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Original Research

Varicella-zoster virus immunity and self-reported history among healthcare workers in Greece

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Abstract

Introduction: Varicella-zoster virus (VZV) remains an occupational hazard for healthcare workers (HCWs), yet serological screening and catch-up vaccination policies are inconsistently implemented. We aimed to estimate VZV IgG seroprevalence and vaccination coverage among Greek HCWs, assess the validity of self-reported immunity, and explore the feasibility and yield of brief cognitive screening in this population.

Methods: In this cross-sectional study, physicians, nurses, paramedical and administrative staff completed a standardized questionnaire on demographic characteristics, varicella/herpes zoster history and vaccination. Serum VZV immunoglobulin G (IgG) was measured using a commercial enzyme-linked immunosorbent assay. Agreement between self-reported immunity and serostatus was quantified with Cohen's κ. Cognitive performance was assessed with the General Practitioner Assessment of Cognition (GPCOG) in an exploratory analysis.

Results: Seventy-four HCWs (mean age 40.8 years; 67.6% female) were enrolled; 77.0% reported prior varicella vaccination and 4.1% reported herpes zoster vaccination. VZV IgG seroprevalence was 93.2% (6.8% seronegative). Self-reported immunity showed high crude agreement but no concordance beyond chance with serostatus (κ=0.03), with 14.9% underestimating and 5.4% overestimating their immunity. GPCOG step 1 scores were strongly skewed to the maximum (mean 8.77/9), yielding marked ceiling effects and no detectable association with VZV markers in exploratory analyses.

Conclusion: In this sample of Greek HCWs, VZV immunity was high but not universal, and self-reported history was an unreliable proxy for serological status. Our findings support serological screening and targeted vaccination of susceptible HCWs for infection-control purposes. Cognitive screening with GPCOG in this relatively young workforce showed minimal discrimination and should be considered exploratory. These findings are particularly relevant to rural and remote health services, where limited staffing flexibility can magnify the impact of susceptible healthcare workers on service continuity and infection control.

Keywords

healthcare workers, healthcare workforce, herpes zoster, rural health services, seroprevalence, vaccination coverage, varicella-zoster virus.

Introduction

Varicella-zoster virus (VZV) is a ubiquitous human alphaherpesvirus that establishes lifelong latency after primary infection and may reactivate as herpes zoster (HZ), particularly with increasing age or immunosenescence, sometimes causing neurological complications such as vasculopathy, myelitis and post-herpetic neuralgia[1,2]. Although childhood varicella is often self-limited, the pre-vaccine burden of complications and hospitalizations is clinically relevant, supporting prevention strategies beyond passive case management[3]. Across Europe, varicella policy adoption has been heterogeneous: Greece has implemented childhood varicella vaccination, but adult and occupational immunization policies, including systematic screening or catch-up vaccination for healthcare workers (HCWs), remain variably applied and incompletely measured[4,5].

HCWs are a priority group for VZV prevention because they may acquire infection from patients and transmit it to vulnerable individuals in healthcare settings. Studies from Asia and Europe consistently show that VZV seroprevalence among HCWs is high but not universal, and that self-reported varicella history is an imperfect proxy for immunity, especially in younger cohorts exposed to changing vaccination patterns[6-8]. European seroprevalence and hospital-based studies similarly identify small but persistent susceptible subgroups and variable vaccine uptake among healthcare personnel[9,10]. The European Centre for Disease Prevention and Control supports vaccination or documented serological immunity for HCWs without definitive evidence of prior disease, while prevaccination screening may be cost-effective in high-seroprevalence populations by avoiding unnecessary vaccination and identifying the susceptible minority[4,8,11,12].

Beyond binary seropositivity, vaccine-induced immunity may wane over time, and primary or secondary vaccine failure can contribute to breakthrough disease and outbreak risk[13-15]. Commercial enzyme-linked immunosorbent assays (ELISAs) are practical for large seroepidemiological studies, although they have recognized limitations in low-titer vaccine recipients compared with more specialized assays[16]. These considerations support the value of serological screening in HCWs with mixed infection and vaccination histories, particularly where occupational policies and vaccine uptake are inconsistent[17].

