

same island off the coast of Tuscany, where, in 2012, the Italian cruise ship Costa Concordia ran aground and overturned after striking an underwater rock.

It remains one of the few places in the world where despite the arrival of the SARS-CoV-2, no case of symptomatic COVID19 has been diagnosed among the inhabitants. This observation has caught a broad international media coverage [4] and is the subject of this article.

2. Methods

The aim of the study was to assess whether the observed “resistance” to SARS-CoV-2 had a serological foundation or to identify asymptomatic cases, seeking to detect SARS-CoV-2 antibodies through the screening process, simultaneously laying the foundation to future investigations focused on unraveling the causal dynamics of the apparent resistance.

The imported cases will be thoroughly described later in the article. All of these, except for one, reached the island prior to implementation of distancing measures, while being asymptomatic and later presented symptoms, exposing the population to significant infectious risk, as both phases have been associated with virus transmission [5–9]. Despite the prolonged exposure in a densely populated scenario, the infectious potential of the affected subjects [5–8] and the lack of distancing measures, the resident population did not develop COVID-19 syndromic features in the following months raising profound interest in the local medical community.

This study received ethical approval on April 25, 2020 by the Ethical Committee of the “Istituto Nazionale Malattie Infettive – Lazzaro Spallanzani”.

2.1. Characterization of the exposure

2.1.1. Geographic and demographic features of the island

Geographically, Giglio Island has a mountainous terrain, with ninety percent of its surface being inhabitable or inaccessible due to natural barriers. The last census dates back to May 2019, counting 1423 inhabitants, in three main settlements. The island covers a surface of 24.1 km² with a population density of 59 inhabitants/km².

To estimate the island population density at the time of the serological screening, our study adjusted the surface area as illustrated in Table 1, excluding extra-urban lots, using the official structural plan and maps, provided as a guidance by the municipality and publicly available online [10].

Given the adjusted surface of 0.44771 km², the resulting population density is 1670.7 inhabitants/km². By omitting “Giglio Campese” to avoid a negatively skewed distribution, the resulting estimate in population density is 2511.62 pp/Km², which would rank the local municipality as the 122th most densely populated in Italy (Top 1.54 percentile out of 7903 Municipalities). This is an important information as population density is a likely factor correlated with spread of COVID-19 [11].

Table 1
Geographic and Demographic characteristics of the Giglio Island.

Settlement	Settlement included Areas	Settlement Surface (m ²)	Population (time of study)	Density (inhabitants/km ²)
Giglio Porto	Area A + B + B* + C** + F1-3	168 170	323	1921
Giglio Castello	Area A + B + B* + C** + F1-3	94 210	336	3566
Giglio Campese	Area A + B + B* + C + F1-3	185 330	89	480

Legend: areas A - B - B* (high-density areas), C - C** (low-density areas). Public areas for communal activities (F1-3) have been considered as well to account for potential physical interactions.

2.1.2. Ferry connection between the island and the mainland

During lockdown, the connection to the mainland was through a ferry route with two daily trips covering 11 marine miles. Despite the maximum capacity of 600 passengers, the ferries carried a daily average of ten individuals, rendering the island practically isolated.

2.1.3. Description of imported COVID-19 cases

From February to April 2020, 5 people were tested positive for SARS-CoV-2 while on Giglio Island. Four of these individuals (three males and one female) reached the island before the Italian government imposed social distancing and preventive measures on March 9, 2020. The following is a description of the cases that reached the island, as summarized in Table 2.

Case 1

The first individual, a male aged 55 from Livorno, Tuscany, arrived on the island on February 18, 2020. Three days prior, the man had visited the region of “Emilia-Romagna”, where the outbreak had already been reported [12]. Despite having developed mild cough [13], the man headed to the island and attended the funeral of a close relative in a local church. A rough estimate, based on multiple witnesses’ reports, pictures a total of 40–50 people in close contact with the infected man. Shortly after the funeral, the man returned to Livorno, where his conditions progressively deteriorated. On March 2, he was admitted to the ICU, testing positive for SARS-CoV-2 on the following day. Unfortunately, he died on March 26, 2020 due to COVID-19-related complications.

Case 2 and Case 3

On March 5, an Italian elderly couple, arrived on the island from the city of Piacenza in Emilia-Romagna, which had become a high-risk zone due to the significant number of COVID-19 reports [14].

They interacted with the locals on multiple occasions. On March 6, 2020 the man developed severe cough and low-grade fever. On March 13, the man tested positive for COVID-19 and was hospitalized in the nearby hospital of Grosseto. The man’s conditions stabilized without requiring ICU care. On April 5, 2020 after being tested negative, the man was discharged from the hospital.

