High-risk human papillomavirus cervical infection prevalence in France, 2020-2023: a nationwide, large-scale, and spatially resolved study comparing opportunistic and organised screening

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Abstract

Background: Since 2020, in France, cervical cancer screening among females aged 30 to 65 years has focused on the detection of high-risk human papillomaviruses (HR HPVs) cervical infection. All females within this age range who do not follow current screening recommendations are actively invited to perform an HPV test through an organised screening program. This represents a novel opportunity to study the prevalence of HR HPV cervical infection at a national level with high spatial resolution.

Methods: The analytic sample contained 362,963 results of HPV tests performed on cervical samples collected on females aged 30 to 66 years, between 2020 and 2023, in Metropolitan France. These tests were performed through either the organised screening program or following spontaneous, i.e. 'opportunistic', screening. A full Bayesian bivariate model involving multiple Gaussian Markov random fields was used to get spatially resolved prevalence maps of HPV cervical infection caused by HPV16 and/or HPV18 (HPV16/HPV18) or caused by at least one of 12 other carcinogenic genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), correcting from the possible systematic inflation associated with opportunistic screening.

Results: A raw description of the data found that 3.7% of tests were positive for HPV16/18 while 9.2% were positive for other high risk genotypes. Among samples collected through organised screening, 2.9% were positive for HPV16/18 and 6.9% for the other group of genotypes, against 3.8% and 9.4%, respectively, for samples collected through opportunistic screening.

As of November 2023, among females aged 30 years, a very likely (probability > 0.95) systematic upward inflation in expected prevalence for opportunistic screening, with respect to organised screening, was found in 89.5% and 100.0% of postcodes for HPV16/18 and other genotypes, respectively.

For Paris, France's capital city, this systematic upward inflation went from a posterior average [equal-tailed interval at 95%] of 1.9 [0.4,3.3] percentage points (pp), at 30 years old, to 1.0 [-0.1,1.9] pp at 66 years old for HPV16/18 and from 9.2 [5.7,12.7] pp to 2.7 [0.4,4.8] pp for other genotypes.

The expected prevalence in the analytic sample, corrected for the systematic upward inflation associated with opportunistic screening, were 3.2 [2.9,3.6]% for HPV16/18 and 7.3 [6.7,7.9]% for other genotypes.

Limits: Screening uptake within the organised screening program is subject to selection.

Implication: The study provides the first spatially resolved picture of HR HPV cervical infection prevalence in France. The analysis highlights that opportunistic screening might be associated with a substantial systematic upward inflation in HPV cervical infection prevalence, compared with organised screening, which should be accounted for in prospective modelling studies.

Keywords: High-risk HPV; Cervical infection prevalence; Organised screening; Opportunistic screening; Gaussian random fields; Gaussian Markov random fields.

1. Introduction

Human papillomaviruses (HPVs) cause a massive public health burden worldwide. In addition to anogenital warts and papillomatosis, HPV infections caused by oncogenic genotypes (high-risk HPV, HR HPVs) are responsible for a substantial proportion of penile, vulval, vaginal, anal, and oropharyngeal cancers and nearly all cervical cancers [1]. In 2020, an estimated 600,000 new cases of cervical cancer occurred worldwide, making it the fourth most common cancer in females [2, 3].

The World Health Organisation (WHO)'s global strategy to accelerate the elimination of cervical cancer as a public health problem promotes HPV screening as one of the key levers to fight against the burden associated with cervical cancer [4]. In May 2018, France announced the launch of its new cervical cancer screening program [5, 6], aiming to reduce the incidence of cervical cancer and associated mortality by 30% over 10 years through an increase in screening coverage rate of up to 80% [7]. The implementation, which began in 2020, was supported by encouraging results from modelling and pilot studies [8, 9] and answered concerns about the observed decreasing trend in opportunistic screening uptake, i.e., prescription-based screening following spontaneous medical consultations [10].

As of 2024, many countries have implemented organised cervical cancer screening programs [11, 12], typically relying on a combination of cytological analyses and HPV DNA detection tests (further simplified as 'HPV tests'). Beyond their contribution to reducing the incidence and mortality of cervical cancer [13–15], screening programs relying on HPV tests offer a unique window on HR HPV cervical infections prevalence. Additionally, due to lower selection biases in screening uptake, prevalence estimates obtained through organised screening programs are expected to differ from those derived from opportunistic screening [16, 17].

