhibit increased susceptibility to bacterial, viral, fungal, and opportunistic infections including *Nocardia* spp., *Pseudomonas* spp., *Candida* spp., *Aspergillus* spp., *Pneumocystis jirovecii*, *Herpesviridae*.[15,16] Circadian disruption of cortisol secretion further exacerbates immune dysfunction and infection risk.[1,17] Observational studies confirm infections remain a leading cause of morbidity and mortality in Cushing's syndrome.[18,19] Proactive immunization provides a critical preventive strategy by priming adaptive immunity even in the context of impaired immune function.[16] Although vaccine responses may be attenuated, they remain clinically meaningful.[8] Current guidelines recommend vaccinations for influenza, pneumococcal disease, COVID-19, and other pathogens during periods of stable disease control.[16]

Overall, patients with Cushing's syndrome have increased susceptibility to infection; adult vaccination is recommended as part of routine preventive care for immunocompromised populations. Despite these recommendations, real-world implementation of adult immunization in endocrine outpatient settings remains poorly characterized.

The present study aimed to evaluate documented vaccination coverage in a tertiary-care Cushing's syndrome cohort using national registry data and to explore vaccination awareness through a pilot telephone survey conducted among a voluntary subgroup.

KEY MESSAGES

- Registry-documented adult vaccination coverage was low in patients with Cushing's syndrome, except for SARS-CoV-2 vaccination.
- While COVID-19 vaccination rates were high, likely reflecting national and global pandemic-driven initiatives, the uptake of other routinely recommended vaccines, including pneumococcal, tetanus-diphtheria, hepatitis, and influenza, was substantially lower.
- Routine immunization assessment and proactive counseling in endocrinology clinics may help close preventable vaccination gaps. Collaboration with infectious disease specialists and primary care providers is essential to ensure adherence to adult vaccination guidelines and to close the existing care gaps.

MATERIALS AND METHODS

Study Place and Design

This record-based, retrospective, cross-sectional analysis included adults with a confirmed diagnosis of Cushing's syndrome who were followed at the Endocrinology and Metabolism Outpatient Clinic of Ege University Faculty of Medicine between January 1, 2017, and May 31, 2023. The study comprised two complementary components: (i) a registry-based retrospective audit evaluating documented vaccination coverage in all eligible patients, and (ii) a voluntary telephone survey conducted in a reachable subgroup to explore vaccination awareness and self-reported vaccination history. These components were analyzed separately because the survey subgroup was a convenience sample and was not intended to represent the full cohort.

Ethical Approval

The study protocol was approved by the Ege University Medical Research Ethics Committee (Approval Number: 23-8T/63, Date: 24.08.2023). For the telephone survey, verbal informed consent was obtained at the beginning of each call.

Patients and Data Collection

Demographic and clinical data were extracted from electronic medical records. Vaccination histories were obtained from the Turkish Ministry of Health Vaccination Tracking System and reflected all vaccinations recorded up to each patient's last clinic visit within the study period. For the survey component, a structured telephone questionnaire assessed awareness of infections (hepatitis A, B, C, and D; pneumococcal disease; herpes zoster; influenza; and COVID-19) and related vaccines. Participation was voluntary, and responses were anonymized and kept confidential.

Diagnostic Criteria

Cushing's syndrome was defined as endogenous hypercortisolism confirmed by an endocrinologist based on standard biochemical testing, with at least two abnormal screening tests (overnight 1-mg dexamethasone suppression test, late-night salivary cortisol, and/or 24-hour urinary free cortisol) followed by etiologic work-up, in line with Endocrine Society guidance.[3]

Definitions

"Registry cohort" refers to all eligible patients with Cushing's syndrome whose vaccine uptake was assessed through the national vaccination registry. "Survey subgroup" refers to the reachable, consenting patients who completed the telephone questionnaire that assessed vaccine awareness and self-reported vaccination history.

Inclusion Criteria

For the registry cohort, inclusion required age ≥18 years and a confirmed diagnosis of Cushing's syndrome with follow-up during the study period. For the survey subgroup, additional inclusion criteria required successful telephone contact and consent to participate.

