Perspective

Seroprevalence of SARS-CoV-2 Antibodies in French Polynesia and Perspective for Vaccine Strategies

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Abstract: In French Polynesia, Wuhan, Delta and Omicron SARS-CoV-2 variants-of-concern (VOCs) caused epidemics with variable severities. We assessed the prevalence and titers of anti-SARS-CoV-2 antibodies related to natural infection and/or vaccination, from a representative sample (N=673) of the adult population of Tahiti recruited during November-December 2021 (after the Delta outbreak and just before the Omicron epidemic). Of the 673 participants tested, 644 (95.7%) had detectable antibodies against SARS-CoV-2-S and/or -N proteins resulting from natural infection and/or vaccination, and 388 (57.7%) were positive only for the detection of anti-N antibodies indicating natural infection. SARS-CoV-2 seroprevalence extrapolated to the adult population of Tahiti was estimated at 95.9%. Concentrations of anti-SARS-CoV-2-S antibodies significantly increased with age, number of self-reported SARS-CoV-2 infections (0 or ≥1), and number of COVID-19 vaccine doses (0, 1, 2, or 3) received by the participants. Elderly people, who are at higher risk of severe outcomes, had received more vaccine doses than younger individuals both in our sample and in the general population. The high level of antibody responses related to past infections and vaccination, especially booster doses, has likely contributed to reducing the severity of the Omicron outbreak in French Polynesia.

Keywords: SARS-CoV-2; COVID-19; seroprevalence; antibodies; vaccine; natural infection; French Polynesia

1. Introduction

In March 2020, while coronavirus disease 2019 (COVID-19) had just been characterized as a pandemic by the World Health Organization (WHO) [1], the first case of infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in French Polynesia [2]. Due to strict control measures immediately implemented by the government of French Polynesia to stop SARS-CoV-2 transmission, including lockdown and closure of borders, only 62 cases of COVID-19 and no deaths were reported between March 10th and June 25th [3]. Following the reopening of the borders to international air traffic in July 2020, a first epidemic wave caused by the original Wuhan strain occurred in French Polynesia [4]. Since then, three additional COVID-19 epidemic waves related to different SARS-CoV-2 variants of public health concern (VOCs), and with variable degrees of severity, have been reported [5-7].

A vaccination campaign was implemented in French Polynesia from January 2021 to reduce the numbers of severe outcomes from SARS-CoV-2 infection [8]. At the beginning

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of the campaign, individuals aged over 75 years old, those with severe co-morbidities, and health care workers were targeted for vaccination. Then, from March 2021, vaccination has been gradually extended to the general population aged over 18 to over 5 years old.

To assess the level of immunity against SARS-CoV-2 at the end of the first epidemic wave, a seroprevalence study was conducted in February 2021 by the Cellule Epi-surveillance COVID and the health department of French Polynesia [4]. A random sample consisting of 463 unvaccinated adults (210 males and 253 females aged from 18 to 88 years old) was recruited on the two islands most affected by the first COVID-19 wave, Tahiti (N=372) and Moorea (N=91). Among the participants, 18% [CI 95% 14.4-22.3] had detectable immunoglobulin type G (IgG) antibodies against SARS-CoV-2: 20.6% [CI 95% 16.3-25.6] in Tahiti and 9.4% [CI 95% 4.6-18.3] in Moorea. No significant difference was found between age groups and genders (unpublished data).

The proportion of the population immunized against SARS-CoV-2 has increased considerably thereafter as a result of the intensive vaccination campaign and the occurrence of new epidemic waves. The aim of the present study was to measure the prevalence and titers of anti-SARS-CoV-2 IgG antibodies related to natural infection and/or vaccination, from a representative sample of the adult population of Tahiti recruited during November-December 2021 (after the end of the second COVID-19 epidemic wave, and just before the beginning of the third wave). Personal data collected from the participants, in particular their history of COVID-19 disease and vaccination status, were also used to identify factors likely associated with protection against infection and occurrence of severe symptoms.

2. Materials and Methods

2.1. Study site and population

French Polynesia is a French overseas collectivity in the Southeast Pacific composed of 74 inhabited islands distributed among five archipelagos (Society, Tuamotu, Marquesas, Austral and Gambier). According to the last census, total population in 2017 was ca 276,000 inhabitants. The most populated islands are Tahiti and Moorea with ca 190,000 and 17,000 inhabitants, respectively (https://www.ispf.pf/content//uploads/Le_recensement_de_la_population_en_Polynesie_francaise_en_2017_3434668982.pdf).