Emerging observational evidence has also suggested possible associations between HZ, antiviral therapy, zoster vaccination and long-term cognitive outcomes, including dementia risk[18-23]. However, these data remain observational and susceptible to residual confounding, healthy-vaccine-recipient bias and differences in healthcare utilization. Moreover, most available evidence concerns HZ vaccination in older adults rather than childhood varicella vaccination or working-age HCW populations. Although biological plausibility has been proposed given the neurotropism of VZV and its recognized neurological complications, current evidence remains insufficient to support causal inferences, and any relationship between VZV-related exposures and cognitive health in HCWs should be considered exploratory and hypothesis-generating[1,20-24].

Greece provides an informative setting because, despite childhood varicella vaccination, adult vaccination uptake and HCW-specific screening policies remain variable[4,25]. Interventions such as education, convenient vaccine access, reminders, leadership endorsement and institutional support may improve HCW vaccination uptake and preparedness in healthcare settings[26,27]. This question is also relevant to rural and remote health services, where primary care facilities may have limited staffing redundancy and where preventing vaccine-preventable infections among HCWs can be important for service continuity and infection control.

Against this background, Greek HCWs represent an important population in whom serological status, vaccination history and exploratory cognitive screening can be assessed jointly within an occupational health framework. Therefore, this two-center cross-sectional seroepidemiological study, conducted in healthcare facilities serving predominantly rural and regional populations in Greece, was designed to estimate VZV IgG seroprevalence, quantify vaccination coverage, assess mismatches between self-reported immunity and serostatus, and, as a secondary exploratory aim, evaluate the feasibility and yield of brief cognitive screening in a working-age HCW population. Rather than testing a causal neurocognitive hypothesis, this integration of occupational immunoepidemiology and cognitive screening was intended to provide hypothesis-generating data for future studies on infection control and potential cognitive health in the healthcare workforce[28-30].

Methods

Study design and setting

This cross-sectional seroepidemiological study was conducted between April and July 2025 among HCWs employed in two healthcare facilities in Greece: a primary healthcare center in the Peloponnese region and a tertiary university hospital in the region of Thessaly. The participating institutions were selected to capture healthcare worker populations from regional healthcare systems serving predominantly rural and geographically dispersed populations in central and southern Greece. The University Hospital of Larissa functions as the major tertiary referral center for the largely agricultural Thessaly region, while the Areopolis Health Center provides primary healthcare services to remote communities in the Mani Peninsula of the Peloponnese. This mixed primary care and tertiary care regional healthcare setting was considered particularly relevant for evaluating occupational health preparedness and infection-control considerations in rural and regional healthcare services. The aim was to explore the relationship between VZV immunity, assessed both subjectively and objectively, and cognitive performance. All participants provided written informed consent prior to inclusion.

Study population

Eligible participants included physicians, nurses, laboratory personnel, and administrative healthcare workers aged 18 years or older. A total of 110 healthcare professionals were invited, of whom 74 agreed to participate. Individuals with acute infectious illness, current HZ infection, neurological or psychiatric conditions affecting cognitive function, or who declined venipuncture, were excluded. Recruitment was voluntary and participation was confidential, therefore all data were anonymized before analysis.

Questionnaire design and variables

Data were collected using a structured questionnaire developed by the research team of the University of Thessaly. The instrument was written in Greek and consisted of three main sections: demographic and occupational characteristics, subjective assessment of immunity, and a brief cognitive screening module. Demographic information included age, sex, professional category, healthcare setting of serving and years of healthcare experience. The subjective immunity section recorded each participant's history of natural infection and prior vaccination with HZ vaccine and/or VZV vaccine. The responses were classified as 'yes' or 'no', reflecting each participant's perceived immunity status. The final section of the questionnaire incorporated a modified Greek version of the GPCOG questionnaire. Cognitive screening was included as an exploratory component to assess feasibility and to describe gross cognitive performance in this working age HCW cohort, not to diagnose impairment or test mechanistic hypotheses. In the Greek-adapted version used in this study, participants first completed step 1, which included five questions assessing orientation, memory, recall, attention, and executive function, each scored individually. The maximum possible score for step 1 was 9 points, consistent with standardized GPCOG scoring. According to the GPCOG guidelines, a score of 9 points indicated no significant cognitive impairment, and no further assessment was required. Scores of between 5 and 8 points indicated possible cognitive impairment, prompting continuation with step 2, the informant section. Scores of 4 points or less suggested probable cognitive impairment, warranting further standardized evaluation. Step 2, the informant section, comprised six questions evaluating changes in the participant's cognitive function compared with several years earlier. The total possible score for step 2 was 6 points, and scores of 3 points or less indicated a need for further investigation of cognitive decline. All interviews and cognitive assessments were conducted face-to-face by trained members of the research team, who completed the questionnaire forms based

