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Seroepidemiology of maternal and childhood pathogen exposure in three European mother-child cohorts

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ABSTRACT

Objectives: To describe the epidemiology of common pathogens and risk factors among pregnant women and their children.

Methods: In three European population-based birth cohorts, we examined 2213 mother-child pairs, contributing 5036 blood samples from pregnancy to 12 years of age. We measured serum immunoglobulin G levels against polyomaviruses (BKPyV, JCPyV, KIPyV, WUPyV, MCPyV), herpesviruses (Epstein-Barr virus [EBV], cytomegalovirus [CMV], varicella-zoster virus), adenovirus 36, *Helicobacter pylori*, and *Toxoplasma gondii* with multiplex serology.

Results: Among pregnant women, seroprevalence ranged from 18.7% (*H. pylori*) to 95.7% (EBV); among 4-6-year-old children, seroprevalence ranged from 3.6% (*H. pylori*) to 88.4% (BKPyV). Although most primary infections occurred in the first 4 years of life, some children had primary infections at later ages. Seropositive mothers were more likely to have seropositive children, but an intergenerational decrease in seroprevalence was evident for herpesviruses and *H. pylori*. There were sizeable differences between countries for *H. pylori* and *T. gondii*. Non-western ethnicity mothers and their children were more likely to be infected. Female sex (WUPyV, MCPyV, CMV), breastfeeding (CMV), early daycare attendance (CMV, *H. pylori*), and obesity (JCPyV, EBV, Adv-36) were associated with child's seroprevalence.

Conclusions: European children acquire common pathogens but often experience first exposure beyond early childhood. Differences are expected between and within countries and across generations.

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Introduction

Childhood is characterized by initial exposure to many pathogens circulating in our communities. Yet in contemporary European settings, there is limited knowledge on which common viruses, bacteria, and parasites children acquire, the typical age at first infection, and whether these patterns have changed over generations. Although common pathogens may not pose an immediate public health threat, shifts in their epidemiology may significantly impact the burden of associated diseases. To illustrate, a delay in the age of first infection with Epstein-Barr virus (EBV)—one of the most ubiquitous viruses—into adolescence and young adulthood increases the incidence of infectious mononucleosis [1]. Beyond acute effects, adverse infectious exposures with respect to the specific pathogen or a non-optimal timing of infection, during fetal life and early childhood, may lead to developmental adaptations of various organ systems, potentially leading to life-long consequences [2,3]. Evidence in this field remains scarce.

In view of this, it is essential to start by describing the current epidemiology of common pathogens across early life stages, including pregnancy, and to identify subgroups of the population that are differentially affected. Although differences in exposure to common pathogens are expected between countries, they remain poorly documented for a broad range of common pathogens [4]. Comparison between countries is essential when studying infectious diseases as they could help understand drivers of infection dynamics [5].

Estimates of exposure to pathogens that rely on surveillance systems (restricted to notifiable infectious diseases), medical registries (capturing mainly severe manifestations of infections), or questionnaires (unsuitable for common infections that often manifest with no or unspecific symptoms) represent just the tip of the iceberg, potentially missing the vast majority of infected individuals. In contrast, the measurement of specific immunoglobulin G (IgG), which develops in response to an infection, is widely used to estimate prior exposure to a particular pathogen. Multiplex serological assays can assess antibody responses to multiple pathogens and can maximize the information extracted from minimal sample volumes available from large-scale epidemiological studies [6–8].

In this cross-cohort collaboration, we measured IgG responses to several common pathogens including five polyomaviruses, three herpesviruses, adenovirus 36 (Adv36), *Toxoplasma gondii*, and *Helicobacter pylori* in repeated blood samples from pregnancy to 12 years of age among participants from three birth cohorts in Europe. We describe the seroepidemiology of these pathogens in pregnancy and across childhood, identify differences between countries, host characteristics, and explore intergenerational differences.

Methods

Study population

The study population arises from a subset of children from three independent European population-based birth-cohorts: the Born in Bradford-BiB (UK, 2007-2011) [9], the INfancia y Medio Ambiente-INMA (Spain at three study areas: Sabadell, 2004-2006; Valencia, 2003-2005; and Gipuzkoa, 2006-2008 [10]), and the Rhea study (Greece, 2007-2008) [11] participating in the SeroEpiC3 project. The SeroEpiC3 project was established to examine the contribution of common pathogens to non-communicable diseases development. Eligible participants included all singleton live births with sufficient blood samples for serological analysis at age 4-6 years (8 years for INMA Valencia). For those participants, additional samples from previous or subsequent follow-ups and maternal blood samples from pregnancy (INMA, BiB) or cord blood (Rhea) were analyzed (Table S1). In the manuscript, we will refer to maternal antibody levels during pregnancy as those measured either during pregnancy or in cord blood samples due to strong correlation [7]. Ethical approval was obtained from the local Research Ethics Committees for each center. Informed consent was obtained from the parents of the children.

Multiplex IgG serology

Serum samples collected and stored at –80°C at cohort sites were shipped on dry ice to the lab and analyzed in April 2021. Multiplex serology was used to quantify serum antibody levels against 11 pathogens selected based on (i) prior evidence of potential links to non-communicable diseases, (ii) their prevalence in Europe, and (iii) the feasibility of serological analysis. The Luminex panel included five polyomaviruses (BKPyV, JCPyV, KIPyV, WUPyV, MCPyV; antigen: viral capsid protein 1), EBV (antigens: ZEBRA, EBNA-1, EA-D, VCA p18), cytomegalovirus (CMV; antigens: pp65, pp150, pp28), varicella-zoster virus (VZV, antigen: envelope glycoprotein VZV gE), Adv36 (antigen: fiber protein), *H. pylori* (antigens: GroEL, UreA, NapA, HpaA, CagA, VacA, HcpC, Omp), and *T. gondii* (antigen: Toxo-sag2). Further details on serology and methods for defining cut-offs are available in Supplementary Material. The serological assays were performed at the Immune Response and Biomarkers Core Facility at ISGlobal [12–14].