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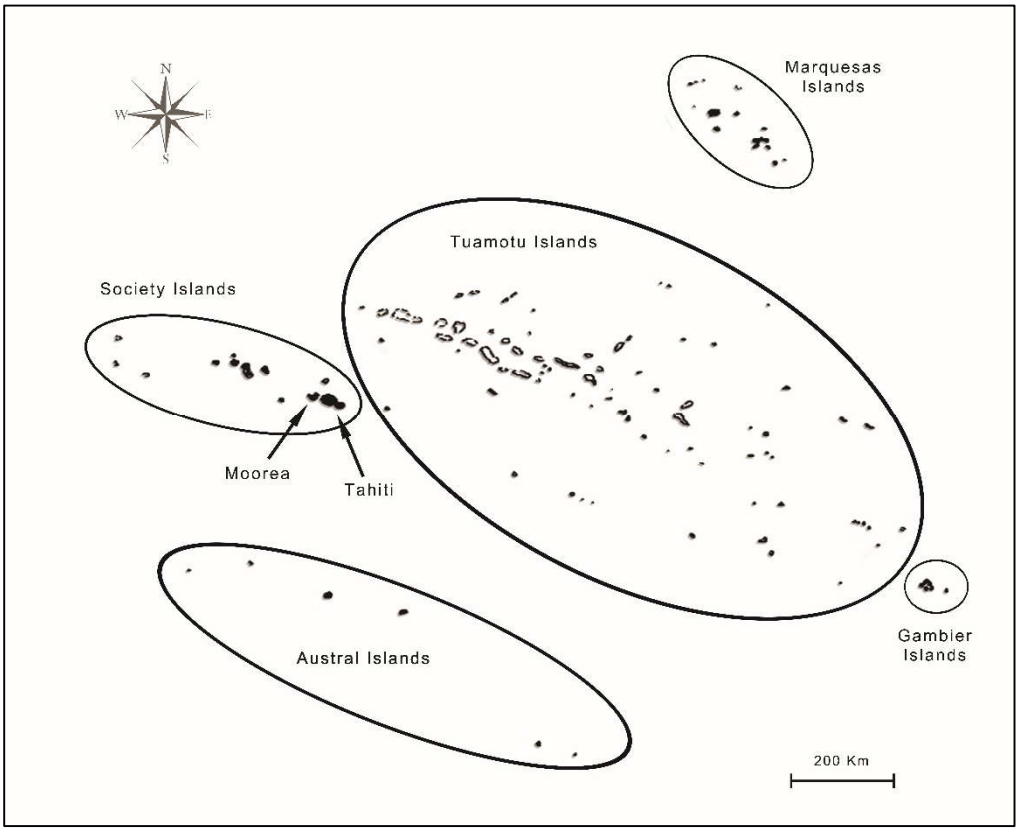

Figure 1. Map of French Polynesia. The five archipelagos of French Polynesia (Society, Tuamotu, Marquesas, Austral and Gambier) are delineated by black circles. The most populated islands (Tahiti and Moorea) are indicated by arrows.

2.2. COVID-19 epidemiological data

During the first months after the introduction of SARS-CoV-2 in French Polynesia, confirmations of COVID-19 cases were exclusively performed at the Institut Louis Malardé (ILM, Papeete, Tahiti) and at the Centre Hospitalier de Polynésie française (CHPF, Pirae, Tahiti) using RT-PCR assays. In October 2020, antigen rapid tests started to be used for COVID-19 diagnosis at ILM, CHPF, and in public health care centers located in the different islands of French Polynesia. RT-PCR and antigen rapid test assays have been subsequently used by private laboratories. In August 2021, the use of antigen rapid tests by pharmacies, as well as sale to individuals for self-testing, was authorized. All data of SARS-CoV-2 infection cases detected by ILM, CHPF, private laboratories and pharmacies (from October 2021), as well as COVID-19-related hospitalizations and deaths that occurred in public hospitals, private clinics, and at home, have been collected by the Cellule Epi-surveillance Covid at French Polynesia Health services.

From July 15, 2020, to March 27, 2022, all travelers aged six years and over entering French Polynesia were tested after arrival to detect potential asymptomatic SARS-CoV-2 infection [9-10]. RT-PCR and/or antigen rapid tests were performed by ILM and positive cases were reported to the Direction de la Santé. Infected travelers were counted in the total number of confirmed cases of COVID-19 in French Polynesia.

To identify viral strains responsible for COVID-19 cases detected in French Polynesia, from February 2021 some of the samples found positive by SARS-CoV-2 RT-PCR or antigenic rapid test have been screened at ILM using variant-specific amplification kits (TIB MOLBIOL, Germany), and the complete sequence of the gene coding for the spike (S) protein has been sometimes determined as previously described [9]. Detection of VOCs was reported to the Direction de la Santé of French Polynesia.

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2.3. COVID-19 vaccination data

In French Polynesia, the messenger RNA (mRNA)-based vaccine Comirnaty®, (Pfizer, USA, and BioNTech, Germany) has been used since the beginning of the vaccination campaign in January 2021. The viral vector-based vaccine Janssen® (Johnson & Johnson, USA) and protein-based vaccine Nuvaxovid® (Novavax, USA) started to be used from May 2021 and April 2022, respectively. The Janssen® vaccine stopped being administrated in French Polynesia in April 2022.

Vaccination was recommended for people aged over 18 years in March 2021, then over 16 in April 2021, over 12 in June 2021 and finally over 5 in February 2022. Janssen® and Nuvaxovid® vaccines have been authorized for primary injection and in very rare instances for secondary injection (N=66) in people aged 18 years and over. Comirnaty® vaccine has been used for primary and subsequent injections in the population over the age of 5. Initially, vaccine schedule was considered complete after one dose of Janssen® or two doses of Comirnaty®. After December 15 2021, two doses of COVID-19 vaccine were required to complete the vaccine schedule.

Information about the age of each vaccinated individual, the type of vaccine administered, and the number of doses received have been recorded by the Direction de la Santé of French Polynesia.

