PLANETARY HEALTH IMPACTS OF PANDEMIC CORONAVIRUSES

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PLANETARY HEALTH IMPACTS OF PANDEMIC CORONAVIRUSES

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Editorial: Planetary health impacts of pandemic coronaviruses

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planetary health, coronavirus (COVID-19), public health, infectious disease, prevention

Editorial on the Research Topic
Planetary health impacts of pandemic coronaviruses

Novel pandemic coronavirus (SARS CoV-2) originated in Asia in late 2019 and has spread rapidly and indiscriminately worldwide. At the time of publication, the virus has caused over 553 million confirmed cases and over 6.3 million deaths globally, resulting in the most devastating pandemic since the Spanish flu in 1918. A distinct feature of the COVID-19 pandemic is that its full range of impacts far exceeds those resulting from the disease itself. No country in the world has been spared by the socio-economic devastation caused by the pandemic lockdown and there is still not yet a full understanding of the direct and indirect implications for human health and wellbeing in the near and longer term. Subsequent collateral impacts on the natural world, as well as our ultimate goals to live sustainably within it, can therefore also be expected. At the same time, lessons and opportunities that could help catalyze change toward a more sustainable, resilient, and healthy future can be identified. With nature itself being the largest source of pathogens that can potentially spillover from their animal reservoirs and affect human health, such wide ranging, intersectoral, and potentially transformational impacts make pandemic emergencies of central relevance to the emerging field of planetary health.

We invited submissions of original research, mini reviews, and perspectives on the planetary health impacts and opportunities of pandemic emergencies, including but not restricted to COVID-19. Contributions drawing key insights from past pandemics were welcome as were articles making novel contributions to the field of future pandemic preparedness, risk assessment and management. Submissions focusing on non-human outbreaks that offer the potential for cross-disciplinary impact were also considered. Ultimately, contributions to the special issue generally fit under two categories: The climate and nature dynamics of pandemic coronaviruses and challenges and potential solutions surrounding public health interventions.

Regarding climate and nature dynamics, the issue published five contributions. Heibati et al. consider how weather might influence the incidence of COVID-19 infection. The authors employed a quasi-Poisson generalized additional model to examine the potential role of various meteorological factors on daily counts of COVID-19 in Finland during several months in 2020. The authors found no associations between daily temperature and COVID-19 incidence. However, daily average relative humidity was negatively related to COVID-19 rates in two hospital districts although no relation was found at the national scale. The authors conclude that there was no statistically significant relation between meteorological variables and COVID-19 incidence at least in the Finnish study context of arctic and subarctic winter and spring. However, given the small period and modest number of cases, future research on the topic is recommended.

In studying the potential connection between people's exposure to nature due to the COVID-19 outbreak, Lenaerts et al. note that confinement measures to reduce viral spread was implemented globally and, as a result, there was an increase in people exercising outdoors. The authors conducted a survey to assess the extent to which people might visit nature and specifically if these visits might have increased in frequency following restrictions to minimize infectious transmission. Based on 11,352 survey participants in Flanders, Belgium, bivariate and multiple regression results suggest that people indeed have visited nature more frequently than before restrictions and furthermore that nature assisted in sustaining social relationships during a time of coronavirus restrictions.

Codeco et al. note that the Amazon ecosystem is threatened by increasing deforestation and biodiversity loss while also maintaining a high level of tropical diseases. The authors research the relative distribution of six archetypal development trajectories in relation to vulnerability to tropical diseases and environmental degradation. The team finds that small farmer trajectories represent approximately half of the Amazon territory, especially in areas where malaria is rife. Along with the dominant peasant development trajectories, cattle (associated with increased deforestation) and large-scale farm and livestock producing trajectories were associated with a high prevalence of neglected tropical diseases, such as leishmaniasis, *Aedes*-borne diseases and Chagas disease along with biodiversity loss. These results show how land-use change and biodiversity loss driven by agricultural expansion and intensification is often associated to undesired and in some cases unexpected negative outcomes for human health.