Individual characteristics

We included a key set of variables longitudinally collected to identify risk factors. We restricted to specific variables that were available and harmonized across cohorts from the LifeCycle [15] and Helix [16] projects, considering existing literature and plausibility. These were maternal age (16-25, 25-35, 35-45 years), education level (high, medium, low), self-reported ethnicity (western: European Union, Andorra, Australia, Canada, Iceland, Liechtenstein, Monaco, New Zealand, Norway, San Marino, Switzerland, USA, UK, and Vatican City; non-western [all other countries]/mixed), smoking during pregnancy (no, yes $<$10 cigarettes/day, yes $\geq$10 cigarettes/day), pre-pregnancy overweight/obese (no, yes when body mass index [BMI] $\geq$30 kg/m^2), delivery type (vaginal, cesarean), child's sex (male, female), older siblings (no, yes), breastfeeding exclusive (never, 1-4 months, $>$4 months), daycare attendance before 2 years (no, yes), passive smoking exposure (age $\geq$3 to $<$6 years, including mother, biological father, social father, any smokers close to the child, or exposure to smoke in the home), and child's BMI status at age 4-6 years as overweight/obese (no, yes) based on BMI-for-age z-scores derived using the World Health Organization growth standard [17,18]. VZV vaccination data (number of doses, dates, type of vaccine) were obtained from vaccination cards (Rhea), questionnaires (INMA), or primary care records (BiB). VZV vaccination policies varied by country: Greece introduced a two-dose scheme in 2006 (modified in 2019), Spain introduced a similar scheme in 2016, whereas the UK had no universal VZV vaccination program.

Statistical analysis

We conducted a non-response analysis by comparing the characteristics of participants with and without repeated samples. Descriptive analyses were performed to summarize the study population's characteristics and seroprevalence data overall and by cohort. We assessed the effect of maternal serostatus (seropositive vs seronegative) on child serostatus at 4-6, 6-9, and 10-12 years of age, as well as on the age of first infection among children with repeated samples, adjusting for cohort, maternal ethnicity,

Table 1
Characteristics of the study population overall and by cohort, SeroEpiC3 project.

		Total n = 2213	BIB (UK) n = 656	INMA (Spain) n = 809	Rhea (Greece) n = 748
Maternal age (years old)	16-25	345 (15.6%)	208 (31.7%)	27 (3.3%)	110 (14.7%)
	25-35	1380 (62.4%)	343 (52.3%)	566 (70.0%)	471 (63.0%)
	35-45	381 (17.2%)	82 (12.5%)	183 (22.6%)	116 (15.5%)
	Missing	107 (4.8%)	23 (3.5%)	33 (4.1%)	51 (6.8%)
Maternal education	High	670 (30.3%)	153 (23.3%)	293 (36.2%)	224 (29.9%)
	Medium	775 (35.0%)	94 (14.3%)	321 (39.7%)	360 (48.1%)
	Low	660 (29.8%)	360 (54.9%)	186 (23.0%)	114 (15.2%)
	Missing	108 (4.9%)	49 (7.5%)	9 (1.1%)	50 (6.7%)
Maternal ethnicity	Western	1738 (78.5%)	216 (32.9%)	787 (97.3%)	735 (98.3%)
	Non-western	467 (21.1%)	439 (66.9%)	16 (2.0%)	12 (1.6%)
	Missing	8 (0.4%)	1 (0.2%)	6 (0.7%)	1 (0.1%)
Smoking in pregnancy	No	1606 (72.6%)	586 (89.3%)	581 (71.8%)	439 (58.7%)
	Yes <10 cigarettes	306 (13.8%)	54 (8.2%)	151 (18.7%)	101 (13.5%)
	Yes ≥10 cigarettes	120 (5.4%)	13 (2.0%)	64 (7.9%)	43 (5.7%)
	Missing	181 (8.2%)	3 (0.5%)	13 (1.6%)	165 (22.1%)
Pre-pregnancy overweight/obese	No	1205 (54.5%)	188 (28.7%)	556 (68.7%)	461 (61.6%)
	Yes	859 (38.8%)	417 (63.6%)	220 (27.2%)	222 (29.7%)
	Missing	149 (6.7%)	51 (7.8%)	33 (4.1%)	65 (8.7%)
Sex	Male	1145 (51.7%)	342 (52.1%)	409 (50.6%)	394 (52.7%)
	Female	1068 (48.3%)	314 (47.9%)	400 (49.4%)	354 (47.3%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Breastfeeding exclusive	Never	673 (30.4%)	113 (17.2%)	103 (12.7%)	457 (61.1%)
	1-4 months	778 (35.2%)	337 (51.4%)	282 (34.9%)	159 (21.3%)
	>4 months	415 (18.8%)	176 (26.8%)	205 (25.3%)	34 (4.5%)
	Missing	347 (15.7%)	30 (4.6%)	219 (27.1%)	98 (13.1%)
Day care attendance before 2 years	No	1347 (60.9%)	566 (86.3%)	181 (22.4%)	600 (80.2%)
	Yes	866 (39.1%)	90 (13.7%)	628 (77.6%)	148 (19.8%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Passive smoking	No	1326 (59.9%)	553 (84.3%)	405 (50.1%)	368 (49.2%)
	Yes	807 (36.5%)	101 (15.4%)	396 (48.9%)	310 (41.4%)
	Missing	80 (3.6%)	2 (0.3%)	8 (1.0%)	70 (9.4%)
Overweight/obese 4 years	No	1583 (71.5%)	493 (75.2%)	583 (72.1%)	507 (67.8%)
	Yes	593 (26.8%)	162 (24.7%)	215 (26.6%)	216 (28.9%)
	Missing	37 (1.7%)	1 (0.2%)	11 (1.4%)	25 (3.3%)