2.4. Sampling procedure

The present study was performed in accordance with the recommendations of the WHO concerning COVID-19 sero-epidemiological surveys as of May 26, 2020 [11]. With respect to these recommendations, a cross-sectional study was conducted after the end of the second COVID-19 epidemic wave in French Polynesia, from a sample of the adult population stratified by age and gender, using a quota sampling method. The sampling of participants was carried out using the system of random phone calls. Epidemiological data (including socio-demographic characteristics, clinical features, COVID-19 vaccination status and previous exposure to SARS-CoV-2) were collected in a questionnaire from each participant, as well as a blood sample for serological analysis. The sampling procedure is detailed in the following sections (2.4.1. to 2.4.4.).

2.4.1. Sample size and inclusion criteria

During the previous COVID-19 serosurvey conducted after the first epidemic wave, the prevalence of IgG antibodies against SARS-CoV-2 in unvaccinated adult participants was estimated at 18% (20.6% [CI 95% 16.3-25.6] in Tahiti and 9.4% [CI 95% 4.6-18.3] in Moorea. In the present study, selection of participants was performed within the adult population of Tahiti, the most inhabited and affected island by the second COVID-19 epidemic wave in French Polynesia. Only people who had resided in Tahiti since March 2020 (date of first introduction of SARS-CoV-2 in French Polynesia) were included in the study.

To calculate the sample size required to achieve a certain level of precision in the seroprevalence estimate, the precision of the 95% confidence interval (95% CI), w, for the expected prevalence, p, was calculated for different values of the sample size, n, and p, using the formula below:

$$w = F^{-1}(1-\alpha/2,np+1,n(1-p)) - F^{-1}(\alpha/2,np,n(1-p)+1)$$

where $F^{-1}(x,a,b)$ is the inverse cumulative distribution function of the beta distribution with shape parameters a and b, and $\alpha=0.05$ is the significance level.

By this method, the minimum size of the sample to be recruited for the study was evaluated at 500 participants, for an expected prevalence between 20% and 80%, and a precision of < 10% (Table 1). The sample size was increased by 20% (i.e. to 600 participants) to ensure that the minimum quota of participants to be recruited (N = 500) would be achieved.

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Table 1. Precision of the 95% confidence interval (w) according to the expected prevalence estimate (p), for a sample size of 500 participants to be recruited in Tahiti.

Prevalence (p)	20%	30%	40%	50%	60%	70%	80%
Precision (w)	0.072	0.082	0.088	0.089	0.088	0.082	0.072

The sample of 600 adult participants to be recruited was divided into five age groups each containing 50% males and 50% females: 18-29 (N=150), 30-39 (N=150), 40-59 (N=150), 60-69 (N=100) and ≥ 70 (N=50).

2.4.2. Random selection of participants

The random sampling of participants was performed by a survey company (Alvea Consulting, Papeete, Tahiti) using a quota sampling method. Briefly, the random sampling was performed from a database of 114,260 cell phone numbers mostly registered in Tahiti. Each cell phone number was called 2 times maximum by the investigators of Alvea Consulting in the order of appearance on the draw list. Among the individuals who answered the first or second call, those who met the age and gender criteria, and had resided in Tahiti since March 2020, were invited to participate in the study. For individuals that gave oral consent to participate, the following data were collected by the investigators: name, gender, age, geographic address, preferred spoken language (French or Tahitian), preferred location (at home or at ILM) and date (from Monday to Saturday) for the appointment with the nurse to perform the blood sampling and complete the questionnaire. All of this information was sent daily to the nurses of ILM who were responsible for calling back each individual to confirm the appointment. During the call, the nurse checked the identity and the inclusion criteria of the individual (including age and gender). Individuals who did not answer after two calls, did not meet all inclusion criteria, or refused the appointment with the nurse, were removed from the study and replaced by other individuals until the quota of participants by age group and gender was reached.

2.4.3. Written consent collection

During each appointment, the nurse first checked the identity and the inclusion criteria of the individual selected by phone before explaining in detail the course of the study. An information sheet describing the study and two copies of the consent form (one for the participant and the other retrieved by the nurse) were then given to the individual. If the individual agreed to sign the consent form after reading the information sheet, a unique identification number (barcode) was immediately assigned to the participant to anonymize the blood sample and data subsequently collected. Individuals who refused to sign the consent form, answer the questionnaire, or have their blood drawn were removed from the study and replaced by other individuals until the quota of participants by age group and gender was reached.

2.4.4. Blood sample and data collection

A venous blood sample (≈ 5 mL) was collected from each participant using a serum separator tube BD Vacutainer SST™ II advance (Becton Dickinson, USA). In addition, a questionnaire including socio-demographic characteristics, clinical features, COVID-19 vaccination status and previous exposure to SARS-CoV-2 of the participant was completed by the nurse using a digital tablet. Individual barcodes were used to identify the blood tube and the questionnaire of each participant. Blood tubes were stored in coolers until being dropped off at ILM. Questionnaires saved on the digital tablets were transferred daily to a secure server at ILM.

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2.5. Serological analysis

Blood tubes were centrifuged for 15 minutes at 3,500 rpm to separate serum from clotted blood. Serological analyses were performed from serum with the Cobas e 601 analyzer using both Elecsys® anti-SARS-CoV-2 S and Elecsys® anti-SARS-CoV-2 kits (Roche diagnostics, Switzerland), following the manufacturer's instructions.