In this study, we used nationwide collected results of HPV tests, performed from 2020 to 2023, through opportunistic or organised screening, in France. This unique dataset represents the largest available collection of HPV test results for this country. Collected data were used along a full Bayesian hierarchical model, allowing us to provide the first spatially resolved prevalence estimates of cervical infection caused by HPV16 and/or HPV18, or caused by at least one of 12 other carcinogenic genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) [18]. In addition, we quantified the systematic differences in prevalence estimates when relying on data collected through opportunistic, instead of organised, screening.

2. Methods

2.1. French cervical cancer screening guidelines

Cervical cancer screening guidelines in France underwent a major update in 2019. Before the age of 30, cytological analyses remain the primary screening tool while the guidelines recommend HPV tests as the primary screening method for females aged 30 to 65 years. The first HPV test should be performed as early as age 30 or 3 years after the last cytological analysis. If this test is negative for all HR HPV, the next one should be performed 5 years later. In the case of a positive result for an HR HPV, a cytological analysis should be performed within the year. If the cytology is normal, an HPV test should be performed one year later [5, 6].

Since 2020, the French organised screening program has proactively invited females who do not follow these screening guidelines to consult a primary care provider and undergo a free HPV test. As an alternative to the organised screening pathway, patients may undergo 'opportunistic screening', meaning that patients perform an HPV test following the spontaneous consultation of a primary care provider, without any invitation from the French National Social Security System. In this case, any subsequent HPV screening is subject to an out-of-pocket cost for the patient. See Supplementary Files S1 for further details.

2.2. Data

The initial dataset contained all results from HPV tests performed on cervical samples, in France, between January 2020 and November 2023, by Cerba, one of the largest networks of medical biology laboratories in the country.

Regardless of the screening pathway, 2 types of biologically and clinically validated assays were used to analyse collected samples: either Alinity m high risk® assay or Roche's Cobas® HPV Test [19]. Both assays target the viral DNA of 14 HPV genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Alinity m high risk® can distinguish between HPV16, HPV18, and HPV45, but not between HPV31, 33, 52, 58 and HPV35, 39, 51, 56, 59, 66, 68. Roche's Cobas® provides distinct results for HPV16 and 18 but only pooled results for other HR genotypes. Data extracted by Cerba provided binary results (i.e., positive or negative) for HPV16 and HPV18 for both assays, for HPV45 only for Alinity m high risk® , and for all other HR genotypes for both assays. Results for HPV45 were not considered distinctly from other genotypes.

In addition to test results, the dataset included the screening pathway, the week and year of the sample analysis, the patients' ages, and the postcodes of the city of residence. Details about these postcodes are provided in Supplementary Files S2. No additional variables were available.

2.3. Analytic samples selection

The detailed description of the sample selection steps and the corresponding flowchart are provided in Supplementary Files S3. In brief, our analyses kept test results from females living in France, aged between 15 and 79 years, for whom information about their anonymous ID, age, spatial location, and type of screening was available.

Three subpopulations were considered. First, patients aged 15 to 79 years, living in Metropolitan France. Second, patients within the same age range and living in Overseas Territories. Both subpopulations were used only for descriptive statistics purpose, reported in Supplementary Files S4. The third subpopulation, the 'analytic sample', was restricted to patients living in Metropolitan France, aged 30 to 66 years, the age range for which HPV tests are recommended as the primary screening tool. This subsample was used for carrying out the statistical inference and produce maps of HR HPV infection prevalence.

2.4. Statistical inference

The statistical inference was carried out in a full Bayesian framework. The number of tests and positive tests was aggregated at the stratum level. Strata were based on postcode, age, week-year of screening, genotype groups, and screening pathway. Two groups of genotypes were considered: HPV16 and/or HPV18 ('HPV16/18') and genotypes other than HPV16/18 ('Other genotypes').