The wife did not manifest noticeable symptoms but tested positive as a household contact of Case 2. She remained in house-quarantine during her husband’s hospitalization. On March 24, 2020 she tested negative by pharyngeal swab RT-PCR. Upon her husband’s discharge, the couple reunited, and started compulsory isolation in “Giglio-Campese.”

Case 4

On March 5, 2020 a 74-year-old man arrived on the island from the area surrounding the “Lago di Garda” in the regions of Lombardy and Veneto. The man had multiple reported social interactions with the locals. Six days following his arrival, on March 11, 2020 he showed malaise and asthenia, with mild respiratory discomfort. The man was tested by RT-PCR for SARS-CoV-2 on March 24, 2020, with inconclusive results and finally tested positive on March 28, 2020. The man quarantined in Giglio-Castello and was allowed to leave the island on April 28, 2020 after two negative tests.

Case 5

Table 2
Characteristics of the Covid-19 cases in the Giglio Island.

Case ID	Gender	Age	Provenance	Date Arrival	Exposure timespan	Date of Onset	Symptoms at Onset	Diagnosis
C – 1	Male	55	Bologna/Livorno	18/02/20	1 day	19/02/20	Cough; Low-grade fever	03/03/20
C – 2	Male	66	Piacenza	05/03/20	8 days	06/03/20	Cough; Low-grade fever	13/03/20
C – 3	Female	65	Piacenza	05/03/20	8 days	06/03/20	Cough; Low-grade fever	13/03/20
C – 4	Male	74	Lago di Garda	05/03/20	23 days	11/03/20	Asthenia; Cough; Malaise	28/03/20
C – 5	Male	30	Abroad	17/03/20	7 days	21/03/20	Cough; Low-grade fever	24/03/20

Table 3
Test overall (IgG or IgM) performance analysis as reported by Manufacturer.

Method	RT-PCR		Total
	Positive	Negative	
Covid-19 IgG/IgM Rapid Test	Positive	87	87
	Negative	12	26
Total		99	113

A male aged 30 arrived on March 17, 2020 after close household contacts known to be positive for COVID-19. After arriving, the man resided in his family home, together with his parents and sister. On March 21, 2020 the patient developed low-grade fever and cough and was ordered to isolate. On March 24, 2020 the man tested positive for COVID-19 and was asked to quarantine in Giglio-Porto. The man's condition remained stable and did not require advanced medical care. On April 9, 2020 he was tested negative by RT-PCR.

2.2. Study population

The population screening by serological rapid test on SARS-CoV-2 began on April 29 and ended on May 3, 2020. We initiated population screening for SARS-CoV-2 by inviting all adult residents who were present on the island. Eighty-five people, including healthcare professionals and volunteers, after testing negative at the serological antibody and salivary molecular tests, assisted in conducting the screening. The participation of island inhabitants was assessed and monitored through cross-checking the updated documents provided by the municipality.

The testing was performed in pre-determined locations. Subjects signed an informed consent. A health professional administered a questionnaire asking for background information (age, gender) permanence on the island and smoking status. All data were recorded in digital form. Each participant underwent rapid serological testing and provided a self-collected sample of saliva.

2.3. Rapid testing serology kit

The island population has been tested through the use of COVID-19 IgG/IgM Rapid Test Cassette (COVID-19 IgG/IgM Rapid Test Cassette (whole blood/serum/plasma), Product/Model: GCCOV-402a, Lot: 2003280, Zhejiang Orient Gene Biotech Co Ltd, Huzhou, Zhejiang, China). This rapid kit is a Lateral-Flow, solid-phase Immunochromatographic Assay (LFIA) for the rapid, qualitative and differential detection of IgG and IgM antibodies.

The studies conducted by the manufacturer, illustrated in Tables 3 and 4, report an overall test sensitivity (IgM or IgG) of 87.9% (87/99) and a specificity (IgM or IgG) of 100% (14/14). The sensitivity for solely IgG test was estimated to be 97.2% (35/36) during the convalescence period. An independent study, by Hoffman et al. [15] evaluated the same assay we used for the screening and reported a 69% sensitivity and 100% specificity for IgM detection, while denoting a 93.1% sensitivity and 99.2% specificity for IgG.

Table 4
Test IgG sensitivity analysis as reported by Manufacturer.