The Elecsys Anti-SARS-CoV-2 S assay uses a recombinant protein representing the receptor binding domain (RBD) of the SARS-CoV-2 S antigen in a double-antigen sandwich assay format. This assay allows quantitation of IgG antibodies specific to SARS-CoV-2 S protein RBD, expressed as U/mL. The analytical measuring interval is 0.40-250 U/mL. Results provided by the analyzer are interpreted as negative or positive for the detection of anti-SARS-CoV-2-S antibodies for values < 0.80 U/mL and ≥ 0.80 U/mL, respectively. In the present study, samples tested positive with a value > 250 U/mL (upper limit of the analytical measuring interval) were diluted from 1:10 to 1:50 to assess more accurately the concentration of anti-SARS-CoV-2-S antibodies.

The Elecsys Anti-SARS-CoV-2 assay uses a recombinant protein representing the SARS-CoV-2 nucleocapsid (N) antigen for the qualitative detection of antibodies (including IgG) specific to SARS-CoV-2-N protein. The result of a sample is given by the analyzer in the form of a cutoff index (COI; signal sample/cutoff), with COI < 1.0 and COI ≥ 1.0 interpreted as negative and positive for the detection of anti-SARS-CoV-2-N antibodies, respectively.

Vaccines used in French Polynesia (Comirnaty®, Janssen®, and Nuvaxovid®) stimulate the production of antibodies against SARS-CoV-2-S protein. Consequently in the present study, the detection of anti-SARS-CoV-2-S antibodies using Elecsys Anti-SARS-CoV-2 S assay indicates a natural infection and/or vaccination, while the detection of anti-SARS-CoV-2-N antibodies using Elecsys Anti-SARS-CoV-2 shows a natural infection only.

2.6. Statistical analysis

Statistical analyses were performed using Stata (version SE 17.0), GraphPad Prism (version 9.2.0) and R (version 4.1.0) softwares. Chi square (X^2) or Fisher exact tests were used to compare serology results between groups of participants with different socio-demographic characteristics, clinical features, COVID-19 vaccination status, and history of exposure to SARS-CoV-2. Mann Whitney and Kruskal-Wallis tests were used to compare anti-SARS-CoV-2-S antibody concentrations according to age groups, genders, number of self-reported SARS-CoV-2 infections and COVID-19 vaccine doses received. Statistical significance was set at $p < 0.05$.

2.7. Ethics statement

The use of data produced within the framework of the present study was approved by the ethics committee of French Polynesia (No. 94 / CEPF of December 06, 2022). Written informed consent was obtained from all participants. People who were unable to express their consent or answer the questionnaire were excluded from the study.

3. Results

3.1. SARS-CoV-2 epidemiological data in French Polynesia

According to the epidemiological data collected by the cellule Epi-surveillance Covid of French Polynesia, four COVID-19 epidemic waves occurred in French Polynesia from the introduction of SARS-CoV-2 in March 2020 to the end of August 2022 (Figure 2). The first wave was caused by the original Wuhan virus and lasted from August 2020 to March 2021. During this period, about 19,000 COVID-19 cases, 1,220 hospitalizations and 150 deaths related to SARS-CoV-2 infections were recorded. The second wave, caused by the Delta (B.1.617.2) VOC between July and October 2021, was of higher magnitude with approximately 29,000 COVID-19 cases, 1900 hospitalizations and 600 deaths reported. The third wave resulted from the transmission of the two Omicron sub-lineages BA.1 and BA.2

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between December 2021 and April 2022. Although more than 26,000 COVID-19 cases were detected, only 133 hospitalizations and 13 deaths were recorded. The fourth wave, characterized by the circulation of several Omicron sub-lineages (mainly BA.5), started in June 2022 and was still ongoing as of August 31. During June-August 2022, about 3,500 COVID-19 cases, 38 hospitalizations and 1 death were recorded.