Exclusion Criteria

Patients without a confirmed diagnosis of Cushing's syndrome and those not followed during the study period were not included in the registry cohort. For the survey component, patients who could not be reached by telephone or who declined participation were excluded.

Clinical, Surgical and Laboratory Investigations

Clinical data were obtained from electronic medical records. Diagnostic biochemical testing and etiologic work-up for Cushing's syndrome were performed as part of routine endocrine care, as described above. Vaccination status was assessed using the national vaccination tracking system. Vaccine awareness and self-reported vaccination history were assessed using a structured telephone questionnaire.

Statistical Analysis

All statistical analyses were performed using Jamovi version 2.5.7 (The Jamovi project; AGPL-3.0 license). Categorical variables are presented as numbers and percentages. Normality of continuous variables was assessed using visual inspection (histograms, Q–Q plots) and the Shapiro–Wilk test. As continuous variables were not normally distributed, they were reported as medians (interquartile range [IQR], 25th–75th percentiles). The chi-square or Fisher's exact test was used to compare categorical variables, as appropriate. Statistical significance was set at $p<0.05$. No correction for multiple comparisons was applied; therefore, subgroup comparisons were interpreted as exploratory. No a priori sample-size calculation was performed because this was a retrospective study that included all eligible patients during the study period.

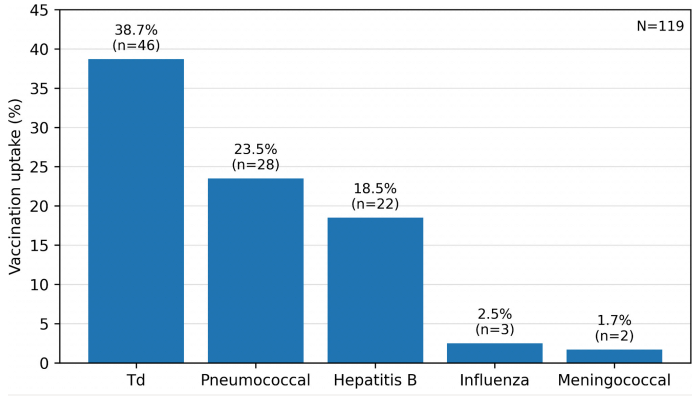

Figure 1. Registry-documented uptake of adult vaccines in the cohort with Cushing's syndrome (n=119). Bars represent the proportion of patients with documentation of each vaccine in the national registry during or prior to the study period.

Td: tetanus–diphtheria; PCV13: 13-valent pneumococcal conjugate vaccine.

RESULTS

A total of 119 patients were included in the study: 99 females (83.2%, n=99) and 20 males (16.8%, n=20). The median age was 51 years (IQR: 39–59.5). The most commonly administered vaccines were tetanus-diphtheria (Td) (38.7%, n=46), pneumococcal (PCV13) (23.5%, n=28), and hepatitis B (18.5%, n=22). In contrast, the uptake of influenza (2.5%, n=3) and meningococcal (1.7%, n=2) vaccines was markedly low (Fig. 1). Of the patients, 43.7% (n=52) had no documented vaccination history other than SARS-CoV-2 vaccination.

When vaccination status was examined by sex, no statistically significant differences were observed in receipt of PCV13, Tdap/Td, influenza, hepatitis B, and meningococcal vaccines (p=0.999, 0.053, 0.999, 0.198, and 0.999, respectively). However, women were more likely than men to have received a Td vaccine (17/41, 41.5% vs 2/78, 2.6%; p=0.004).

According to the national vaccination registry, all patients in the record-based cohort had received at least one dose of a SARS-CoV-2 vaccine. Most participants had received at least one dose of the mRNA vaccine BNT162b2 (n=104, 87.4%), at least one dose of the CoronaVac vaccine (n=99, 83.2%), or both. In total, 84 patients (70.6%) had received both vaccines.