child's sex, and exact age. To identify risk factors associated with serostatus in mothers during pregnancy and in children aged 4-6 years, we first fitted Poisson regression models with robust variance, minimally adjusted for cohort and child's exact age (only for children's models). We explored determinants of seroprevalence in western origin mothers and their children, as the non-western ethnicity group was predominant in only one cohort (BiB). We applied the False Discovery Rate correction [19] to identify significant results while limiting the proportion of false positives among them, ensuring a more reliable interpretation of findings. Predictors with q-values <0.05 were considered significant under a false discovery rate of 5%. We computed cohort-specific estimates. Results are reported as prevalence ratios with 95% confidence intervals. All analyses were limited to participants with complete covariate data. *P*-values were based on two-sided hypothesis tests and considered significant at $P < 0.05$. All analyses were conducted using Stata version 14.0 (StataCorp LP, College Station, Texas).

Results

Participants and samples analyzed

Our study population included 2213 mother-child pairs, contributing 5036 blood samples from pregnancy to 12 years of age. Table 1 shows characteristics of participants overall and by cohort. Children with vs without repeated samples had mothers with higher education, western ethnicity, and normal pre-pregnancy BMI status. They were more likely to attend daycare early, be exposed to smoking, and less likely to be from the BiB cohort (Table S2).

Seroprevalence among pregnant mothers and their children from 2 to 12 years of age

At the time of pregnancy, almost all mothers (>90%) had detectable antibodies against BKPyV, MCPyV, and EBV; 40-70% were JCPyV, KIPyV, WUPyV, CMV, VZV, and *T. gondii* seropositive; and <35% were Adv36 or *H. pylori* seropositive (Figure 1 and Table S3). CMV, VZV, and *T. gondii* were more prevalent in mothers from Rhea (Greece), whereas MCPyV, Adv36, and *H. pylori* were more prevalent in mothers from INMA (Spain). Across most pathogens, seroprevalence was the lowest in BiB (UK).

During childhood, seroprevalence for all pathogens was the lowest at age 2 and increased with age (Figure 1 and Table S3). At 4-6 years of age follow-up, BKPyV, MCPyV, and EBV were the most prevalent pathogens (>67%), whereas the least prevalent was *H. pylori* (3.6%). Children across ages from Rhea study (Greece) displayed higher seroprevalence for several pathogens, including KIPyV, WUPyV, MCPyV, Adv36, and *T. gondii* compared with children from INMA (Spain) and BiB (UK) cohorts. VZV seroprevalence at 4-6 years was 49% in vaccinated children and 42% in non-vaccinated children (Table S3). Comparison of vaccinated and non-vaccinated children is presented in Table S4.

After stratification by ethnicity of the ethnically diverse BiB cohort, we observed higher seroprevalences among non-western than western participants (Figure S1). For most pathogens, there were consistent ethnic differences across follow-ups (Figure S1a). Nonetheless, for MCPyV and EBV, maternal seroprevalence was comparable across ethnic groups, but differences emerged in children at age 2, persisting for EBV and diminishing for MCPyV by age 4 (Figure S1b). For *H. pylori* and CMV, maternal seroprevalence showed substantial ethnic variation, but differences among