Kalema-Zikusoka et al. also work in a tropical forest environment and research potential links between COVID-19 and the health and conservation of endangered mountain gorillas. They provide the example of reduced tourism income leading to increased poaching and ultimately the killing of a gorilla at the hands of a hungry community member. Conservation Through Public Health (CTPH), an NGO that promotes biodiversity conservation, animal and human health and livelihoods in the area of Africa's protected areas along with the Uganda Wildlife Authority have taken steps to improve great ape viewing while preventing COVID-19 transmission between people and gorillas. Behaviors to decrease transmission included the use of face masks, improved hand hygiene, and a 10-meter great ape viewing distance.

Rounding out the nature-infectious disease collection of articles in the special issue, Nova reviews the state of knowledge regarding cross-species transmission of coronaviruses in humans and domestic mammals. She finds that several novel coronaviruses have emerged in humans, domestic and wild animals during the last several decades and has been facilitated by cross-species transmission. She further finds that the coronaviruses were closely related and likely associated with high-host-density environments that facilitate multi-species interactions. She concludes with a call for further research on cross-species transmission, especially in the context of increasing environmental change and degradation.

Public health interventions included six papers in the special issue. Himmel and Frey examine controversial biological and political issues surrounding COVID-19. The authors make various recommendations for actions under the rubric of the World Health Organization and the Biological Weapons Convention.

Rakotonanahary et al. respond to the question of how to control the global COVID-19 pandemic, especially in Africa. The authors argue that the primary challenge in responding to COVID-19 is the integration of several health areas including "prevention, testing, front line health care, and reliable data to inform policies." The team presents a COVID-19 strategy in Ifanadiana District with the Malagasy Ministry of Public Health and non-governmental organizations as partners. The authors describe the contours and challenges of their integrated response and how various data sources can be used to address the science of COVID-19. Despite a second COVID-19 wave in March 2021, results showed fewer cases in Ifanadiana than for many other diseases (e.g., malaria).

Baker et al. argue that the COVID-19 pandemic has exposed the inadequacy of the U.S. healthcare system, which was exacerbated by the estimated $202 billion loss for the healthcare industry from the disease. They argue that while the demand for personal protective equipment (PPE) grows, more sustainable solutions will be necessary to reduce supply, cost, and waste challenges. As a proposed solution, the authors examine the advantages of reusable gowns. Among reusable gown advantages, polyester material reduces microbial cross-transmission, hospitals report a 50% lower cost than with disposable gowns, and reusable gowns reduce energy and water use as they can last through 75–100 launderings compared to single-use disposable gowns.

Huntigford et al. confront the important issue of vaccine justice. Using a Susceptible-Infected-Recovered-Vaccinated

(SIRV) compartmental model, the authors simulate COVID-19 dynamics within and between two countries. Nation one produces a vaccine and decides how it may be shared with nation two. Overlapping with the authors' mathematical structure is the effect of travel between the two nations during a pandemic. Results show that, even when taking into account substantial travel between the two nations, nation one minimizes its total mortality by retaining vaccines and aspiring for full inoculation as quickly as possible. This result suggests that travel risks can be reduced by a fast vaccination campaign. The authors find also that, while a country is better off when it maximizes its own vaccination rate, the total number of COVID-19 associated deaths can be minimized only when vaccine-producing countries share vaccines with countries lacking the capacity to produce one. This raises important political and ethical questions regarding vaccine sharing between wealthier and poorer nations.

Pan et al. estimate national and sub-national effect sizes of non-pharmaceutical interventions (NPI) to control COVID-19 during the initial months of the US pandemic. A problem in such endeavors to date is that effect size estimates "have not accounted for heterogeneity in social or environmental factors that may influence NPI effectiveness" according to the authors. Using daily county-level COVID-19 cases and deaths, doubling times and mortality rates were compared to "four increasingly restrictive NPI levels." Using a "stepped-wedge cluster-randomized trial analysis" results suggest that "aggressive (level 4) NPIs were associated with slower COVID-19 propagation" and a longer duration of level 4 NPIs was related to lower case rates and longer doubling times. They also found heterogeneity in NPI effectiveness across US Census regions which suggests that control strategies may be most optimally designed at the community-level.