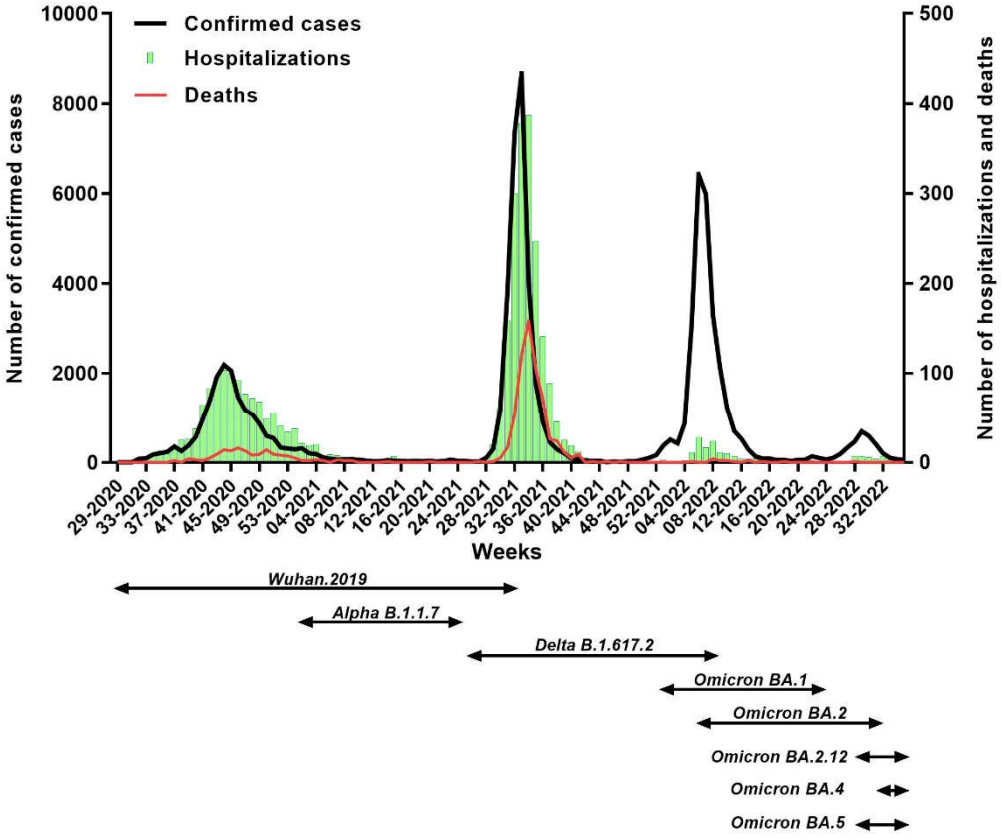

Figure 2. Weekly number of COVID-19 confirmed cases, related hospitalizations and deaths, and circulation periods of SARS-CoV-2 variants of concern in French Polynesia between July 15, 2020, and August 31, 2022.

3.2. COVID-19 vaccination data in French Polynesia

Between January 2021 (the beginning of the vaccination campaign in French Polynesia) and the end of August 2022, a total of 189,677 individuals received a first dose of COVID-19 vaccine including Comirnaty® (N=156,444), Janssen® (N=33,205), and Nuvaxovid® (N=28) (Figure 3). Among them, 111,670 and 8,962 subsequently received a first and second booster dose with the Comirnaty® vaccine, respectively.

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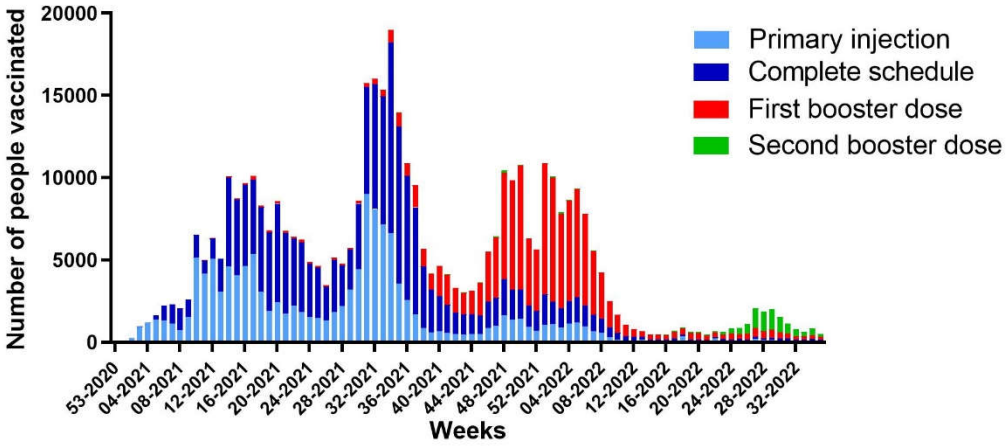

Figure 3. Weekly evolution of COVID-19 vaccination in the population of French Polynesia between January 2021 and August 2022.

3.3. Analysis of serological results and data collected from the study participants

Between November 22 and December 11, 2021, a total of 673 individuals aged 18 years and over were recruited in Tahiti for our COVID-19 serosurvey. All participants gave their written consent, completed the questionnaire and had interpretable results for the SARS-CoV-2 serological analyses. Characteristics of the participants and serological results (detection of antibodies against SARS-CoV-2-S and –N proteins and concentrations of anti-SARS-CoV-2-S antibodies) are detailed in Table S1.

Among the 673 participants, 644 (95.7%) had detectable anti-S and/or anti-N antibodies resulting from a natural infection and/or vaccination, while 388 (57.7%) were positive only for the detection of anti-N antibodies thus indicating past natural infection (Table 2). To assess the prevalence of SARS-CoV-2 antibodies within the adult population of Tahiti, raw data obtained from the sample of 673 participants (detection of anti-S and/or anti-N antibodies) were adjusted using a bootstrap sampling method (1000 replicates) and age distribution data for the population of Tahiti aged 18 years and over. Using this method, SARS-CoV-2 seroprevalence in the adult population of Tahiti was estimated at 95.9% [CI 95% 94.0–97.7].

Analysis of the results obtained for the detection of anti-S and/or anti-N antibodies shows that the proportions of participants found positive are not significantly different according to age groups (p=0.8), gender (p=0.7), number of inhabitants in the household (p=0.2), occupation (p=0.3), education level (p=0.6), and severity of the disease indicated by a hospitalization and/or home oxygen therapy (p>0.9) (Table 2). In contrast, prevalence rates of anti-S and/or anti-N antibodies were significantly lower in participants who self-reported no history of SARS-CoV-2 infection (p=0.0003) and COVID-19 vaccination (p<0.0001). Interestingly, anti-S and/or anti-N antibodies were detected in 100% of participants that received at least one dose of COVID-19 vaccine, in 99.5% of individuals that self-reported at least one SARS-CoV-2 infection, and in 100% of the patients who had COVID-19-related complications.