Method	COVID-19 patients in convalescence		Total
	Positive	Negative	
Covid-19 IgG/IgM Rapid Test	Positive	35	35
	Negative	1	1
Total		36	36

In manufacturer's analyses the rapid kit's specificity was comparable the results of both Hoffman's study and the pooled results from a recent meta-analysis (MA) by Bastos et al. [16]. On the other hand the analyses concerning the test sensitivity presented a much higher estimate when compared to the MA's results on LFIAs' sensitivity, pooled from 17 diagnostic test studies involving 1857 patients: 66.0% (95%CI: 49.3 to 79.3).

2.4. Nucleic Acid Amplification Tests (NAAT) on saliva

Samples of saliva were refrigerated after collection and stocked in a facility on the island. Upon its completion, they have been transferred to the Onco-genomics and Epigenetics Unit of "IRCCS - Regina Elena National Cancer Institute" to avoid bias associated to point-of-care NAAT assays [17]. Viral genetic material was extracted using Nextractor® NX-48S DNA/RNA Extraction System (Genolution).

The saliva specimens have been analyzed with Allplex 2019-nCoV Assay (Seegene), a real-time reverse transcriptase polymerase chain reaction (RT-PCR) test.

The NAAT testing on saliva has been the object of mixed criticism with studies warning against a reduced sensitivity compared to the upper respiratory tract [18,19]. In contrast, other studies yielded a satisfactory sensitivity for NAATs self-collected saliva, suggesting that they might be a valid alternative to testing on nasopharyngeal samples, especially in settings with resources constraints [20–23].

3. Results

The study successfully screened a total of 723 people, including 634 of 748 residents present at the time of the study (84.8%), and 89 non-residents (including 85 healthcare professionals and Cases 3 and 4).

The screening population (residents and non-residents) consisted of 364 males and 359 females. Out of 723 individuals, 195 identified themselves as smokers, 175 as ex-smokers and 353 denied any previous direct smoking history. The currently smoking portion of the study population is largely made of cigarette-smokers (185 out of 195, 94.9%), with an average daily count of 14 cigarettes/day. The median age of the population was 58.5 years (IQR 27.9 years). The stratified analysis on the smoking population highlighted a slightly uneven gender distribution (108 males vs 87 females) with a median age of 48.7 years (IQR 22.4 years).

3.1. Rapid Testing Serology Kit

The Rapid Testing Serology Kit identified only one previously undiagnosed positive asymptomatic subject by IgM positivity and

confirmed the presence of anti-SARS-CoV-2 antibodies in the two tested patients previously recognized as positive by RT-PCR on the rhino-pharyngeal swab, for a total of 3 positives for anti-SARS-CoV-2 IgG/IgM out of 723 participants. The asymptomatic subject found IgM-positive was tested twice more to corroborate the finding. The man had reached the island on the same ferry as Case 4. Case 1 could not be tested as deceased prior to study beginning; Cases 2 and 5 refused to be tested or provide a biological specimen.

3.2. Nucleic acid amplification tests on saliva

A total of 723 samples of saliva were collected from the population. Of these, 66 could not be analyzed due to collection of insufficient material. The NAAT on patients' saliva did not identify any subject positive for SARS-CoV-2 RNA.

4. Discussion

4.1. Summary of findings

Despite of the introduction of SARS-CoV-2 on Giglio Island by five cases, known to have had physical interaction with local population, our study found one asymptomatic subject, positive to IgM but negative to RT-qPCR and confirmed the absence of either current or past viral infection in 633 residents of this highly populated area through qualitative assessment of anti-SARS-CoV-2 antibodies and RNA in saliva. We monitored the island population for two additional weeks after the study termination, so to detect possible false negatives to rapid ki, but no inhabitants developed any COVID19 related signs or symptoms.

4.2. Strengths and limitations

There are several strengths to our study. The fact that the island population remained isolated throughout the lockdown period creates a closed cohort model with few confounding factors and a reasonably well characterized exposure. Also, the data and sample collection of our study has been properly standardized on the basis of predetermined criteria, as to increase reproducibility and limit bias. The high participation rate also reduces concerns of selection bias.

There are also some limitations. A portion (15.2%) of the resident population did not participate to the serologic screening. This factor, associated to the inevitable lack of blinding among the islanders and the voluntary basis of participation, might have biased the results, underestimating the positive rate. The great variability in rapid serological test performances, particularly in regard of its sensitivity, might have led to overestimate the negative rate. The molecular tests, despite having a confirmatory role, given the time interval between the actual beginning of the study and the time of possible exposure, might have biased the results to finding no cases, failing to recognize a low viral count from the prior month's infection. While the sample size is limited, it is naturally given by the island's population. However, chance as a possible explanation of our findings cannot be excluded.