on participants' responses. This interviewer-administered approach ensured consistency, minimized missing data and improved comprehension, particularly among older participants.

Serological testing

Venous blood samples were obtained from all participants for the determination of VZV specific immunoglobulin G (IgG) antibodies. Serological testing was performed at the Laboratory of Public Health and Adult Immunization, Department of Nursing, University of Thessaly, following standardized protocols. Each serum sample was assigned to a unique anonymized identification code. Blood samples were centrifuged for 10 minutes at 2500 rpm, and sera were temporarily stored at –20°C before transfer to the reference laboratory, where they were maintained at –80°C until testing. Quantitative analysis was performed using the SERION ELISA classic VZV IgG immunoassay (Institut Virion/Serion GmbH, Germany), a validated enzyme-linked immunosorbent assay for detecting human antibodies against VZV in serum or plasma. The assay was conducted using a fully automated platform, according to the manufacturer's instructions. Based on the manufacturer's guidelines, anti-VZV IgG concentrations were interpreted as follows: <50 milli-international units (mIU)/mL as negative (non-immune), 50–100 mIU/mL as borderline, and >100 mIU/mL as positive (immune). For statistical analysis, values ≥50 mIU/mL were considered seropositive (immune) as per the assay interpretation framework.

Statistical analysis

All analyses were performed using SPSS v29 (IBM Corp; https://www.ibm.com/products/spss-statistics). Continuous variables were summarized as mean±standard deviation (min–max) or median (interquartile range), and categorical variables as frequencies (%). Descriptive analyses detailed demographic, occupational, vaccination, serological, and cognitive characteristics of participants. Agreement between self-reported varicella immunity and measured VZV serostatus was evaluated using Cohen's κ (95% confidence interval). Associations between immunity and cognition were examined with non-parametric tests due to the ceiling distribution of GPCOG scores. Primary analyses included correlation between anti-VZV IgG titer and GPCOG step 1 total (Spearman's ρ), and comparison of GPCOG step 1 between seropositive and seronegative participants (Mann–Whitney *U*-test). Secondary analyses compared GPCOG by varicella vaccination and sex (Mann–Whitney *U*-test) and assessed correlation with age (Spearman's ρ). A minimal linear regression explored GPCOG step 1 as the dependent variable with IgG titer (per 100 mIU/mL), age, and sex as predictors; site and profession were tested in sensitivity models. Significance was set at $p<0.05$. Given the small sample size and marked ceiling distribution of GPCOG scores, all cognitive analyses were considered exploratory and hypothesis-generating; no formal sample size calculation was performed for these endpoints.

Ethics approval

Participation was voluntary and cognitive screening results were anonymized; participants identified as having potential impairment were privately advised to seek further evaluation. Data were handled in compliance with the European Union General Data Protection Regulation (GDPR 2016/679). The study was conducted in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Committee of the University Hospital of Larissa (approval no. 7/4th/06-03-2025) and the Ethics and Research Committee of the Department of Nursing, University of Thessaly (approval no. 39/27-11-2024).

Results

Participant characteristics

A total of 74 healthcare workers were enrolled, with a mean age of 40.80±11.70 years (range 21–65); 67.60% were female. Physicians, nurses, and paramedical personnel were almost equally represented, and the majority (63.50%) were employed in a primary care setting. The mean duration of healthcare experience was 14±11.55 years. Regarding VZV exposure, 4.10% reported a previous episode of HZ and 77.00% had received varicella vaccination, whereas only 4.10% had been vaccinated against HZ. Serological testing showed that 93.20% of participants were VZV-IgG seropositive and 6.80% seronegative, with a mean antibody level of 259.7±82.0 mIU/mL. All demographic, occupational, vaccination, and serological data are summarized in Table 1. Exploratory comparisons between HCWs employed in primary care and tertiary care settings showed generally similar demographic, serological, vaccination, and cognitive characteristics, with no major differences in VZV seropositivity, self-reported immunity or vaccination history between groups, as shown in Table 2.