The number of positive tests within each stratum was assigned a binomial distribution, the size parameter of which was the total number of tests performed within each stratum. The expected proportion of positive tests within a stratum was linked to the stratum's characteristics through a logit link.

Each stratum's linear predictor included a common intercept and the full two-way interaction between the group of genotypes and the type of screening. Other components were split into 2 groups. The first group was common to both data collected through opportunistic and organised screening while the second was specific to data collected through opportunistic screening. Each group of parameters contained spatially-varying, age-varying, and time-varying parameters to which we assigned multivariate hierarchical priors.

Spatially-varying parameters were specified either through 2-dimensional continuous functions, to which we assigned a Gaussian random field (GRF) prior [20–22] (models 1 and 2) or through discrete spatially-indexed parameters to which we assigned a reparametrised Besag-York-Mollié (BYM2) prior, a Gaussian Markov random field prior (GMRF) (models 3 to 5). Age-specific and time-specific components were each specified through ordered parameters to which we assigned Random Walk of order 2 (RW2) as priors [23, 24].

All models accounted for the bivariate nature of the outcome through an exchangeable separable correlation structure between the two groups of genotypes superimposed to each age, space, and time-specific components following [25]. All parameter priors were large.

The five competing structures were discriminated through the log-score [26], computed using the leave-one-group-out cross-validation approach described in [27, 28]. The sensitivity analyses compared the results of the selected model with the non-selected ones and a change in the variance of correlation parameters.

The model was estimated using the `inlabru` package [29, 30], a wrapper around the `R-INLA` package [31, 32], in R version 4.4.0 [33]. Further details are provided in Supplementary Files S5.

3. Results

Descriptive reporting for the analytic sample

The analytic sample contained 362,963 tests from patients aged from 30 to 66 years. These patients came from 4,502 unique postcodes (out of a total of 6,033 postcodes). Only 2,198 of these postcodes had recorded tests performed through the organised screening pathway, compared to 4,445 for the opportunistic one. Test dates ranged from the week of 2020-08-17 to that of 2023-11-27 (i.e., a total of 174 weeks), see Supplementary Files S6.

Of these HPV tests, 3.7% and 9.2% were positive for HPV16/18 and for other genotypes, respectively. For opportunistic screening, these percentages were 3.8% and 9.4%, for HPV16/18 and other genotypes, respectively. For organised screening, they were 2.9% and 6.9% for both groups, respectively. Stratified observed prevalence within the analytic sample can be found in Supplementary Files S7.

Posterior predictive check for the selected model

The selected model had spatial components specified through the BYM2 prior, with the first order Queen contiguity structure as the neighbourhood matrix. The model was able to reproduce observed prevalence: the posterior average [equal-tailed interval at 95%, ETI95%] predictive cervical infection prevalence from the fitted model was 3.7 [3.7,3.8]% for HPV16/18 and 9.3 [9.2,9.4]% for other genotypes. Keeping the same order for the genotypes, the posterior average [ETI95%] predictive cervical infection prevalence among opportunistic tests was 3.8 [3.7,3.9]% and 9.4 [9.3,9.5]%, respectively. For organised screening, they were 2.9 [2.6,3.2]% and 6.9 [6.5,7.3]%, respectively. Further stratification can be found in Supplementary Files S7.

Spatial-specific expected difference between HR HPV cervical prevalence from opportunistic and organised screening among 30 year old, as of November 2023

The posterior distribution of the spatial-specific difference between the expected HR HPV cervical infection prevalence generated using the model specific to each type of screening made it possible to quantify the difference in expected prevalence associated with opportunistic screening compared with organised screening. For comparison purposes and given the non-linear relation between the expected prevalence and strata characteristics, we focused here on 30 years old, the age at which the recommendation to use HPV tests begins, considering the last observed week, as of November 2023.

A very likely (probability > 0.95) systematic upward inflation in expected prevalence for opportunistic screening, with respect to organised screening, was found in 89.5% and 100.0% of postcodes, respectively for HPV16/18 and for other genotypes (see Supplementary Files S8). The postcode having the greatest ETI95% upper bound provided the plausible maximum expected systematic inflation, whose posterior average [ETI95%] was 2.9 [0.8,5.4] pp for HPV16/18 and 12.3 [7.8,17.0] pp for other genotypes (Figure 1).