In addition to vaccination records, we conducted a telephone questionnaire to evaluate vaccination knowledge and awareness among a subgroup of 35 patients who voluntarily

Table 1. Hepatitis and vaccine awareness in survey participants, overall and by age group

Variables	All participants (n=35) n (%)	<60 years (n=25) n (%)	≥60 years (n=10) n (%)	p
Hepatitis A infection awareness	23 (65.7)	16 (64.0)	7 (70.0)	0.999
Hepatitis A vaccine awareness	10 (28.6)	8 (32.0)	2 (20.0)	0.686
Hepatitis B infection awareness	28 (80.0)	21 (84.0)	7 (70.0)	0.381
Hepatitis B vaccine awareness	18 (51.4)	13 (52.0)	5 (50.0)	0.999
Hepatitis C awareness	21 (60.0)	15 (71.0)	6 (60.0)	0.999
Pneumococcal vaccine awareness	28 (80.0)	21 (84.0)	7 (70.0)	0.381
Pneumococcal vaccine awareness	28 (80.0)	21 (84.0)	7 (70.0)	0.381

P values are from Fisher's exact test.

agreed to participate. The surveyed subgroup consisted of 30 females (85.7%) and 5 males (14.3%), with a median age of 51 years (IQR: 42–61). The subgroup was predominantly female, reflecting the composition of the overall cohort. The median duration of Cushing's syndrome among surveyed patients was 4 years (IQR: 2–7). 25 participants (71.4%) were under 60 years of age, and 10 (28.6%) were 60 years of age or older.

When asked about their awareness of viral hepatitis infections, 28 participants (80.0%) reported having heard of hepatitis B; 22 (62.9%) reported hepatitis A; 21 (60.0%) reported hepatitis C; and only 6 (17.1%) reported hepatitis D. Awareness of hepatitis D was markedly lower than that of other hepatitis types. In terms of vaccine knowledge, 18 participants (51.4%) reported knowing that a hepatitis B vaccine exists, whereas only 10 (28.6%) were aware of the hepatitis A vaccine. Only 5 participants (14.3%) believed that there was a vaccine for hepatitis C, while 26 (74.3%) stated that they did not know.

Regarding prior serological testing for hepatitis B, 14 participants (40.0%) did not recall whether they had been tested; 9 (25.7%) reported they had never been tested; 8 (22.9%) reported being vaccinated after testing; and 4 participants (11.4%) did not provide an answer. For hepatitis A, 10 participants (28.6%) reported never being tested and 20 (57.1%) participants could not remember whether testing had been performed; 5 participants (14.3%) did not provide an answer. When asked about past childhood infections, 14 participants (40.0%) reported that a family member had told them they had measles; 11 (31.4%) reported rubella, and 17 (48.6%) reported mumps. Varicella (chickenpox) was the most frequently reported infection, with 23 participants (65.7%) stating they had it during childhood. Only 5 participants (14.3%) reported having received the measles, mumps, and rubella (MMR) vaccine; 26 (74.3%) reported not having received it; and 4 (11.4%) could not recall or did not respond.

While 28 participants (80.0%) reported awareness of the pneumococcal vaccine, only 7 (20.0%) stated they had ever received it. The most common reasons for not receiving the pneumococcal vaccine were that participants deemed it unnecessary (21 participants, 60.0%) or were unaware of its existence (6 participants, 17.1%). Influenza vaccination was infrequent: 22 participants (62.9%) reported never having received an influenza vaccine, 4 (11.4%) reported receiving it annually, 4 (11.4%) reported having received a single prior dose, and 5 (14.3%) reported receiving it occasionally. COVID-19 vaccination uptake was high: 32 participants (91.4%)reported more than one dose; one participant (2.9%) reported a single dose; and two participants (5.7%) reported no vaccination. In contrast, the national vaccination registry documented at least one SARS-CoV-2 vaccine dose for all patients in the record-based cohort, indicating disagreement between self-report and registry documentation. For tetanus-diphtheria (Td) vaccination, 14 participants (40.0%) had received one dose, 6 (17.1%) reported receiving regular vaccination, 11 (31.4%) could not remember, and 4 (11.4%) had never received it or were unaware of it.