Table 1: Demographic and occupational characteristics of healthcare workers (*N*=74)

Characteristic	Variable	*n* (%)/mean±SD (min–max)
Age (years)		40.80±11.67 (21–65)
Sex	Male	24 (32.40)
	Female	50 (67.60)
Profession	Physician	23 (31.10)
	Nurse	25 (33.80)
	Paramedical	25 (33.80)
	Other	1 (1.40)
Experience in health care (years)		14±11.55 (1–48)
Healthcare setting of service	Primary care center	47 (63.50)
	Tertiary university hospital	27 (36.50)
History of herpes zoster	Yes	3 (4.10)
	No	71 (95.90)
Vaccinated for varicella	Yes	57 (77.00)
	No	17 (23.00)

Vaccinated for herpes zoster	Yes	3 (4.10)
	No	71 (95.90)
Serostatus	Positive	69 (93.20)
	Negative	5 (6.80)
	Borderline	0 (0.00)
VZV-IgG antibody level (mIU/mL)		259.65±82.00 (5–335)

IgG, immunoglobulin G. SD, standard deviation. VZV, varicella-zoster virus.

Table 2: Exploratory comparison of demographic, occupational, serological, and vaccination characteristics between healthcare workers employed in primary care and tertiary care settings[†]

Characteristic	Variable	Primary care (*n*=47) mean±SD (min–max) or *n* (%)	Tertiary care (*n*=27) mean±SD (min–max) or *n* (%)	*p*-value
Age (years)		42.5±11.2 (23–65)	37.8±12.1 (21–63)	0.096
Female sex		28 (59.6)	22 (81.5)	0.053
Profession	Physician	13 (27.7)	10 (37)	0.072
	Nurse	13 (27.7)	12 (44.4)	
	Paramedical + Other	21 (44.7)	5 (18.5)	
Years of experience in health care		14.77±10.89 (1–37)	12.67±12.72 (1–48)	0.427
Self-reported history of herpes zoster		1 (2.1)	2 (7.4)	0.550
Vaccinated for varicella		39 (83)	18 (66.7)	0.108
Vaccinated for herpes zoster		2 (4.3)	1 (3.7)	1.000
Positive serostatus		44 (93.6)	25 (92.6)	1.000
VZV-IgG antibodies level (mIU/mL)		260.48±77.79 (5.62–335)	258.21±90.39 (5.50–321.63)	0.372

[†] Continuous variables are presented as mean±standard deviation (range) and categorical variables as number (%). Comparisons were performed using student's *t*-test for continuous variables and χ^2 or Fisher's exact test for categorical variables, as appropriate.
IgG, immunoglobulin G. SD, standard deviation. VZV, varicella-zoster virus.

Cognitive performance

On the GPCOG, the mean step 1 score was 8.77±0.79 (range 5–9). Most participants (89.20%) achieved the maximum score of 9, indicating no cognitive impairment, while 10.80% scored between 5 and 8, prompting step 2 evaluation. Among the eight participants who completed step 2, the mean score was 4.13±1.13 (range 3–6). Three individuals (37.50%) met the threshold for probable cognitive impairment (score ≤3 points). These distributions indicate a pronounced ceiling effect of the GPCOG in this working-age HCW cohort, with very limited variability available for detecting subtle differences in cognitive performance. All item-level and total GPCOG scores are presented in Table 3.