4.3. Findings in comparison to other studies

There are few comparisons with other studies, because, despite sharing similarities with other seroprevalence investigations [24], it refers to a small and quasi-segregated population where it was possible to carefully track every case of COVID-19 and the social network of exposed individuals related to it.

4.4. Implications for research

Because at the time of arrival of four of the five documented COVID-19 cases, social distancing measures had not yet been put in practice and given the densely populated urban area, we inferred that the absence of confirmed cases is attributable to other factors, such as (A) external environmental determinants; (B) intrinsic determinants to the population; (C) the infectious agent; (D) chance.

Apart from chance, among the plausible environmental determinants, we hypothesize that the scarcity of air pollution, during the months of February and March, [25] might have played a role in limiting the COVID-19 spread. This hypothesis would be consistent with previous studies that highlighted a correlation between lack of air pollutants and low number of infections [26] and COVID-19 mortality [27,28]. Other hypothetical co-determinants are the peculiar geo-climatic and microenvironmental conditions present on the island, possibly reducing the viral load in the aerosol or limiting its infectiveness once exposure occurs.

Another theory to explain this apparent resistance of the population lies in the possibility of a cross-reactive immunity, conferring either protection or reducing the severity of COVID-19, after the exposure to a closely related pathogen. This hypothesis is consistent with some studies showing the presence of a SARS-CoV-2 reactive CD4 T cell subpopulation, manifesting cross reactivity with antigens of endemic coronaviruses, the causative agents of common cold [29–31].

5. Conclusions

Despite extensive exposure to SARS-CoV-2, only one new asymptomatic infection occurred in this population, as documented by IgM but not by RT-qPCR. This may be due to unknown protective factors or chance. On the basis of this first descriptive study, we will carry out further investigations to test the advanced hypotheses using its population as a reference model. In particular, our immediate research activities will focus on examining cross-reactivity to SARS-CoV-2, investigating a possible humoral contribution, both systemic (IgG/IgM mediated) and localized (IgA mediated), accounting also for potential interaction with the residing microbiota. We will also conduct a second serological screening following the population's exposure during a busy summer season that brought thousands of tourists to the island. We will study whether and how the island inhabitants were potentially infected with SARS-Co V-2 during that period.

CRedit authorship contribution statement

Antonio Bognanni: Conceptualization, Methodology, Investigation. **Armando Schiaffino:** Conceptualization, Methodology, Investigation. **Fulvia Pimpinelli:** Validation, Investigation. **Sara Donzelli:** Investigation. **Iliaria Celesti:** Investigation. **Sabrina Strano:** Writing - review & editing. **Elena Solari:** . **Giorgia Schiaffino:** Investigation. **Gabriele Solari:** Investigation. **Domenico Solari:** Investigation. **Serena Delbue:** Investigation. **Marta Rigoni:** Conceptualization, Methodology, Writing - review & editing. **Giandomenico Nollo:** Conceptualization, Methodology, Writing - review & editing. **Greta E. Muti:** Investigation. **Giovanna E.U. Muti Schünemann:** Investigation, Writing, Review Conceptualization, Writing - review & editing, Methodology. **Holger J Schünemann:** Conceptualization, Methodology, Writing - review & editing. **Giovanni Blandino:** Resources, Writing - review & editing. **Aldo Morrone:** Resources, Writing - review & editing. **Paola Muti:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Project administration.