Awareness was broadly similar across age groups (<60 years, n=25; ≥60 years, n=10). Awareness of hepatitis A was 16/25 (64.0%) in those aged <60 versus 7/10 (70.0%) in those aged ≥60 (p=0.999). The differences in awareness of hepatitis B (21/25, 84.0% vs 7/10, 70.0%; p=0.381) and of the pneumococcal vaccine (21/25, 84.0% vs 7/10, 70.0%; p=0.381) were not statistically significant. Awareness of the hepatitis A vaccine (8/25, 32.0% vs 2/10, 20.0%; p=0.686) and of the hepatitis B vaccine (13/25, 52.0% vs 5/10, 50.0%; p=0.999) was also similar (Table 1).

There were no statistically significant differences between male and female participants in awareness of hepatitis A, hepatitis B, and pneumococcal vaccination (all p>0.05). Participants receiving corticosteroid treatment (n=13) were more likely than those not receiving corticosteroid treatment (n=22) to be aware of hepatitis B but not of hepatitis A or of the hepatitis A

vaccine (p=0.004, 0.999, and 0.999, respectively). Participants diagnosed with Cushing's syndrome for less than 5 years (n=18) showed higher awareness of the hepatitis A vaccine (7/18, 38.9% vs. 3/17, 17.6%) and hepatitis B vaccine (11/18, 61.1% vs. 7/17, 41.2%) than those with a diagnosis ≥5 years. Awareness of hepatitis A infection was also slightly higher in the <5-year group (12/18, 66.7% vs. 10/17, 58.8%) (p>0.05). However, these observed differences were exploratory; therefore, these should be interpreted cautiously given the small sample size.

DISCUSSION

This study combined a registry-based vaccination audit with a pilot awareness survey. The primary finding is that documented adult vaccination coverage was low in a tertiary-care Cushing's syndrome cohort, while awareness remained limited among a voluntary subgroup of engaged patients. The two datasets address complementary but distinct aspects of preventive care implementation. Consistent with previous studies, our results indicate that patients with Cushing's syndrome are susceptible to infectious diseases because excess glucocorticoids exert immunosuppressive effects. Cortisol impairs both innate and adaptive immune responses through mechanisms such as lymphopenia, T-cell suppression, inhibition of pro-inflammatory cytokines, and impaired neutrophil and natural killer cell function.[3–6,17] These alterations predispose patients to a range of infections, including opportunistic pathogens, as shown in earlier studies.[5,7,8,11] Because of the immunological vulnerabilities resulting from this syndrome, ensuring adequate immunization is crucial to prevent infection in this high-risk group.

Our results are in line with those of Te Linde et al.,[2] who analyzed vaccination practices in a large cohort of immunocompromised adults and found substantial gaps in coverage despite high medical need. In their study, only 19% had received the pneumococcal vaccine and only 1% had received the herpes zoster vaccine, despite clear indications. By comparison, our study found pneumococcal vaccine uptake to be 23.5%, while herpes zoster vaccine awareness among Cushing's patients was remarkably low, less than 6% in the survey subgroup, even among those aged 60 or older. These parallel results indicate systemic gaps in adult immunization, even among clinically vulnerable populations. Interestingly, COVID-19 vaccine uptake exceeded 90% in both studies, likely reflecting the effects of strong public health messaging and pandemic-era interventions rather than standard preventive care delivery. This disparity between COVID-19 and uptake of other vaccines suggests that system-wide incentives, accessibility, and policy play critical roles in improving adult vaccination.

The coverage of other routinely recommended adult vaccines was notably low. Although 80.0% of participants were aware of the pneumococcal vaccine, only 23.5% had received it; only 38.7% had received at least one dose of the tetanus-diphtheria vaccine. Influenza vaccination was also underutilized: only 11.4% reported receiving it annually. Notably, 74.3% had never received the MMR vaccine, and awareness of hepatitis A and B was limited. Awareness of herpes zoster vaccines was remarkably low, with over 90% of patients unaware of vaccine availability. Despite recommendations for herpes zoster vaccination in older adults,[12] age-stratified analysis revealed no significant increase in awareness or uptake among participants aged 60 and above.