Table 3: Item-level and total score distribution on the General Practitioner Assessment of Cognition among healthcare workers

Step number	GPCOG item	Correct *n* (%)	Incorrect *n* (%)
Step 1 (*n*=74) (mean score 8.77±0.79 (range 5–9))	Orientation (date)	72 (97.30)	2 (2.70)
	Clock drawing (numbers)	71 (95.90)	3 (4.10)
	Clock hands (11:10)	71 (95.90)	3 (4.10)
	Recent news recall	74 (100.00)	0 (0.00)
	Delayed recall of name or address	67 (90.50)	7 (9.50)
Cognitive classification	9 (no cognitive impairment)	66 (89.20)	
	5–8 (possible impairment)	8 (10.80)	
	≤4 (probable impairment)	0 (0.00)	
		Yes *n* (%)	**No, don't know, N/A *n* (%)**
Step 2 (*n*=8; 10.80% of total 74 participants) (mean score 4.13±1.13 (range 3–6))	Trouble remembering things that happened recently	5 (62.50)	3 (37.50)
	Trouble recalling conversations a few days later	3 (37.50)	5 (62.50)
	Difficulty finding the right word or using the wrong words more often	3 (37.50)	5 (62.50)
	Less able to manage money or financial affairs	2 (25.00)	6 (75.00)
	Less able to manage medication independently	2 (25.00)	6 (75.00)
	Needs more assistance with transport	0 (0.00)	8 (100.00)
Cognitive classification	>3 (no significant impairment)	5 (62.50)	
	≤3 (probable significant impairment)	3 (37.50)	

GPCOG, General Practitioner Assessment of Cognition. N/A, not available.

Agreement between self-reported and measured immunity

Agreement between self-reported varicella immunity, defined as prior infection or vaccination, and laboratory-confirmed VZV-IgG serostatus was evaluated using Cohen's κ. Overall agreement was 79.70%, corresponding to κ=0.03 (95% confidence interval –0.20–0.25, p=0.81), suggesting that, despite high crude agreement, subjective history did not reliably align with serostatus. Among the 74 participants, 11 HCWs (14.86%) underestimated their immunity, reporting no prior infection or vaccination despite being seropositive, whereas four HCWs (5.41%) overestimated their immunity, reporting previous vaccination or infection despite being seronegative. Among these four overestimating HCWs, all reported prior varicella vaccination but no HZ vaccination, and none reported a history of infection. Together, these findings highlight poor concordance between perceived and actual immunity among HCWs.

Exploratory analyses of cognitive performance

No statistically significant associations were identified between VZV-related variables and cognitive performance. Anti-VZV IgG concentration was not correlated with GPCOG step 1 score (Spearman's ρ=–0.087, p=0.461), and GPCOG performance did not differ between seropositive and seronegative participants (U=152.5, p=0.424). Similarly, no significant associations were observed between cognitive performance and self-reported immunity, vaccination status, age, sex, profession, or healthcare setting. Multivariable regression analyses likewise demonstrated no independent associations between cognitive performance and IgG titer, age, sex, profession, or healthcare setting, with models explaining minimal variance in GPCOG scores (adjusted R^2 values near zero). Given the pronounced ceiling distribution of GPCOG scores and the limited variability within this relatively young HCW cohort, all cognitive analyses should be interpreted as exploratory and hypothesis-generating rather than confirmatory. Full univariable and multivariable results are presented in Table 4 and Table 5.

Table 4: Associations between immunity markers, demographic variables, occupational factors, and General Practitioner Assessment of Cognition step 1 performance

Exposure variable	Test statistic	p-value
IgG titre (mIU/mL)	Spearman's ρ=–0.087	0.461
Serostatus (positive v negative)	U=152.5	0.424
Reported immunity (yes v no)	U=359.0	0.724
VZV vaccination (yes v no)	U=442.5	0.317
Age (years)	Spearman's ρ=–0.025	0.832
Sex (male v female)	U=544.0	0.230
Profession (physician v non-physician)	U=529.5	0.217
Healthcare setting (primary v tertiary)	U=560.0	0.121

IgG, immunoglobulin G. VZV, varicella-zoster virus.

Table 5: Multivariable linear regression predicting General Practitioner Assessment of Cognition score

Predictor	Unstandardized β	95%CI	Standardized β	p-value
IgG titre (per 100 mIU/mL)	–0.001	–0.003–0.001	–0.116	0.327
Age (years)	–0.008	–0.024–0.009	–0.113	0.351
Female sex (v male)	–0.142	–0.543–0.258	–0.085	0.481
Sensitivity predictors				
Profession (physician v non-physician)	–0.305	–0.700–0.091	–0.181	0.129
Healthcare setting of serving (primary v tertiary)	–0.209	–0.590–0.171	–0.129	0.276

CI, confidence interval. IgG, immunoglobulin G.