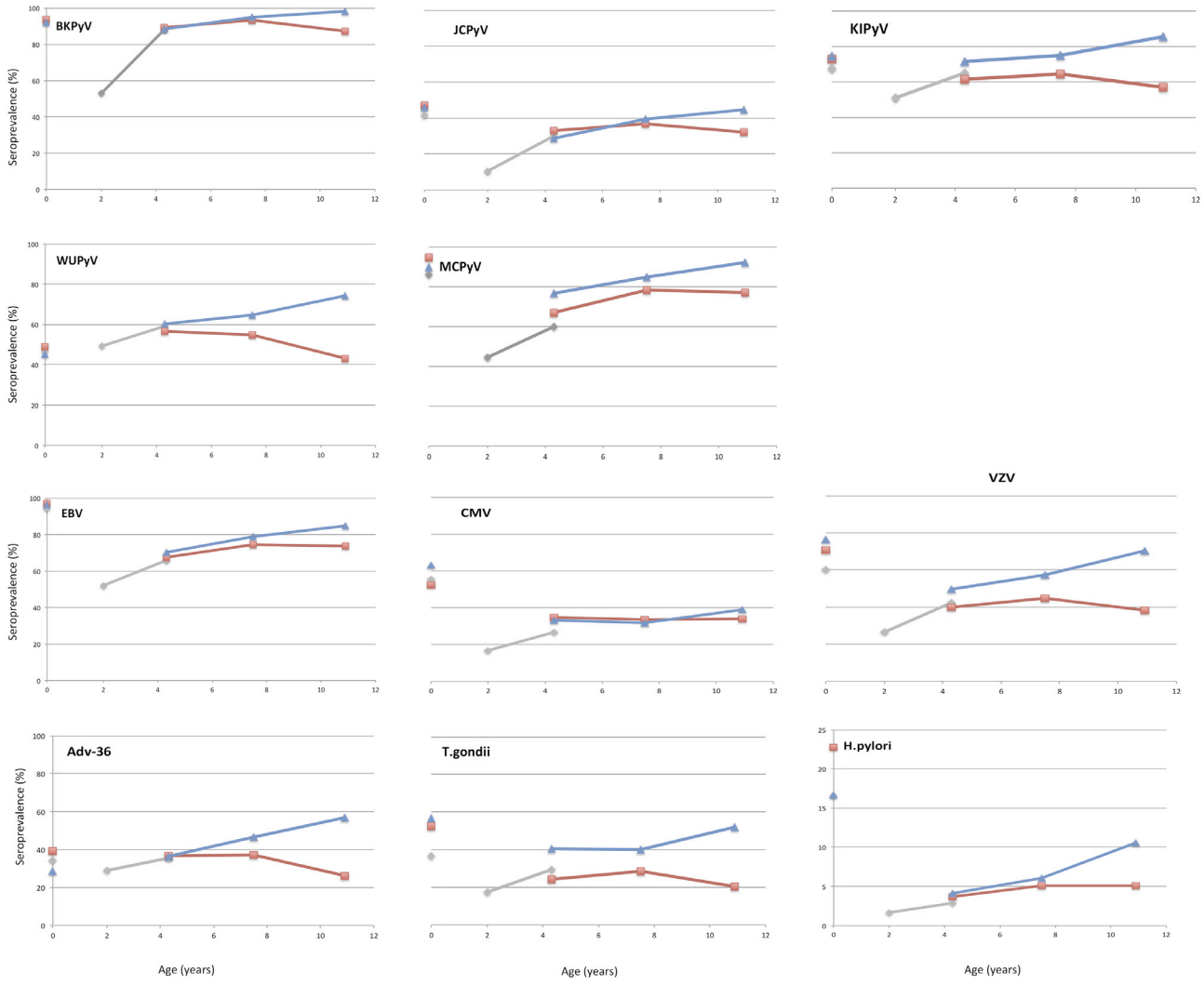

Figure 1. Seroprevalence (%) to common pathogens in mothers during pregnancy (age 0) and children from 2 to 12 years of age by cohort (BiB: grey; Rhea: blue; INMA: red). Age is the median age of children at each follow-up visit. Corresponding results with 95% confidence intervals are presented in Table S3.
Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; VZV, varicella-zoster virus.

children were much smaller (Figure S1c). Particularly, non-western children's seroprevalence rates appeared to converge toward those of western populations.

Age at first infection

Among the 366 participants of the INMA and Rhea cohorts with three repeated samples starting from the age of 4-6 years, we were able to determine whether children experienced their first infection during preschool years (seropositive at the 4-6 years of age sample), early school years (seronegative in earlier sample and seropositive at the 6-9 years of age sample), or late school years (seronegative in earlier samples and seropositive at the 10-12 years of age sample). First exposure to almost all pathogens occurred predominantly in preschool years, but acquisition continued at later ages (Figure 2 and Figure S2a for children with two repeated samples). To illustrate, for EBV, 71% of children tested seropositive in preschool years, 13% during early school years, 4% in late school years, and 12% remained unexposed until 12 years of age (Figure 2). *H. pylori* deviated from this pattern, as we detected similar exposure rates across preschool, early childhood, and late childhood. In the BiB cohort, the only cohort with samples at 2 years of age, we observed that primary infections occurred before age 2, except for *H. pylori*, which followed the aforementioned pattern (Figure S2b).

Association of maternal serostatus with child's serostatus and age at infection

For almost all pathogens, maternal seropositivity was associated with higher seroprevalence to the corresponding pathogens in their children after adjusting for child's exact age, sex, cohort, and maternal ethnicity (Table 2). The strongest associations were observed at early ages, but for some pathogens, maternal status was also important at later ages, including JCPyV, KIPyV, WUPyV, CMV, Adv36, and *T. gondii*. Further, maternal seropositivity was associated with earlier age of infection for KIPyV, WUPyV, CMV, VZV, and *T. gondii* (Table 2).

Host characteristics as determinants of seroprevalence in western populations

Among western origin mothers, we identified negative associations between maternal age and BKPyV seroprevalence, pre-pregnancy overweight/obesity and MCPyV, and between smoking during pregnancy (≥10 cigarettes vs none) and VZV. Low vs high