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References

- [1] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Yi, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497–506.
- [2] Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003;348(20):1953–66.
- [3] Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012;367(19):1814–20.
- [4] Frances D'Emilio, Miles F, White D, Beitrag von Patrick Nüscheler, NRK TV. Multiple Web Newspaper articles and Norwegian TV news [Internet]. Associate Press; the Sun: Nau. Available from: <https://tv.nrk.no/serie/dagsrevyen/202006/NNFA03060720/avspiller>.
- [5] Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med* 2020;382(12).
- [6] To K-W, Tsang O-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis* 2020;20(5):565–74.
- [7] Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020;581(7809):465–9.
- [8] He Xi, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020;26(5):672–5.
- [9] Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-NCoV infection from an asymptomatic contact in Germany. *N Engl J Med* 2020;382(10):970–1.
- [10] Comune “Isola del Giglio.” Piano Strutturale “Isola del Giglio” [Internet]. Available from: http://www.comune.isoladelgiglio.gr.it/index.php?option=com_content&view=category&id=82:pianostrutturaledocumentazione&Itemid=2179.
- [11] Kadi N, Khelfaoui M. Population density, a factor in the spread of COVID-19 in Algeria: statistic study. *Bull Natl Res Cent* 2020;44(138).
- [12] Regione Emilia-Romagna. Coronavirus aggiornamento, altri 3 nuovi casi. In Emilia-Romagna ora sono 26. Venturi: “Agiamo con tenacia e competenza”.
- [13] Tacchi G. Coronavirus, la moglie del 55enne contagiato: «Il nostro medico sapeva di Bologna, ci ha detto lui di non chiamare il 118». Il Tirreno, Livorno.
- [14] Emilia-Romagna R. Coronavirus: 698 i casi positivi in Emilia-Romagna, quasi 300 in cura a casa. Salgono a 10 i clinicamente guariti.
- [15] Hoffman T, Nissen K, Krambrich J, Rönnberg B, Akaberi D, Esmailzadeh M, et al. Evaluation of a COVID-19 IgM and IgG rapid test; an efficient tool for assessment of past exposure to SARS-CoV-2. *Infect Ecol Epidemiol* 2020;10(1).
- [16] Lisboa Bastos M, Tavaziva G, Abidi SK, Campbell JR, Haraoui LP, Johnston JC, et al. Diagnostic accuracy of serological tests for covid-19: Systematic review and meta-analysis. *BMJ*. 2020;370.
- [17] Administration UF and D. Coronavirus (COVID-19) Update: FDA Informs Public About Possible Accuracy Concerns with Abbott ID NOW Point-of-Care Test [Internet]. Available from: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-informs-public-about-possible-accuracy-concerns-abbott-id-now-point>.
- [18] Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA - J Am Med Assoc* 2020;323(18):1843–4.
- [19] Kujawski SA, Wong KK, Collins JP, Epstein L, Killerby ME, Midgley CM, et al. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. *Nat Med* 2020;26:861–8.
- [20] Jamal AJ, Mozafarihashjin M, Coomes E, Powis J, Li AX, Paterson A, et al. Sensitivity of Nasopharyngeal Swabs and Saliva for the Detection of Severe Acute Respiratory Syndrome Coronavirus 2. *Clin Infect Dis* [Internet]. 2020 Jun 25; Available from: DOI:10.1093/cid/ciaa848/5862658.
- [21] Williams E, Bond K, Zhang B, Putland M, Williamson DA, McAdam AJ. Saliva as a noninvasive specimen for detection of sars-cov-2. *J Clin Microbiol* 2020;58(8).
- [22] Rao M, Rashid FA, Sabri FSAH, Jamil NN, Zain R, Hashim R, et al. Comparing nasopharyngeal swab and early morning saliva for the identification of SARS-CoV-2. *Clin Infect Dis* 2020.
- [23] Pasomsu B, Watcharananan SP, Boonyawat K, Janchompoo P, Wongtabtim G, Sukuwan W, et al. Saliva sample as a non-invasive specimen for the diagnosis of coronavirus disease 2019: a cross-sectional study. *Clin Microbiol Infect*. 2020;(in press).
- [24] Chen X, Chen Z, Azman AS, Deng X, Lu W, Zhao Z, et al. Serological evidence of human infection with SARS-CoV-2: a systematic review and meta-analysis. Preprint [Internet]. 2020; Available from: DOI:10.1101/2020.09.11.20192773.
- [25] Tenerani L, Lazzarini A, Equizi M, Dalle Mura C, Petrini A, Lubrani G. Structural Plan, Integrated Assessment Process And Strategic Environmental Assessment containing The Environmental Report. 2015;1–167. Available from: http://comune.isoladelgiglio.gr.it/attachments/188_Comune Isola del Giglio - Piano Strutturale - Relazione di Sintesi e Rapporto Ambientale.pdf.
- [26] Zhu Y, Xie J, Huang F, Cao L. Association between short-term exposure to air pollution and COVID-19 infection: evidence from China. *Sci Total Environ*. 2020;727:138704.
- [27] Conticini E, Frediani B, Caro D. Can atmospheric pollution be considered a cofactor in extremely high level of SARS-CoV-2 lethality in Northern Italy?. *Environ Pollut* 2020;261:114465.
- [28] Wu X, Nethery RC, Sabath BM, Braun D, Dominici F. Exposure to air pollution and COVID-19 mortality in the United States. medRxiv (preprint) [Internet]. 2020; Available from: DOI:10.1101/2020.04.05.20054502.
- [29] Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell* 2020;181(7):1489–1501.e15.
- [30] Mateus J, Grifoni A, Tarke A, Sidney J, Ramirez SI, Dan JM, et al. Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. *Science* (80-) 2020;370(6512):89–94.
- [31] Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F, et al. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. *Nature* 2020;587(7833).