Discussion

Varicella-zoster virus seroprevalence and immunity awareness among healthcare workers

In this cross-sectional study of Greek HCWs, we found a high overall VZV IgG seroprevalence (93.2%) in a relatively young working population, with most participants reporting previous varicella infection and/or vaccination. At the same time, HZ vaccination coverage was extremely low, a finding likely explained by the relatively young age of our cohort, which is below the age threshold recommended for routine zoster vaccination; almost all participants scored at ceiling on the GPCOG step 1, with no detectable association between VZV serostatus, IgG titers, vaccination history, or self-reported HZ and cognitive performance. Taken together, these findings suggest that, from an infection control standpoint, VZV immunity among Greek HCWs is largely satisfactory but not universal, whereas any potential long-term cognitive consequences of VZV infection or vaccination lie well beyond the temporal and statistical resolution of our current design.

Our seroprevalence estimate aligns with prior work indicating that the majority of adult HCWs in high-income settings are immune to VZV, but a non-trivial susceptible fraction persists[6-9,31]. Studies from Taiwan and Korea report immunity rates exceeding 90% among HCWs, yet consistently identify 2–10% seronegative individuals, particularly in younger age groups and more recent birth cohorts[7,8,31]. Similar patterns emerge from Italian and other European data, where adult seroprevalence is high overall but shows age- and cohort-related gaps that have practical implications for outbreak control[5,9,32]. In this context, our 6.8% seronegative rate is neither negligible nor unexpected and

underscores that 'almost universal' immunity is epidemiologically very different from 'universal' immunity in clinical environments caring for immunocompromised or pregnant patients.

The operational question of whether self-reported history of varicella or vaccination can be trusted as a proxy for immunity remains highly relevant to occupational health policies. Concordant with earlier data, we observed imperfect agreement between self-perceived immune status and laboratory serology. Prior studies have repeatedly shown that self-reported varicella history has limited sensitivity and specificity in HCWs, particularly among those with uncertain or negative histories[6-8,16]. The recent systematic review and meta-analysis by Riccò et al. concluded that clinical history alone is an unreliable screening tool and recommended serological testing, particularly at hiring and in outbreak settings[17]. Our findings in Greek HCWs are consistent with this body of evidence and argue against relying on anamnesis alone when the goal is to minimize nosocomial VZV transmission.

Our findings can also be contextualized against recent Greek data on healthcare personnel vaccination practices. In a large multicenter survey conducted in eight tertiary care hospitals across Greece, Maltezou et al reported that only 5.7% of HCWs self-reported full varicella vaccination, while 22.2% were classified as susceptible based on self-reported history and vaccination status[33]. Although direct comparison with our study should be made cautiously because we used serological confirmation rather than self-reported immunity estimates, both studies consistently identify the persistence of a susceptible subgroup among Greek HCWs despite generally high levels of presumed population immunity. Together, these findings support the need for more systematic occupational vaccination strategies and improved approaches to immunity assessment among HCWs in Greece.

These findings should also be interpreted within the broader European context of heterogeneous healthcare personnel vaccination policies. Maltezou et al demonstrated substantial variation across Europe regarding recommendations and mandatory vaccination strategies for healthcare personnel, with varicella vaccination policies absent in 17 of 36 surveyed countries and often restricted to selected high-risk healthcare settings rather than universally implemented[34]. In Greece, varicella vaccination for healthcare personnel has primarily been recommended for staff in contact with high-risk patients, reflecting the broader variability in occupational vaccination policies across Europe[34]. This heterogeneity highlights the ongoing importance of local seroepidemiological data to guide infection-control strategies and targeted vaccination approaches, particularly in healthcare systems with limited staffing flexibility and rural or remote service provision.

Occupational and health system implications

From a broader health system perspective, there is robust evidence that varicella vaccination of susceptible HCWs is not only clinically beneficial but also economically sound. Early economic evaluations and cost-effectiveness analyses have shown that preventing even a small number of nosocomial varicella cases can offset the costs of screening and vaccination by reducing staff absenteeism, ward closures, contact tracing and post-exposure prophylaxis[3,11,12,35]. Our local data, demonstrating a small but potentially epidemiologically relevant susceptible subgroup, fit well within this framework and provide contemporary seroepidemiological input for Greek decision-makers considering whether to implement systematic screening and catch-up vaccination programs for HCWs.