Insert Figure 1 here.

Figure 1: Posterior average difference (in percentage points), between opportunistic and organised screening, in the expected HR HPV cervical infection prevalence in France (upper row) and Paris region (bottom row), among 30 years old, as of November 2023 for HPV16/18 (A) and other genotypes (B). Maps with ETI95% are provided in Supplementary Files S8.

Mapping of the expected HR HPV cervical infection prevalence among 30 years old as of November 2023

The joint posterior distribution of the model specific to organised screening allowed us to generate the spatial-specific expected HR HPV cervical infection prevalence under organised screening, among 30

years old, as of November 2023. This made it possible to produce the first spatially resolved nationwide mapping of this quantity.

The postcode with the minimum ETI95% lower bound provided the plausible minimum expected prevalence, whose posterior average [ETI95%] expected prevalence was 2.5 [1.0,4.7]% for HPV16/18 and 5.8 [3.3,8.7]% for other genotypes. By contrast, the maximum upper bound had a posterior average [ETI95%] expected prevalence of 7.2 [3.1,13.6]% for HPV16/18 and 25.4 [13.0,41.5]% for other genotypes (Figure 2A and B). Maps with ETI95% upper and lower bounds are provided in Supplementary Files S9.

Insert Figure 2 here.

Figure 2: Posterior average expected HR HPV cervical infection prevalence in France (top rows) and Paris region (bottom row), among 30 years old, as of November 2023, for HPV16/18 (A) and other genotypes (B). Maps with ETI95% upper and lower bounds are provided in Supplementary Files S9.

Age-specific expected HR HPV cervical infection prevalence in major French cities

To study how the expected HR HPV cervical infection prevalence changed with age, as of November 2023, we restricted the evaluation of the posterior expected prevalence to eleven major French cities. We did so because the grid defined over all postcodes and ages was too large to draw from the joint posterior distribution. These cities were spread around mainland France, Supplementary Files S2 shows their locations.

The likely systematic upward inflation identified among females age 30 extended to almost all ages in major French cities. For example, in Paris, the posterior ETI95% lower bound for this upward inflation went from 1.9 [0.4,3.3] pp for HPV16/18 and 9.2 [5.7,12.7] pp for other genotypes at 30 years old to, 1.0 [-0.1,1.9] pp and 2.7 [0.4,4.8] pp at 66 years old, respectively. When removing the systematic inflation associated with opportunistic screening, the posterior average [ETI95%] expected HPV16/18 cervical infection prevalence in Paris, France's capital city, went from 4.7 [3.5,6.1]% among the 30 years old down to 3.4 [2.5,4.5]% at 66 years old. For other genotypes, it went from 16.3 [13.0,20.0]% to 9.6 [7.6,12.1]% (Figure 3A and B). Supplementary Files S10 compares the infection prevalence between HPV16/18 and other genotypes.

Insert Figure 3 here.

Figure 3: A) Summary of the posterior distribution of the expected HR HPV cervical infection prevalence, in major French cities, as of November 2023, stratified by age and genotype group. B) Summary of the posterior distribution of the difference (in percentage points), between the two groups of genotypes (other genotypes and HPV16/18), in the expected prevalence of cervical infection, in major French cities, as of November 2023, stratified by age. The table counterparts are provided in Supplementary Files S11.

Temporal changes in the expected HR HPV cervical infection prevalence

The posterior distribution for the expected HR HPV cervical infection prevalence under opportunistic screening favored an increase of the expected infection prevalence between the last and first week of the study period, for both groups of genotypes. However, when considering organised screening such a positive temporal trend was not found with high certainty (Figure 4A and Supplementary Files S12).

Insert Figure 4 here.

Figure 4: A) Posterior odds ratio between the expected HR HPV cervical infection prevalence during the last and first week of the study period, stratified by type of screening and genotype groups. B) Posterior expected HR HPV cervical infection prevalence simulated for the analytic sample assuming that all data would have been collected only through opportunistic or organised screening, stratified by year of screening. C) Posterior marginal difference in expected prevalence of opportunistic screening in the analytic sample, stratified by year of screening and age class. Panels B and C are available in table format in Supplementary Files S13.