In our survey subgroup, awareness of hepatitis A, hepatitis B, and pneumococcal vaccination was broadly similar in participants aged <60 and ≥60 years, with no statistically significant differences (all p>0.05) (Table 1). For instance, patients aged <60 years had slightly higher awareness of hepatitis A (68.0% vs. 50.0%) and B (84.0% vs. 70.0%) than those ≥60 years, respectively, although the differences were not statistically significant. Patients on corticosteroids had higher awareness of the pneumococcal vaccine (92.3% vs. 72.7%) and hepatitis B vaccine (61.5% vs. 45.5%) compared with those not on treatment, although the differences were not statistically significant.

Greater awareness of the hepatitis A and B vaccines and the pneumococcal vaccine was observed among younger patients, corticosteroid users, and patients with a shorter duration of Cushing's syndrome. These findings may reflect increased healthcare engagement or education in these subgroups. Having said this, it should be kept in mind that adult vaccine awareness is shaped by multiple factors, including health literacy, clinician recommendation, and perceived susceptibility, and may vary across settings and populations.[12,14] While subgroup comparisons were exploratory and not statistically significant, certain descriptive differences were observed. These findings do not support conclusions regarding determinants of awareness, but may guide future hypothesis-driven research.

Interestingly, longer disease duration (≥5 years) was not associated with improved vaccine knowledge. One might expect that patients with chronic diseases would have more frequent contact with healthcare providers, and thus greater exposure to preventive care counseling. However, our findings align with previous reports that preventive care discussions, including immunization, are often underemphasized in specialty settings such as endocrinology clinics.[8–10]

These results suggest that vaccination is underutilized among patients with Cushing's syndrome. While the high rate of COVID-19 vaccination is encouraging, it appears to be an exception rather than the rule, influenced more by global public

health campaigns than by individualized preventive care.[11] The consistently low uptake of other vaccines highlights the need for more integrated care strategies involving endocrinologists, primary care providers, and infectious disease specialists.

There are several limitations to our study. First, it was conducted at a single tertiary center, and the findings may not be generalizable. Second, only 35 participants completed the telephone survey, and participation was voluntary, raising the possibility of selection bias. Third, we performed several subgroup comparisons without adjustment for multiple testing; therefore, subgroup findings should be regarded as exploratory. Finally, vaccination awareness and self-reported histories are subject to recall bias, as illustrated by discordance between self-reported and registry-derived SARS-CoV-2 vaccination data in a small number of participants. Future multicenter prospective studies with standardized vaccination counseling interventions may help to better define immunization needs and improve vaccination rates in patients with Cushing's syndrome.

CONCLUSION

Patients with Cushing's syndrome are uniquely vulnerable to infections because of cortisol-mediated immunosuppression. Documented adult vaccination coverage in patients with Cushing's syndrome was low in our routine clinical practice. A voluntary subgroup survey demonstrated limited awareness, even among engaged patients. Together, our findings suggest gaps in preventive care implementation, rather than patient-level behavioral resistance.

While COVID-19 vaccination rates were high, likely reflecting national and global pandemic-driven initiatives, the uptake of other routinely recommended vaccines, including pneumococcal, tetanus-diphtheria, hepatitis, and influenza, was substantially lower. Understanding the determinants of high COVID-19 and influenza vaccine uptake could provide valuable insights for enhancing the uptake of other guideline-recommended vaccines in immunocompromised populations.

Endocrinologists should routinely assess immunization status and initiate vaccination discussions during outpatient visits. Collaboration with infectious disease specialists and primary care providers is essential to ensure adherence to adult vaccination guidelines and to close the existing care gaps. Integrating vaccination assessments into electronic health records and specialist workflow may also enhance preventive care delivery. The need for proactive vaccination protocols, comprehensive patient education, and integration of preventive strategies into routine care for patients with Cushing's syndrome is evident. Vaccination should be a cornerstone of infection prevention, reducing morbidity and hospitalizations and improving survival outcomes in this high-risk population.

Ethics Committee Approval: Ethics committee approval was obtained from Ege University Medical Research Ethics Committee (Approval Number: 23-8T/63, Date: 24.08.2023).

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