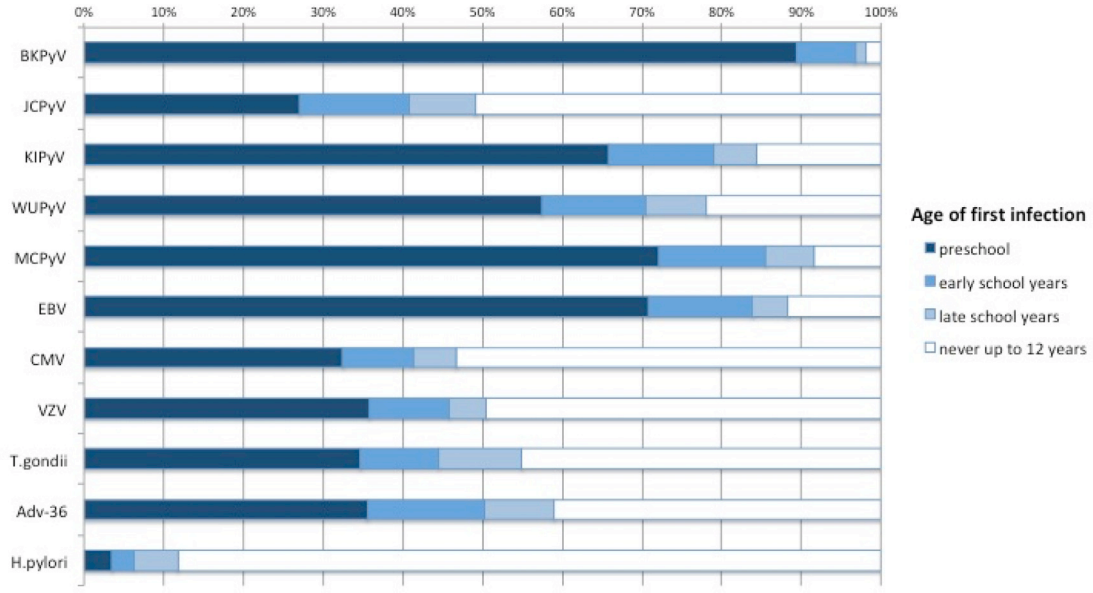

Figure 2. Age of first infection by pathogen based on 366 children (n = 248 from Rhea cohort; n = 118 from INMA Gipuzkoa cohort) with three repeated samples at ages 4-6, 6-9, and 10-12 years. Results on VZV are based on 109 children non-vaccinated up to 12 years of age. Corresponding results among children with two repeated samples are presented in Figure S2.
Abbreviations: CI, confidence interval; CMV, cytomegalovirus; EBV, Epstein-Barr virus; VZV, varicella-zoster virus.
Figure caption: Definition of age of first infection: preschool, when first seropositive at the 4-6 years of age sample; early school years, when first seropositive at the 6-9 years of age sample; late childhood, when first seropositive at the 10-12 years of age sample; never, when never detected seropositive in the three repeated samples.

Table 2
Association (PR [95% CI]) between maternal seropositivity in pregnancy with child's seropositivity at each follow-up and timing of infection up to 12 years of age, SeroEpiC3 project.

Maternal seropositivity	Child's seropositivity at each follow-up[a]				Timing of infection[b]
	2 years n = 219	4-6 years n = 1193	6-9 years n = 610	10-12 years n = 134	Infected in preschool years vs early school years
	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)
BKPyV	2.21 (0.84, 5.76)	1.42 (1.18, 1.70)	1.21 (1.04, 1.40)	0.98 (0.96, 1.01)	1.12 (0.89, 1.43) (n = 417)
JCPyV	6.50 (2.38, 17.77)	2.37 (1.97, 2.85)	2.09 (1.66, 2.63)	1.79 (1.20, 2.65)	1.19 (0.95, 1.49) (n = 186)
KIPyV	3.63 (2.19, 6.01)	2.16 (1.86, 2.50)	1.85 (1.54, 2.22)	1.28 (1.00, 1.63)	1.35 (1.10, 1.65) (n = 355)
WUPyV	1.64 (1.23, 2.19)	1.88 (1.69, 2.08)	1.86 (1.62, 2.15)	1.31 (1.08, 1.60)	1.20 (1.06, 1.36) (n = 310)
MCPyV	2.10 (1.00, 4.40)	1.74 (1.40, 2.17)	1.06 (0.90, 1.25)	1.05 (0.85, 1.31)	1.08 (0.87, 1.33) (n = 376)
EBV	2.41 (0.89, 6.59)	1.42 (1.07, 1.88)	1.15 (0.80, 1.63)	1.04 (0.66, 1.63)	2.45 (0.78, 7.64) (n = 355)
CMV	2.73 (1.17, 6.37)	2.79 (2.22, 3.52)	2.99 (2.21, 4.05)	4.29 (2.09, 8.83)	1.25 (1.01, 1.55) (n = 185)
VZV[c]	6.44 (2.67, 15.52)	2.96 (2.28, 3.84)	2.65 (1.66, 4.21)	NA	3.34 (1.03, 10.87) (n = 109)
Adv-36	3.73 (2.42, 5.74)	3.18 (2.72, 3.72)	2.94 (2.41, 3.59)	1.53 (1.16, 2.03)	1.14 (0.95, 1.36) (n = 221)
Toxoplasma gondii	5.47 (2.67, 11.21)	2.95 (2.42, 3.59)	2.93 (2.18, 3.93)	1.61 (1.10, 2.35)	1.47 (1.09,1 .99) (n = 189)
Helicobacter pylori	1.48 (0.16, 13.77)	2.52 (1.33, 4.75)	2.31 (1.20, 4.42)	0.53 (0.08, 3.57)	0.75 (0.32, 1.74) (n = 38)

CI, confidence interval; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PR, prevalence ratio; VZV, varicella-zoster virus.
[a] Models adjusted for cohort, maternal ethnicity, child's sex and exact age.
[b] Among infected participants with repeated samples at 4-6 and 6-9 years of age follow-up; models adjusted for cohort, maternal ethnicity, and child's sex. Infected in preschool years (seropositive at the 4-6 years of age sample); Infected in early school years (seronegative in earlier sample and seropositive at the 6-9 years of age sample).
[c] Only among VZV non-vaccinated children.

maternal education was associated with higher seroprevalence to CMV (Table 3). In children, female sex was associated with higher seroprevalence to WUPyV, MCPyV, and CMV; low vs high maternal education with lower *H. pylori* seroprevalence; and medium vs high maternal education with lower Adv36 seroprevalence; maternal age and cesarean delivery with higher BKPyV seroprevalence; breastfeeding with higher CMV seroprevalence; early daycare attendance with higher CMV and *H. pylori* seroprevalence; child's overweight/obese status was positively associated with JCPyV, EBV, and Adv36 (Table 3). When applying the false discovery rate (FDR) correction, the only association that remained was between female sex and higher MCPyV seroprevalence in children 4-6 years of age. The observed associations were mostly consistent between cohorts (Table S5).