Marginal difference in expected HR HPV cervical infection prevalence associated with screening pathway

To go beyond the conditional picture explored so far, we computed the Marginal Difference in Expected Prevalence (MDEP). The MDEP measures the average difference in expected prevalence if all data had been collected via opportunistic rather than organised screening. It accounts for all interactions and reflects how the within sample expected prevalence would change depending on screening type.

Assuming all data would have been collected under organised screening, the posterior average [ETI95%] expected prevalence was 3.2 [2.9,3.6]% for HPV16/18 and 7.3 [6.7,7.9]% for other genotypes. The alternative situation, in which all strata would have been collected through opportunistic screening would be associated with an average [ETI95%] change in the expected prevalence of 0.5 [0.1,0.9] pp and 2.1 [1.5,2.7] pp, for HPV16/18 and other genotypes, respectively (Figure 4A and B). The MDEP stratified by age and year is provided in Figure 4C.

Sensitivity analyses

Supplementary Files S14 report the results of the sensitivity analyses. Only slight changes in the posterior average and ETI95% for the MDEP were observed.

4. Discussion

Screening and vaccination are key elements of the WHO strategy to eliminate cervical cancer [2, 3, 34]. Spatially-resolved maps of HR HPV infection prevalence can help identify areas where vaccination and screening uptake are essential. However, such analyses are rare.

This study provides the first spatially resolved picture of HR HPV cervical infection prevalence in France, using the largest dataset published so far for this country, both in terms of the number of tests and spatial coverage. Unlike most studies, our modelling approach was designed to handle non-linear age-specific prevalence patterns, the spatial structure of the data, and multiple genotype groups and screening types within a unified statistical modelling approach.

The analysis highlighted the systematic inflation of HR HPV cervical infection prevalence when using data from opportunistic screening compared to those collected through organised screening. After adjusting for this, we estimated the prevalence for all females aged 30 years across France, those aged 30-66 years in 11 major cities, and then the entire analytic sample.

HR HPV cervical infection prevalence

A meta-analysis of 194 studies published between 1995 and 2009, focusing on females with normal cytological results, estimated a global HR HPV cervical infection prevalence of 11.7% (95% confidence interval, CI95%: [11.6,11.7]) [35]. In Western Europe, based on a total of 77,445 tests (compared to 1,016,719 for the global pooled estimate), they found a crude prevalence of 7.3 [7.1,7.5]% and an adjusted prevalence of 9.0 [8.8,9.2]%.

As of 2014, for France, the WHO identified 12 studies [36–47] estimating HR HPV cervical infection prevalence [48]. Within these studies, the number of tests ranged from 221 to 7,339 and the infection prevalence ranged from 10.5 [9.9,11.3]% to 48.3 [42.8,54.0]%. In addition to small sample sizes, most of these studies relied on data collected within a single centre, usually a hospital [36–38, 40, 42, 44, 45, 47] or a clinic [41], or multiple centres located within the same district [39, 43]. Heard *et al.* [46] however stands out through the use of a dataset collected in 16 sites, located in different regions, from July 2009 to November 2012, following a stratified sampling scheme, according to age class, restricted to females aged 25-65 years. The authors found a HR HPV in 13.7 [11.7,15.6]% of the cervical samples, collected on 3,037 females with normal cytological analysis.

For HPV16/18, among females with normal cytology, the WHO report found a pooled prevalence [CI95%] of 3.8 [3.6,4.0]% and 2.6 [2.5,2.7]%, in Southern and Western Europe, respectively [48]. For France, Heard *et al.* [46] reported a prevalence of 3.9 [2.8,5.1]% for HPV16/18 in the same population. In the analytic sample collected through organised screening, we observed a prevalence for HPV16/18 of 2.9% and our model produced a posterior average [ETI95%] of 2.9 [2.6,3.2]%. Considering the distribution of the explanatory variables observed within the analytic sample, assuming a collection through organised screening, the expected posterior average [ETI95%] prevalence was 3.2 [2.9,3.6]%.