Although our study did not directly evaluate healthcare service disruption or outbreak dynamics, the identification of a susceptible subgroup among HCWs may have practical implications for rural and remote healthcare settings, where workforce shortages and limited staffing redundancy can magnify the operational consequences of vaccine-preventable infections. In such settings, staff isolation, sickness absence, or post-exposure restrictions may disproportionately affect service continuity and infection-control capacity. These considerations further support targeted serological screening and vaccination strategies for HCWs, particularly in smaller healthcare systems with limited surge capacity. Exploratory comparisons between primary care and tertiary care HCWs showed no major differences in immunity patterns, vaccination history, or cognitive performance, suggesting that residual VZV susceptibility may be relevant across regional healthcare systems serving rural and geographically dispersed populations rather than being confined to a single healthcare setting.

The immunological profile observed in our cohort, predominantly high IgG titers with a minority of seronegative individuals, needs to be interpreted in light of the evolving understanding of vaccine-induced and infection-induced VZV immunity. It is now well recognized that one-dose varicella vaccination is associated with waning protection and an increased risk of breakthrough disease over time, which has led to the implementation of two-dose schedules in many countries[13,14,36]. Breakthrough varicella outbreaks have been documented in highly vaccinated settings, often linked to primary vaccine failure, secondary waning, or high exposure intensity[37,38]. Our cross-sectional design cannot disentangle these mechanisms; we did not systematically capture the number and timing of doses, nor distinguish vaccine-derived from infection-derived immunity beyond self-report. Nevertheless, the coexistence of a largely immune workforce with a small susceptible fraction, and the experience from other settings that breakthrough infections cluster in these susceptible pockets, supports continued vigilance and targeted immunization strategies for HCWs.

Beyond humoral responses, the durability of VZV immunity is also shaped by cell-mediated immunity (CMI), which remains crucial for protection against HZ and severe disease[1,2,39]. Prior studies have shown that VZV antibodies may decline while CMI persists, including in vaccinated HCWs and older adults receiving zoster vaccines[28,29,40,41]. By relying solely on IgG serology, our study likely underestimates the true proportion of functionally protected individuals and cannot comment on the quality or longevity of CMI. This limitation is particularly relevant when considering HZ and its sequelae, which depend more on CMI than on antibody titres alone.

Exploratory cognitive findings and implications for future research

An exploratory component of our study is the integration of VZV serology and vaccination history with cognitive screening in HCWs, motivated by emerging evidence linking HZ, antiviral treatment, and especially HZ vaccination to dementia risk[18-23]. Large observational studies and quasi-experimental natural experiments consistently report that HZ vaccination may be associated with a

reduced risk of incident dementia in older adults, with effect estimates broadly in the range of a 15–30% relative reduction[18,20,21]. While residual confounding and healthy-vaccine-recipient bias remain possible explanations, systematic reviews and meta-analyses generally converge on a potentially protective association[21,22], supported by population-based studies of antiviral therapy[23].

Mechanistically, this association is biologically plausible. VZV is a neurotropic virus establishing lifelong latency in sensory ganglia and, upon reactivation, can induce inflammatory responses with downstream effects relevant to neurodegenerative pathways[1,2,39]. Preventing reactivation or modifying host–virus interactions through vaccination could therefore plausibly influence long-term neurocognitive trajectories.

In this context, our null findings regarding GPCOG scores should not be interpreted as evidence against a VZV–dementia link or the potential neuroprotective effects of HZ vaccination. Instead, they reflect fundamental limitations of our population, endpoint, and design. Our cohort consists of relatively young, actively working HCWs, in whom dementia and mild cognitive impairment are rare. GPCOG was validated as a case-finding tool for cognitive impairment in older primary care populations, not for detecting subtle cognitive variability in middle-aged professionals[30]. The pronounced ceiling effect in our data (mean 8.77/9) indicates that the instrument lacked sensitivity for detecting fine cognitive differences in this age group. Moreover, dementia is a long-latency outcome, and our cross-sectional design captures neither cumulative lifetime zoster burden nor long-term exposure to HZ vaccination, with vaccination uptake remaining extremely low given the cohort's age. Under these constraints, the absence of detectable associations between VZV markers and GPCOG performance is more plausibly attributable to methodological limitations rather than to absence of an underlying biological relationship.