Discussion

We used objective serological markers to uncover the epidemiology of common pathogens among pregnant women and their children up to 12 years of age, participating in population-based cohort studies established in the UK, Spain, and Greece. Sizeable differences in the seroprevalence of specific pathogens, including *H. pylori* and *T. gondii*, were seen between cohorts, showing that country of residence determines acquisition of specific infections. Ethnic sub-groups, in particular, exhibit distinct frequency of common infections and patterns of acquisition. Children of seropositive mothers were more likely to be seropositive, but we observed an intergenerational reduction, particularly for herpesviruses and *H. pylori*. Besides maternal status, no other single driver of the acqui-

Table 3
Determinants of seropositivity in western origin mothers and their children at 4-6 years of age follow-up, SeroEpiC3 project.

	BKPyV PR (95% CI)	JCPyV PR (95% CI)	KIPyV PR (95% CI)	WUPyV PR (95% CI)	MCPyV PR (95% CI)	EBV PR (95% CI)	CMV PR (95% CI)	VZV[3] PR (95% CI)	Adv-36 PR (95% CI)	*Toxoplasma gondii* PR (95% CI)	*Helicobacter pylori* PR (95% CI)
Mothers [a]											
25-35 vs 16-25 years old	0.94 (0.89, 0.99)	1.08 (0.85, 1.38)	1.03 (0.90, 1.18)	0.96 (0.76, 1.20)	1.01 (0.94, 1.09)	0.98 (0.95, 1.02)	1.05 (0.85, 1.28)	1.09 (0.94, 1.27)	0.99 (0.72, 1.34)	1.01 (0.82, 1.25)	0.86 (0.53, 1.39)
35-45 vs 16-25 years old	0.93 (0.87, 0.99)	1.14 (0.87, 1.50)	1.04 (0.89, 1.22)	1.09 (0.84, 1.40)	1.05 (0.97, 1.14)	0.96 (0.91, 1.01)	1.09 (0.87, 1.37)	1.08 (0.91, 1.27)	1.10 (0.79, 1.55)	1.13 (0.90, 1.43)	1.43 (0.87, 2.35)
Medium vs high education	1.00 (0.96, 1.04)	0.98 (0.82, 1.17)	1.03 (0.94, 1.13)	1.05 (0.89, 1.24)	0.96 (0.92, 1.01)	1.01 (0.98, 1.03)	1.04 (0.89, 1.21)	0.95 (0.86, 1.04)	0.88 (0.71, 1.09)	0.97 (0.84, 1.13)	1.09 (0.78, 1.52)
Low vs high education	1.00 (0.95, 1.05)	1.03 (0.85, 1.26)	0.94 (0.84, 1.05)	0.94 (0.77, 1.14)	0.95 (0.90, 1.00)	0.97 (0.94, 1.01)	1.19 (1.01, 1.40)	0.90 (0.80, 1.01)	0.91 (0.72, 1.15)	0.87 (0.72, 1.04)	1.05 (0.73, 1.53)
<10 cigarettes vs none	0.98 (0.93, 1.03)	1.00 (0.82, 1.21)	0.92 (0.82, 1.04)	0.90 (0.74, 1.09)	0.96 (0.90, 1.02)	0.98 (0.95, 1.02)	1.08 (0.92, 1.26)	0.88 (0.78, 1.00)	0.89 (0.69, 1.14)	0.85 (0.71, 1.02)	0.97 (0.67, 1.40)
≥10 cigarettes vs none	0.90 (0.81, 1.00)	0.91 (0.68, 1.21)	0.89 (0.74, 1.07)	0.85 (0.63, 1.15)	0.99 (0.92, 1.07)	0.97 (0.92, 1.03)	1.07 (0.85, 1.35)	0.73 (0.58, 0.92)	0.89 (0.62, 1.27)	0.82 (0.62, 1.09)	1.09 (0.66, 1.83)
Pre-pregnancy obese	0.99 (0.95, 1.03)	0.92 (0.79, 1.08)	0.96 (0.88, 1.05)	0.88 (0.75, 1.03)	0.94 (0.90, 0.98)	0.98 (0.96, 1.01)	0.92 (0.80, 1.05)	1.01 (0.92, 1.11)	1.05 (0.86, 1.27)	0.99 (0.86, 1.13)	0.82 (0.60, 1.11)
Older children	0.98 (0.94, 1.02)	0.98 (0.85, 1.14)	1.01 (0.93, 1.10)	1.15 (0.99, 1.33)	1.01 (0.97, 1.05)	1.00 (0.98, 1.03)	1.03 (0.91, 1.16)	1.03 (0.95, 1.12)	1.05 (0.88, 1.26)	1.05 (0.92, 1.20)	1.21 (0.92, 1.59)
Children 4-6 years old[2]											
Girls	1.02 (0.98, 1.06)	1.13 (0.96, 1.33)	1.03 (0.96, 1.11)	1.13 (1.04, 1.24)	1.14[4] (1.07, 1.22)	1.02 (0.95, 1.10)	1.17 (1.00, 1.36)	1.06 (0.86, 1.31)	0.97 (0.84, 1.12)	1.15 (0.99, 1.33)	1.29 (0.74, 2.23)