The differences between earlier prevalence results, notably that from Heard *et al.* [46], and ours, could primarily be due to differences in sample composition. First, differences in age composition: Heard *et al.* [46] selected participants based on a stratified sampling scheme while we used all tests collected by one of the leading networks of biology laboratories in France and provided age-specific infection prevalence estimates. Second, differences in spatial coverage is an additional explanatory factor: we used test results from all over France whereas Heard *et al.* [46] had samples coming from only 5 of the 22 regions of France. Last but not least, vaccination coverage against HR HPV genotypes increased in France between previous studies and ours. As of 2024, vaccination is recommended for girls and boys aged between 11 and 19 years and for men who have sex with men, up to the age of 26. Vaccination for girls has been recommended since 2007 [49]. In 2022, 33.8% of girls aged 16 years had a full vaccination scheme, against 15.5% in 2017 [50]. The differences in modelling approach and the limited descriptive analysis reported in Heard *et al.* [46] limits further discussion.

Public health and future research implications

Many countries, especially in Europe, have implemented nationwide organised HPV testing programs, with the intent to increase screening uptake [12, 35]. In France, according to the latest assessment carried out by the French National Public Health Institute (Santé publique France), the coverage of cervical cancer screening uptake among the [30-65] years old, between 2020 and 2022, was 59.5%, below the 80% targeted by the program [7]. In most of these organised screening programs, including France, invitations are dispatched based on time since the previous screening [12]. However, our analysis revealed a highly non-linear variation in the expected prevalence with age and space, suggesting that adjusting the frequency of these invitations based on these factors could improve the effectiveness and efficiency of organised screening programs.

We showed that data from opportunistic screening were likely associated with a systematic inflation in HR HPV infection prevalence across mainland France compared to organised screening. Our quantification offers a valuable reference for future modelling studies that use opportunistic screening data and aim to correct for this effect. However, it remains uncertain whether opportunistic or organised screening gives a more accurate reflection of the true prevalence.

Limits

Our work has three main limitations. First, the large grid used to define strata caused high computational and storage costs, preventing interaction between dimensions from being considered. As a result, all models, despite their flexibility, treated each dimension independently, thereby assuming perfect separation between them on the linear scale.

Second, the dataset did not allow for the study of organised screening uptake among eligible females. A complementary report by Santé publique France found that 11.6% of screening tests for females aged 30-65 in 2020-2022 were through organised screening [7].

Lastly, because organised screening is not mandatory, residual selection bias may affect the estimated prevalence. Modelling the selection process could address this concern, however this is typically impossible using data routinely collected by medical biology laboratories.

Perspectives

This study provides an original, nationwide, and spatially resolved picture of HR HPV cervical infection prevalence in France. It also highlights the very likely systematic upward inflation in expected prevalence yielded by opportunistic screening compared with organised screening.

Similar quantification of the differences between screening pathways for other pathogens, whose prevalence studies heavily rely on opportunistic sampling, should be performed to improve the reliability of future prospective modelling work.

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Statement

Ethical considerations

Study declared to the French Data Protection Authority (the *Commission nationale de l'informatique et des libertés*, CNIL) by the French National Centre for Scientific Research (CNRS) Data Protection Department (DPD) on the 05/07/2024 (number 2228349/3, UMR7241 record). All data processing was compliant with the French reference methodology MR-004 (research not involving the human person, studies and evaluations in the field of health).

Declaration of Competing Interests

The authors have nothing to declare.