The proportion of participants who tested positive for the detection of anti-N antibodies was not significantly different between males and females (p=0.6) (Table 2). In contrast, the prevalence of anti-N antibodies was significantly lower in participants aged 70 years and over compared to the three youngest categories (p=0.005, p=0.001 and p=0.008 for 18-29, 30-39 and 40-59 age categories, respectively), and in participants aged 60-69 years compared to those aged 30-39 years (p=0.02). The prevalence of anti-N antibodies was also significantly lower in participants who did not report any previous SARS-CoV-2 infection (p<0.0001); in those who received three doses of COVID-19 vaccine compared to zero (p<0.0001), one (p<0.0001) or two (p=0.0001) doses, or who received two doses compared to zero (p=0.0007) or one (p=0.0003) dose; in individuals living in households

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with less than 5 people compared to those from larger families (p<0.0001); in retired or pre-retired persons compared to working people (p=0.005); in participants with the highest education level compared to elementary-middle school (p=0.003) and secondary school (p=0.001) levels; and in individuals who did not have COVID-19-related complications (p=0.003) while 100% of the patients who required hospitalization and/or home oxygen therapy had anti-N antibodies.

Table 2. Seropositivity for SARS-CoV-2 among 673 adult participants randomly recruited in Tahiti between November 22 and December 11, 2021.

Variable	Participants (N)	Positive IgG anti-S and/or anti-N		Positive IgG anti-N	
		N	% [IC 95%]	N	% [IC 95%]
Age group					
18-29	169	161	95.3 [90.9–97.9]	103	60.9 [53.2–68.3]
30-39	163	156	95.7 [91.3–98.3]	105	64.4 [56.6–71.7]
40-59	171	165	96.5 [92.5–98.7]	102	59.7 [51.9–67.1]
60-69	113	109	96.5 [91.2–99.0]	56	49.6 [40.0–59.1]
≥70	57	53	93.0 [83.0–98.1]	22	38.6 [26.0–52.4]
Gender					
Male	329	316	96.1 [93.3–97.9]	193	58.7 [53.1–64.0]
Female	344	328	95.4 [92.6–97.3]	195	56.7 [51.3–62.0]
Number of self-reported SARS-CoV-2 infections[1]					
0	461	433	93.9 [91.3–95.9]	195	42.3 [37.7–46.9]
≥1	212	211	99.5 [97.4–100]	193	91.0 [86.4–94.5]
Number of COVID-19 vaccine doses received[2]					
0	182	153	84.1 [77.9–89.1]	125	68.7 [61.4–75.3]
1	99	99	100 [96.3–100]	73	73.7 [63.9–82.1]
2	320	320	100 [98.9–100]	170	53.1 [47.5–58.7]
3	72	72	100 [95.0–100]	20	27.8 [17.9–39.6]
Number of inhabitants in the household					
1	54	49	90.1 [79.7–96.9]	21	38.9 [25.9–53.1]
2	134	127	94.8 [89.6–97.9]	62	46.3 [37.6–55.1]
3-4	262	253	96.6 [93.6–98.4]	142	54.2 [47.9–60.3]
≥5	223	215	96.4 [93.1–98.4]	163	73.1 [66.8–78.8]
Occupation					
Unemployed[3]	155	145	93.6 [88.5–96.9]	90	58.1 [49.9–65.9]
Workers[4]	377	364	96.6 [94.2–98.2]	231	61.3 [56.2–66.2]
Retired or pre-retired	141	135	95.7 [91.0–98.4]	67	47.5 [39.1–56.1]
Education level					
Elementary-middle school	155	147	94.8 [90.1–97.8]	99	63.9 [55.8–71.4]
Secondary school	263	254	96.6 [93.6–98.4]	165	62.7 [56.6–68.6]
University	255	243	95.3 [91.9–97.6]	124	48.6 [42.3–54.9]
Hospitalization and/or O_2 at home[5]					
Yes	11	11	100 [72.7-100]	11	100 [72.7-100]
No	662	633	95.6 [94.0-97.2]	377	56.9 [53.2-60.7]
TOTAL	**673**	**644**	**95.7 [93.9–97.1]**	**388**	**57.7 [53.8–61.4]**

[1] Self-reported SARS-CoV-2 infection corresponds to a positive RT-PCR or antigenic test specific to SARS-CoV-2 detection as declared by the participant. [2] Of the 491 participants who self-reported having been vaccinated before the beginning of the study, 419 (85.3%), 71 (14.5%) and 1 (0.2%) received a first dose of Comirnaty®, Janssen® or Vaxzevria® (AstraZeneca - Oxford, UK) vaccine, respectively. Subsequent vaccine doses were performed exclusively with Comirnaty®. [3] Unemployed participants included homemakers, students and trainees. [4] Workers included both employees and self-employed people. [5] COVID-19-related hospitalization and home oxygen therapy were considered as indicators of severity.