Completing the special issue, Fendt et al. examine the demand for face masks in Germany. They note that non-reusable masks are often incorrectly disposed and are not biodegradable, increasing their environmental impact. The authors question, however, to what extent mask users are conscious of this, and the factors that may impact face mask choice. Investigating "user preferences, perceived effectiveness, and the sustainability of different mouth/nose protection (MNP)," the authors use a national sample of 1,036 participants to describe trends among respondents. Results suggest that protective effectiveness, and the reusability of MNP are important to most respondents and especially to older informants. Conversely, "the price, shape, and design were not as important." The authors conclude that there appears to be a preference for sustainable MNP so long as their protection remains equivalent to medical or FFP2/FFP3 masks.

Author contributions

DL-C drafted the bulk of the paper. SS and GD wrote parts of the paper. All authors contributed to the conceptualization and editing of the paper.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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COVID-19 Solutions Are Climate Solutions: Lessons From Reusable Gowns

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The COVID-19 pandemic has laid bare the inadequacy of the U.S. healthcare system to deliver timely and resilient care. According to the American Hospital Association, the pandemic has created a $202 billion loss across the healthcare industry, forcing health care systems to lay off workers and making hospitals scramble to minimize supply chain costs. However, as the demand for personal protective equipment (PPE) grows, hospitals have sacrificed sustainable solutions for disposable options that, although convenient, will exacerbate supply strains, financial burden, and waste. We advocate for reusable gowns as a means to lower health care costs, address climate change, and improve resilience while preserving the safety of health care workers. Reusable gowns' polyester material provides comparable capacity to reduce microbial cross-transmission and liquid penetration. In addition, previous hospitals have reported a 50% cost reduction in gown expenditures after adopting reusable gowns; given the current 2000% price increase in isolation gowns during COVID-19, reusable gown use will build both healthcare resilience and security from price fluctuations. Finally, with the United States' medical waste stream worsening, reusable isolation gowns show promising reductions in energy and water use, solid waste, and carbon footprint. The gowns are shown to withstand laundering 75–100 times in contrast to the single-use disposable gown. The circumstances of the pandemic forewarn the need to shift our single-use PPE practices to standardized reusable applications. Ultimately, sustainable forms of protective equipment can help us prepare for future crises that challenge the resilience of the healthcare system.

Keywords: reusable gown, isolation gown, climate-smart healthcare, safety, resilience, sustainability, COVID-19, PPE

INTRODUCTION

In the spring of 2020, the COVID-19 pandemic swept across the United States and overwhelmed the supply of personal protective equipment. Countries around the world saw images of US nurses wearing garbage bags due to gown shortages (1). Nurses and doctors were given one mask for multiple patient encounters, which both increased their risk of infection and the risk of infecting others (2). A pandemic of this nature has long been predicted given our expedited intrusion into wildlife habitats and exposure to pathogens (3). Lessons from building healthcare resiliency during COVID-19 could hold the key for dealing with another, perhaps greater, health crisis: climate change.

Fossil fuel pollution from healthcare harms patient health. Air pollution from the healthcare industry is estimated to cause 405,000 lost disability-adjusted life years in the U.S. every year (4). Preventing the worst impacts of climate change requires achieving net-zero greenhouse gas emissions by 2050 (5). The U.S. healthcare sector alone is responsible for 10% of U.S. greenhouse gas emissions, 64% of which comes from supply chain (4); therefore, averting the worst effects of climate change requires substantial supply chain emissions reductions (6).

Climate-smart healthcare is healthcare that is both low-carbon and builds resilience to climate change (3). Here, we provide one example of how COVID-19 solutions can be climate solutions: a review of the literature surrounding reusable isolation gowns, the second-most-used piece of personal protective equipment (PPE) following gloves (7).