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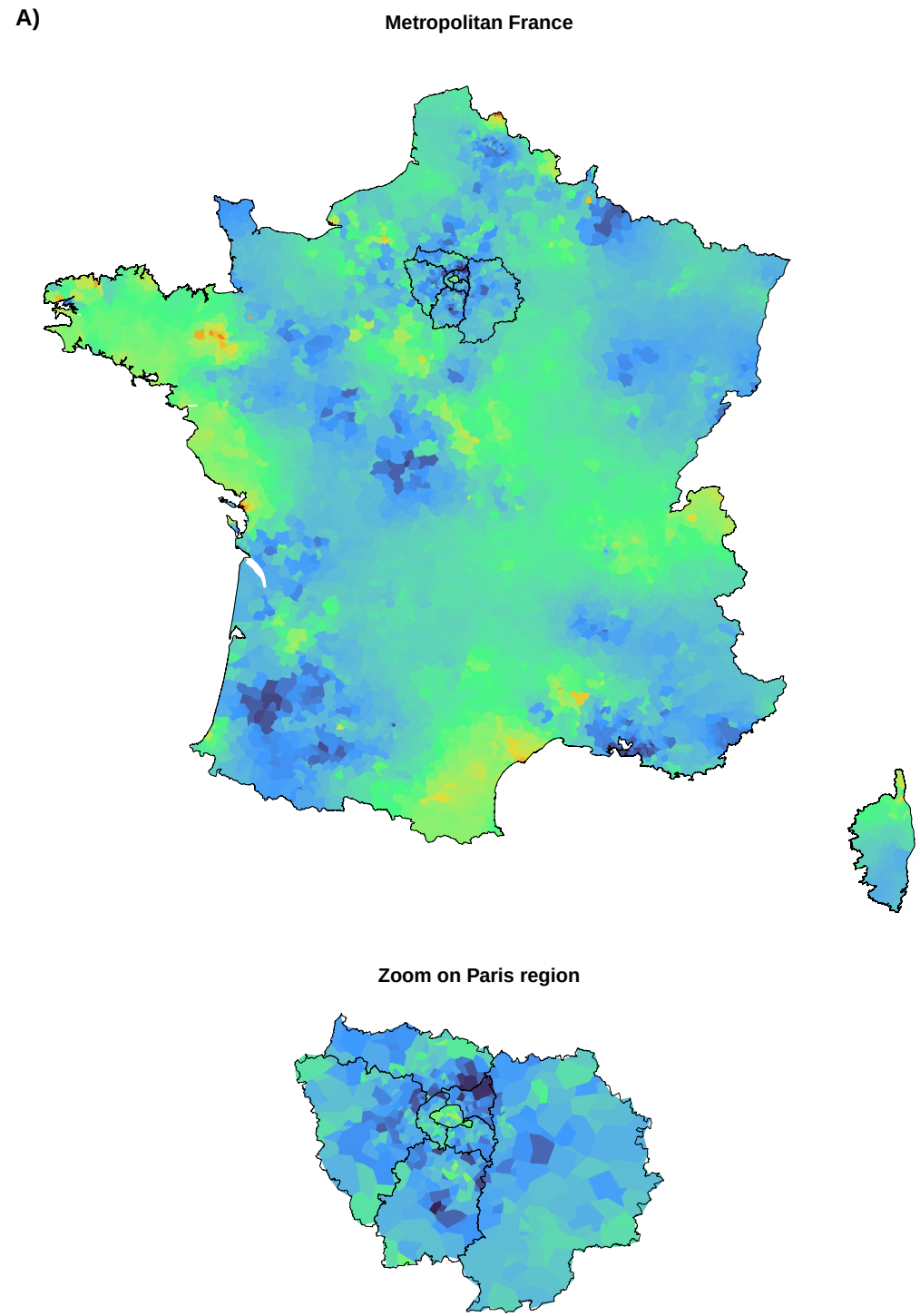
Authors contributions

- Study conceptualisation: O.S., S.H.B., S.A., M.T.S.
- Administrative work: O.S., S.A.
- Funding acquisition: O.S., S.H.B., M.T.S, S.A., S.B.
- Initial data extraction and cleaning: M.R.
- Secondary data cleaning: O.S.
- Initial statistical analysis: O.S.
- Initial draft: O.S.
- Specific domain knowledge: M.R., S.H.B., S.B., S.A., N.T.
- Review of first draft: M.T.S, S.A.
- Review of subsequent drafts: All authors
- Supervision of the statistical analysis: S.A., M.T.S.
- Supervision: S.H.B., M.T.S, S.A., S.B.