Medium vs high education	0.99 (0.95, 1.04)	0.86 (0.71, 1.03)	1.05 (0.96, 1.14)	0.99 (0.89, 1.10)	0.98 (0.91, 1.06)	1.00 (0.91, 1.09)	0.89 (0.75, 1.06)	0.97 (0.75, 1.25)	0.84 (0.72, 0.99)	1.02 (0.86, 1.21)	0.59 (0.33, 1.05)
Low vs high education	1.01 (0.96, 1.06)	0.85 (0.68, 1.08)	1.02 (0.91, 1.14)	0.98 (0.86, 1.12)	1.01 (0.92, 1.12)	1.07 (0.97, 1.19)	0.79 (0.62, 1.00)	1.13 (0.86, 1.48)	0.86 (0.70, 1.06)	1.07 (0.86, 1.33)	0.23 (0.07 - 0.77)
25-35 vs 16-25 years old	1.10 (1.02, 1.19)	0.97 (0.75, 1.26)	1.13 (0.99, 1.28)	1.08 (0.93, 1.26)	1.02 (0.92, 1.14)	0.98 (0.87, 1.10)	0.97 (0.75, 1.25)	0.79 (0.56, 1.13)	1.27 (0.98, 1.65)	0.96 (0.76, 1.20)	0.83 (0.35, 1.97)
35-45 vs 16-25 years old	1.09 (0.99, 1.19)	0.91 (0.66, 1.24)	1.02 (0.88, 1.20)	1.01 (0.84, 1.21)	1.01 (0.89, 1.15)	0.98 (0.85, 1.12)	0.91 (0.68, 1.23)	0.72 (0.48, 1.09)	1.21 (0.90, 1.63)	0.77 (0.58, 1.03)	0.93 (0.35, 2.49)
Cesarean delivery	1.06 (1.01, 1.11)	1.16 (0.96, 1.39)	1.03 (0.95, 1.12)	0.97 (0.87, 1.07)	1.04 (0.96, 1.12)	1.03 (0.95, 1.12)	0.94 (0.79, 1.13)	0.99 (0.75, 1.31)	1.13 (0.96, 1.32)	1.09 (0.92, 1.28)	0.87 (0.46, 1.65)
1-4 months vs never eb	1.03 (0.98, 1.08)	1.08 (0.87, 1.33)	1.08 (0.99, 1.19)	1.05 (0.93, 1.18)	0.99 (0.91, 1.08)	1.01 (0.92, 1.12)	1.27 (1.04, 1.55)	1.14 (0.84, 1.55)	1.05 (0.87, 1.26)	1.09 (0.90, 1.31)	1.73 (0.91, 3.31)
>4 months vs never eb	1.00 (0.94, 1.06)	0.89 (0.67, 1.18)	0.99 (0.87, 1.13)	1.04 (0.89, 1.21)	0.99 (0.88, 1.11)	1.03 (0.91, 1.16)	1.33 (1.03, 1.71)	1.08 (0.79, 1.49)	1.12 (0.89, 1.41)	0.99 (0.75, 1.31)	1.47 (0.58, 3.71)
Older siblings	1.00 (0.96, 1.04)	0.81 (0.69, 0.96)	0.95 (0.88, 1.02)	0.92 (0.83, 1.00)	0.94 (0.88, 1.01)	0.97 (0.90, 1.05)	1.00 (0.86, 1.17)	1.04 (0.83, 1.29)	0.83 (0.72, 0.96)	0.89 (0.76, 1.04)	0.92 (0.53, 1.61)
Early daycare	0.97 (0.93, 1.02)	1.11 (0.92, 1.35)	0.99 (0.91, 1.09)	0.91 (0.82, 1.02)	0.93 (0.85, 1.01)	1.08 (0.99, 1.18)	1.30 (1.08, 1.55)	1.28 (0.98, 1.68)	1.00 (0.84, 1.20)	1.04 (0.87, 1.25)	2.25 (1.11, 4.57)
Passive smoking at 4-6 years	0.99 (0.96, 1.04)	0.98 (0.83, 1.16)	0.99 (0.92, 1.08)	0.99 (0.90, 1.09)	0.94 (0.87, 1.00)	0.97 (0.90, 1.05)	1.00 (0.85, 1.17)	0.94 (0.75, 1.18)	0.90 (0.77, 1.04)	0.95 (0.81, 1.11)	1.01 (0.59, 1.73)
Overweight or obese 4-6 years	0.98 (0.94, 1.03)	1.25 (1.06, 1.48)	0.99 (0.91, 1.08)	1.03 (0.93, 1.13)	0.95 (0.87, 1.02)	1.09 (1.01, 1.18)	1.08 (0.91, 1.27)	1.04 (0.82, 1.30)	1.22 (1.06, 1.42)	1.02 (0.86, 1.20)	1.41 (0.80, 2.47)

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; eb, exclusive breastfeeding; EBV, Epstein-Barr virus; PR,; prevalence ratio; VZV, varicella-zoster virus.
[a] All models adjusted for cohort; [b]All models adjusted for cohort and child's exact age; [c]Among non-vaccinated children; [d]significant after False Discovery Rate correction (q-values <0.05 under a false discovery rate of 5%).
All analyses among participants with available covariate data.

sition of these common pathogens at an early age was identified, but certain risk factors emerged for each pathogen.