Although no association between VZV markers and GPCOG performance was identified, the exploratory cognitive component of our study may still inform future research directions. Specifically, our findings highlight the methodological challenges of assessing subtle cognitive variability in relatively young HCW populations using brief screening tools with marked ceiling effects. Future studies investigating potential relationships between VZV exposure, HZ vaccination, and cognitive health in HCWs will likely require larger longitudinal cohorts, more sensitive neuropsychological assessments, detailed characterization of vaccination and infection histories, and incorporation of biological or neuroimaging markers. In this context, our study primarily serves as a feasibility and hypothesis-generating framework rather than evidence supporting a direct association between VZV immunity and cognitive performance.

Interpreted pragmatically, the absence of an association between VZV markers and GPCOG scores in our regression models (which explained minimal variance in cognitive performance) is best seen as evidence of methodological mismatch rather than a negative finding on the underlying biological hypothesis[18,20,21,30]. Any serious attempt to test the VZV–dementia hypothesis in HCWs would require large, longitudinal cohorts followed into older age, detailed capture of HZ events and vaccination status, more sensitive neuropsychological batteries, and ideally structural and molecular markers of neurodegeneration.

Strengths and limitations

Several limitations of our study must be acknowledged. The sample size was modest and restricted to two centers, limiting generalizability and reducing statistical power for subgroup analyses. Participation was voluntary, raising the possibility of selection bias; HCWs with greater interest in preventive health may have been overrepresented. Our serological assessment relied on a single commercial IgG assay and did not measure CMI, which is central to protection against zoster[28,29,40,41]. Varicella and zoster vaccination histories were partially self-reported and not fully validated against occupational or national immunization records, which may introduce misclassification. Cognitive assessment was limited to GPCOG, resulting in a ceiling effect that precludes nuanced analysis of cognitive variability in a relatively young cohort[30]. Additionally, correlations involving HZ vaccination could not be meaningfully evaluated because routine zoster vaccination is recommended for immunocompetent adults aged ≥65 years, whereas our cohort was substantially younger (mean 40.8 years; range 21–65 years). Thus, the very low HZ vaccination coverage observed reflects age-based eligibility rather than true uptake behavior. Finally, the cross-sectional design prevents any causal inference regarding future dementia risk or the long-term neurocognitive impact of VZV infection and vaccination.

Strengths of our study include its focus on HCWs, a group of high relevance for infection control and health system resilience, its integration of serological, clinical, and cognitive data, and its positioning of local Greek data within a rapidly evolving international literature on VZV, vaccination strategies, and brain health[1,5,17,18,20,24,42]. By documenting both the residual susceptibility to VZV and the limited penetration of HZ vaccination in HCWs, we provide a concrete evidence base for occupational and public health authorities considering more systematic varicella and zoster immunization policies.

Conclusion

In summary, most Greek HCWs in our cohort were immune to VZV, but a small proportion remained susceptible. Self-reported history of varicella or vaccination did not reliably identify immune individuals, supporting the use of serological screening, at least in high-risk departments or at the time of hiring. Our exploratory cognitive analyses showed no association between VZV markers and GPCOG performance; given the young age of the cohort and the pronounced ceiling effects of the instrument, this likely reflects methodological limitations rather than evidence against a possible VZV–dementia link. Future work should use larger, longitudinal cohorts with detailed immunological assessments, robust capture of vaccine and disease histories, and more sensitive cognitive and neuroimaging outcomes to address neurocognitive questions. In the meantime, strengthening varicella and zoster vaccination strategies for HCWs appears justified on traditional infection-control grounds and may, if current evidence is borne out, also contribute to long-term brain health in this essential workforce.

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Conflicts of interest

The authors declare no conflicts of interest.

AI disclosure statement

No generative AI or AI-assisted artificial tools were used in the conduct of this research or the preparation of this manuscript.

Data availability

The original contributions presented in this study are included in the article. Further enquiries can be directed to the corresponding author.

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