Data and codes

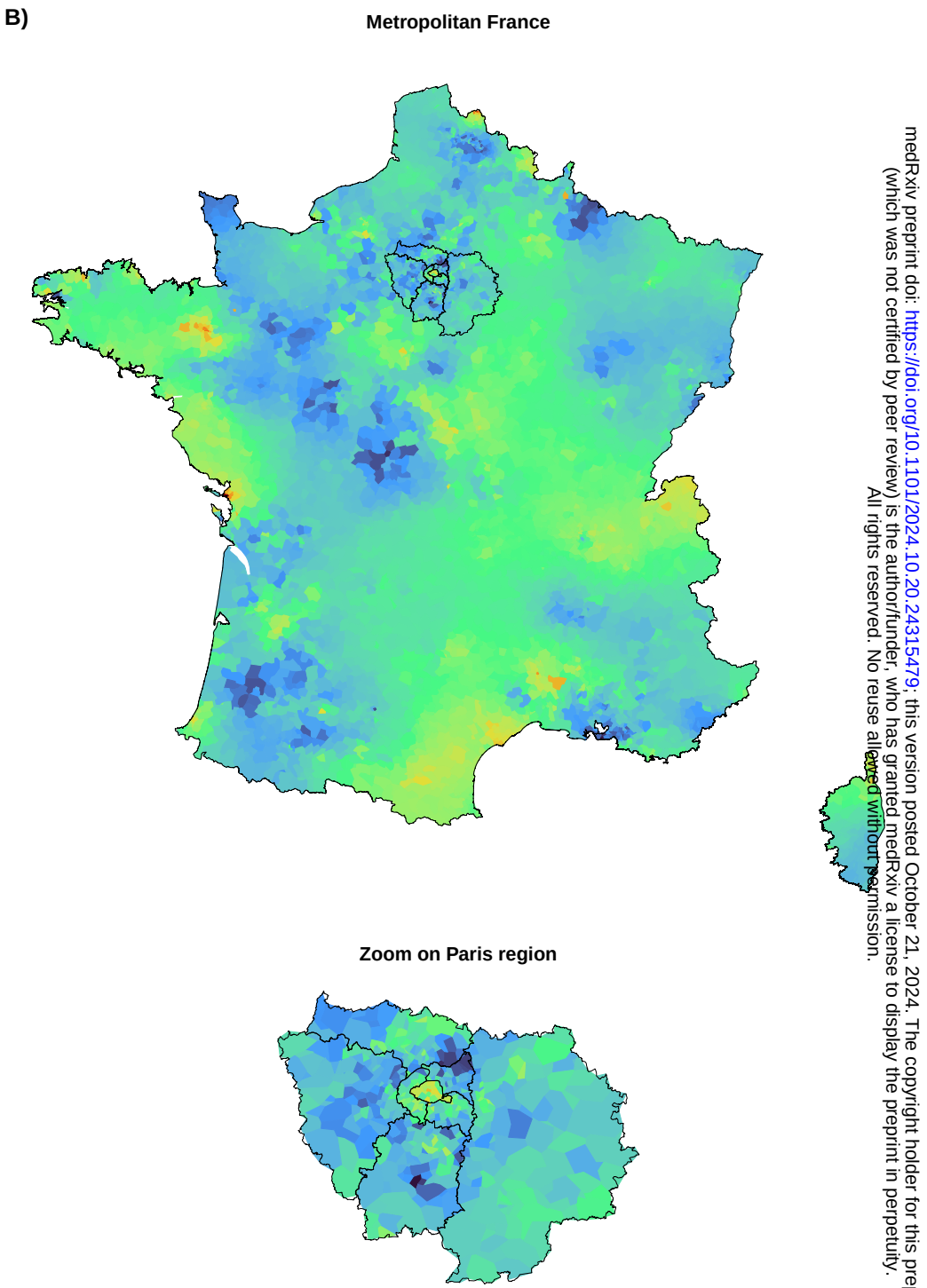
Data cannot be shared due to legal constraints associated with the use of the French reference methodology MR-004.

Codes are available on the first author's GitHub page: https://github.com/osupplisson/hpv_prevalence.



Difference (in percentage points) in expected prevalence between opportunistic and organised screening, among 30−year−olds, as of November 2023, for HPV16/18

1pp 1.5pp 2pp 2.5pp 3pp



Difference (in percentage points) in expected prevalence between opportunistic and organised screening, among 30−year−olds, as of November 2023, for other genotypes

4pp 6pp 8pp 10pp 12pp