Our data suggest that the spectrum of traditional childhood infections has receded in current generations of European children. This was evident from much lower seroprevalence rates in children compared with their mothers in pathogens that are historically acquired in childhood. Particularly, an intergenerational reduction was evident for herpesviruses and *H. pylori* across all three countries. Characteristically, in our population at the age of 10-12 years, there is still a significant proportion of children (19%) that remain EBV-seronegative. Given that EBV is a ubiquitous pathogen, it is expected that these children will acquire a late EBV infection, which is strongly linked with development of infectious mononucleosis and long-term consequences, especially Hodgkin lymphoma and multiple sclerosis [20]. Support on this comes from Kuri et al., showing a sharp increase in EBV seroprevalence in adolescents and an increase in the incidence of infectious mononucleosis requiring hospitalization in the UK [21]. Even larger intergenerational differences were found for CMV, VZV, and *H. pylori*. These changes in the epidemiology of common infections in future generations may drive changes in several infectious-associated chronic diseases. To illustrate, a recent systematic review and meta-analysis demonstrated that the decrease in the incidence of gastric cancer was concomitant with a declining trend in *H. pylori* prevalence [22]. Among children vaccinated against varicella, seropositivity ranged from 48.9% at ages 4-6 years to 68% at ages 10-12 years. Similar immunity gaps have been reported in other studies [1–4], underscoring the importance of conducting serosurveys to assess population immunity, beyond relying solely on disease surveillance and vaccination coverage data.

Important differences between cohorts were evident for specific pathogens such as *H. pylori* and *T. gondii*, underscoring the importance of providing regional indices of infectious diseases epidemiology. In addition, within the same community, different subgroups can have varying risks of acquiring common pathogens. All studied pathogens were more common in non-western ethnic families than western, in line with previous studies on *H. pylori* [23] and herpesviruses [24]. These descriptive data are particularly relevant for understanding potential differences in the burden of diseases associated with these infections and developing targeted and effective interventions. For instance, the high *T. gondii* seroprevalence in Greece and among non-western ethnic groups (e.g., 42% in non-western pregnant women in the UK vs 26% in western women) may indicate an increased risk of toxoplasmosis-related complications in vulnerable populations, such as pregnant women, highlighting the need for congenital toxoplasmosis screening [25].

Besides maternal status, no single factor drove early acquisition of these common pathogens. Previously, early enrolment in childcare has been used as a proxy of exposure to common infections, but it may not apply for all pathogens in the current settings and has been shown to be transient [26]. In our study, daycare attendance before 2 years of age was associated with higher seroprevalence only to CMV and *H. pylori*. This association suggests horizontal transmission of these pathogens between children and daycare personnel. Another risk factor suggesting pathogen-specific route of transmission was breastfeeding, which was positively associated with CMV seroprevalence. It is well known that CMV can be transmitted via breastmilk from mother to child. Interestingly, female sex was associated with higher seroprevalence to WUPyV, MCPyV, and CMV. Sex differences in children's social behavior as well as in child-rearing practices may determine exposure to these common pathogens in young children, but biological factors may also play a role [27]. Previous studies have also indicated higher CMV seroprevalence in females than males [28].

Other novel associations were between BMI and prevalence of specific pathogens. Several lines of evidence suggest that obesity may impair host defenses, potentially increasing susceptibility to infections [29]. It remains uncertain whether this vulnerability extends to specific pathogens. Notably, there is emerging evidence from animal and epidemiological studies supporting a positive association between Adv36 and obesity [30] similar to what we observed among 4-6-year-old children in our analysis.

Strengths and limitations

Our study is strengthened by the use of serological markers to identify prior infections. The antigen panel, while extensive, did not include all relevant infections (e.g., HHV-6). All samples were analyzed in the same laboratory after sample randomization, ensuring data comparability. However, comparability with other serosurveys may be affected by differences in assay characteristics (e.g., antigens), procedures, and apparatus. The cohorts were established in similar calendar years, allowing cross-country comparisons. We were able to analyze an early age sample (4-6 years) for all participants in the three cohorts and integrate repeated samples up to 10-12 years among them and a pregnancy sample to study intergenerational differences. However, we acknowledge that the BiB cohort did not provide samples after age 6, restricting the interpretation of results at later ages in the UK cohort. The samples were collected over a decade ago, and infectious dynamics may have shifted due to the COVID-19 pandemic in post-2020 generations.

Conclusion

Our study confirms that children in Greece, Spain, and the UK are exposed to common pathogens. However, substantial and previously underexplored differences exist between and within countries (e.g., ethnic diverse communities). Furthermore, our findings suggest that the epidemiology of several common pathogens is undergoing a transition, particularly in Western Europe, with a noticeable shift toward later ages of first infection. This shift may also indicate a potential lack of exposure across the life-course. This is an initiative among birth cohort studies in Europe, highlighting the value of serological evaluation of the population for informing public health strategies and exploring the broader impact of these infections on health and disease.

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Ethical approval statement

Ethical approval was obtained from the local Research Ethics Committees for each center. Informed consent was obtained from the parents of the children.

Author contributions

Conceptualization: MKar, LP, MB, CD, MKog; Data curation: MKar, RA, MV; Formal analysis: MKar, MB, DC, AE; Funding acquisition: MKar, MKog; Investigation: MV, RA, CD, DM, TR, VB, NM, JMDS, SMRL, JI; Methodology: MKar, MKog, MV, RA, CD, DM, TR, VB, NM, JMDS, SMRL, JI; Project administration: MKar; Resources: LP, DM, MB, MV, NM, JMDS, SMRL, JI; Supervision, MKar, MKog, CD; Writing-original daft preparation MKar; Writing-review and editing all.

Data statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Protocol information will be available on reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107994.

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