3.3. Analysis of anti-SARS-CoV-2-S antibody levels

Samples tested positive with a value > 250 U/mL (upper limit of the analytical measuring interval) using the Elecsys Anti-SARS-CoV-2 S kit were diluted from 1:10 to 1:50 to

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assess more accurately the concentration of anti-SARS-CoV-2-S antibodies. Due to the limited number of kits available to perform the serological analyses, 49 samples found positive with a value >12,500 U/mL (dilution 1:50) were not further diluted. The value of 12,500 U/mL was considered as the most accurate concentration for these samples. Moreover, 44 samples tested positive with a value >5,000 U/mL (dilution 1:20) could not be further diluted either to determinate exact concentration values.

Of the 673 samples analyzed, 30 with values <0.80 U/mL (considered as negative for the detection of anti-SARS-CoV-2-S antibodies) and 44 with values >5,000 U/mL (that could not be further diluted) were removed from the analysis of anti-SARS-CoV-2-S antibody concentrations according to different variables (Table 3). Among the 599 remaining samples, concentrations of anti-SARS-CoV-2-S antibodies are not significantly different between males and females (p=0.8). In contrast, they significantly increase with age (p<0.0001), number of self-reported SARS-CoV-2 infections (p=0.0004), and number of COVID-19 vaccine doses (p<0.0001).

Table 3. Concentrations of anti-SARS-CoV-2-S IgG antibodies (U/mL) among adult participants (N=599) randomly recruited in Tahiti between November 22 and December 11, 2021.

Variable	Participants (N)	Anti-S IgG concentration (U/mL) [3]	
		Median [IQR]	Range
Age group			
18-29	154	629 [73-1997]	4-12500
30-39	149	772 [100-2608]	4-12500
40-59	155	847 [215-3942]	4-12500
60-69	96	953 [183-8406]	4-12500
≥70	45	4619 [518-12425]	8-12500
Gender			
Male	290	807 [129-4171]	4-12500
Female	309	912 [160-3404]	4-12500
Number of self-reported SARS-CoV-2 infections[1]			
0	406	701 [129-2709]	4-12500
≥1	193	1799 [221-6133]	6-12500
Number of COVID-19 vaccine doses[2] received			
0	151	57 [15-301]	4-12500
1	94	691 [101-3193]	4-12500
2	295	1547 [465-4917]	13-12500
3	59	7643 [2630-12500]	24-12500

[1] Self-reported SARS-CoV-2 infection corresponds to a positive RT-PCR or antigenic test specific to SARS-CoV-2 detection as declared by the participant. [2] Of the 448 participants who self-reported having been vaccinated before the beginning of the study, 378 (84.4%), 69 (15.4%) and 1 (0.2%) received a first dose of Comirnaty®, Janssen® or Vaxzevria® vaccine, respectively. Subsequent vaccine doses were performed exclusively with Comirnaty®. [3] Samples with values <0.80 U/mL (N=30) or >5,000 U/mL that could not be further diluted (N=44) were removed from the analysis.

4. Discussion

At the end of the first COVID-19 epidemic wave in French Polynesia, while the vaccination campaign had just begun, evidence of SARS-CoV-2 infection (*ie* the presence of specific antibodies) was found in 20.6% [CI 95% 16.3-25.6] of 372 unvaccinated adults recruited in Tahiti in February 2021. In our serosurvey conducted after the second epidemic wave caused by the Delta VOC, 388/673 (57.7%) adult participants from Tahiti were positive for the detection of anti-SARS-CoV-2-N antibodies indicating natural infection. This almost 3-fold increase in the prevalence of SARS-CoV-2 infections is consistent with the high number of cases reported during the Delta-related outbreak (Figure 2). Using data of anti-SARS-COV-2-N and –S antibodies detected in the 673 participants, resulting from natural infections and/or vaccination, we estimated the SARS-CoV-2 seroprevalence in the

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adult population of Tahiti at 95.9% [CI 95% 94.0–97.7]. This high seroprevalence is consistent with the magnitude of the first two epidemic waves added to the increased vaccination coverage in French Polynesia, with 71% of the individuals aged 12 and over who had received at least one dose of COVID-19 vaccine by the date the study started (Figure 3).

Serological results associated with information obtained from the questionnaire showed that the proportion of participants with evidence of SARS-CoV-2 infection (detection of anti-SARS-CoV-2-N antibodies) was significantly lower in the oldest age group (Table 2). Elderly people might have been less exposed to SARS-CoV-2 infection due to better individual protection, in particular respect of barrier gestures (such as wearing a mask, regularly sanitizing hands and keeping distance from other people), and reduced social contacts notably for retired people. This last hypothesis is supported by the observation that the rate of detection of anti-SARS-CoV-2-N antibodies was significantly lower in retired/pre-retired people compared with working individuals.

Analysis of serological data according to the number of COVID-19 vaccine doses received showed that 100% of participants who had received at least one dose had anti-SARS-CoV-2 antibodies against 84.1% for those who had not received any dose (Table 2). Vaccination has contributed to increasing anti-SARS-CoV-2 immunity in the population and, at the same time, to reducing the risk of infection as suggested, on the one hand, by the increasing concentrations of anti-SARS-CoV-2 antibodies depending on the number of vaccine doses received (Table 3) and, on the other hand, by the low rates of naturally infected participants among those who received three doses of vaccine (27.8%) (Table 2).

Education level and number of inhabitants in the household also seemed to have an impact on the risk of infection by SARS-CoV-2 (Table 2). Indeed, participants with the highest education level (University) had the lowest proportion of natural infections (48.6%), which could be related to better individual protection within this population. Moreover, the rate of SARS-CoV-2 infections was significantly higher in the largest families (73.1%), where the risk of infection might be increased by social interactions with other inhabitants of the household.

Among participants who did not self-report any SARS-CoV-2 infection, 42.3% had evidence of past infection (Table 2). This result might be explained by the absence of symptoms at the time of infection, or by the presence of symptoms that were insufficiently pronounced to encourage these participants to be tested. Consequently, the incidence rate during the first two epidemic waves was certainly greatly underestimated due to unscreened people. Conversely, among participants who self-reported having been infected by SARS-CoV-2 at least once, only 91.0% had anti-SARS-CoV-2-N antibodies, suggesting a decrease or disappearance of detectable antibodies in some people infected previously. However, there could also be mistakes in the information self-reported by the participants.

During the study period, the first case of infection by Omicron VOC (BA.1 lineage) was detected on December 06, 2021, in a traveler that had just arrived in French Polynesia. A third COVID-19 epidemic wave rapidly started with similar attack rate but lower severity (≈ 26,000 cases, 133 hospitalizations and 13 deaths) compared to the previous outbreak caused by Delta VOC (≈ 29,000 cases, 1900 hospitalizations and 600 deaths) (Figure 2). Several studies conducted in other countries have also shown that the risk of severe clinical outcomes following SARS-CoV-2 infection was reduced with Omicron compared with Delta [12-18]. Animal experiments with mice, hamsters and cats suggested attenuated pathogenicity of Omicron compared with previous VOCs including Delta [19-22], which could be related to specific mutations notably in the E protein [23].

Another factor that could have contributed to the lower severity of the Omicron-related outbreak in French Polynesia is the high pre-existing immunity against SARS-CoV-2 that resulted from both natural infections and vaccination as shown in our study. Indeed following the Delta-related outbreak, the number of individuals who received a booster (third dose) of Comirnaty® vaccine increased sharply (Figure 3). Although it has been shown that receiving a third dose of Comirnaty® COVID-19 vaccine could not prevent

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infection with the Omicron BA.1 variant during the following months [24], it decreases the risk of severe outcomes requiring hospitalization [25]. Several studies have reported that a booster of Comirnaty® vaccine increases the neutralizing antibody titers against Omicron [26-30]. In our study, quantitation of anti-SARS-CoV-2-S antibodies revealed that concentrations were significantly higher in participants who self-reported at least one past infection (median 1799 U/mL), who had received three doses of COVID-19 vaccine including at least two doses of Comirnaty® vaccine (median 7643 U/mL), and who belonged to the older age groups (median 953 U/mL and 4619 U/mL in 60-69 and ≥70 age groups, respectively) (Table 3). Individuals aged 60 years and over, who are at higher risk of severe outcomes, had received more boosters before the Omicron outbreak than other age groups, both in our sample (Supplementary Table S2) and in the general population of French Polynesia [31]. Past infections associated with vaccine boosters likely contributed to increasing the level of protective antibodies against Omicron in the population and thus reducing the risk of severe disease during the third COVID-19 epidemic wave.

The number of individuals who received a first (third dose) or second (fourth dose) vaccine booster increased before and during the fourth COVID-19 epidemic wave caused by Omicron sub-lineages (Figure 3). As of August 31, 2022, 81.2% of the population aged 60 and over had received a third or fourth dose of Comirnaty® vaccine. A previous study showed that a fourth dose of mRNA vaccine increases protection against infection with Omicron, symptomatic infection, and severe outcomes [32]. Another study suggested that maximal immunogenicity of mRNA vaccines is achieved after three doses, and levels of neutralizing antibodies against Omicron can be restored by a fourth dose administered four months later [33]. Vaccine boosters have certainly contributed to the weak magnitude of the fourth COVID-19 epidemic wave which was still ongoing at the end of August 2022.

Our study has some limitations. First, participants were recruited only in Tahiti while SARS-CoV-2 has circulated in all archipelagos of French Polynesia. Secondly, our analyses rely on self-reported information collected from participants which may be inaccurate. Finally, the number of participants who required hospitalization and/or oxygen therapy at home (N=11) was insufficient to investigate a possible link between the severity of the disease and anti-SARS-CoV-2 antibodies titers.

5. Conclusions

In French Polynesia, the combination of the increase in natural infections and mRNA vaccine boosters just before the emergence of Omicron VOCs seems to have contributed to reducing the burden of severe outcomes in the more recent COVID-19 epidemic waves. Consequently it seems essential to maintain effective vaccination coverage, in anticipation of possible new seasonal waves. SARS-CoV-2 VOCs were introduced from countries having frequent air exchanges with French Polynesia such as Metropolitan France and the USA. There was a lag of several weeks between the emergence of these new VOCs in continental countries and their first detection in French Polynesia. Consequently, in the event of a threat due to a new VOC circulating in France or in the USA, intense and rapid vaccination booster campaigns could be implemented in French Polynesia to increase the level of immunity against SARS-CoV-2 which tends to decrease overtime [26]. This would require quickly mobilizing a large vaccination system over targeted periods. Before implementing such a booster campaign, the cost and associated benefit need to be estimated.

Supplementary Materials: Table S1: Characteristics of the study participants (N=673) and results of SARS-CoV-2 serological analysis; Table S2: Number of COVID-19 vaccine doses received by the study participants (N = 673) in each age group.

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