Johns Hopkins estimated that a single 100-day COVID-19 wave would require an additional 321,000,000 isolation gowns on top of baseline isolation gown use in hospital inpatients, emergency departments, emergency medical services, outpatient visits, and nursing homes in the U.S. (8). As this model assumed strict social distancing, even more PPE may be needed if and when compliance decreases (9). Prominent successful deployments of reusable gowns at institutions like the Ronald Reagan UCLA Medical Center and Carilion Clinic in Roanoke, Virginia, have demonstrated how reusable gowns are safer, cheaper, and more sustainable than disposable gowns. Reusable PPE is especially relevant during the pandemic, as it ensures supply stability given increased demand. Finally, replacement of disposable isolation gowns with reusable isolation gowns demonstrated a 28% reduction in energy consumption, a 30% reduction in greenhouse gas emissions, a 41% reduction in blue water consumption, and a 93% reduction in solid waste generation (10).

Although reusable gowns have clear benefits, 80% of U.S. hospitals currently use disposable isolation gowns (7). In this literature review, we use MeSH terms and keywords to index PubMed articles and catalog websites and procurement guides. We find that reusable isolation gowns are poised as an excellent first step for hospitals to save money, stay safe, and transition to climate-smart healthcare practices.

SAFETY

The purpose of PPE is to protect wearers from the spread of infectious diseases. The type and need for an isolation gown depend on the anticipated amount of contact with potentially infectious material. This is reflected in two classification systems for protective apparel safety, the Association for the Advancement of Medical Instrumentation (AAMI) and the Occupational Safety and Health Administration (OSHA) (11, 12). Although many reusable and disposable isolation gowns on the market are OSHA-compliant and follow the AAMI criteria, we now assess whether certain textiles are more effective barriers than others.

Reusable isolation gowns are typically composed of polyester, but several are composed of cotton or a blend of both fabrics (13). Synthetic fibers such as polypropylene and polyester have been shown to exhibit less liquid penetration compared to natural fibers such as cotton (14). Loosely woven cotton gowns, which were common historically, have since been pulled from the market due to high permeability (15). Reusable gown cuffs are typically knitted; however, limited research exists comparing the safety of knitted cuffs to the woven and nonwoven designs in disposable gowns. To reinforce their strength and further minimize the risk of cross-transmission, reusable gowns can be treated with repellant and antibacterial finishes. Studies have shown that these treatments may reduce the risk of bacterial cross-transmission and microorganism penetration, even when gowns show no visible liquid penetration (7). Research into new, eco-friendly antimicrobial finishes such as chitosan or peroxy acids is ongoing (15). Reusable gowns can typically withstand 75–100 washes while retaining maximum repellency. Laundry services can track the number of washes using marked grids or add chlorofluorocarbon to the gown wash to ensure reusability (16).

Disposable gowns are typically composed of synthetic fibers such as polypropylene, polyester, and polyethylene. They are designed with nonwoven processes which utilize either thermal, chemical, or mechanical fiber-bonding; meanwhile, reusable gowns tend to be woven. Although the random order of fibers in nonwoven fabrics has been shown to limit penetration by liquids, there is high variability in gown production, and no existing literature shows nonwoven fabrics to be safer than impermeable woven fabrics, especially woven polyester (T280) (15, 17, 18). The comparable safety provided by reusable gowns is especially important as the demand for gowns soars during and potentially after the global pandemic.

The CDC recommends a shift toward reusable isolation gowns composed of polyester and polyester-cotton fabrics (19).

COST

The pandemic has created enormous financial burdens on hospitals and health systems with an estimated loss of $202 billion across the industry (20). With these losses, health care systems have already started to furlough and lay off health care workers. Solutions that can decrease the cost of the pandemic for hospital systems could help relieve this impact.

Case studies demonstrate that a transition to reusable isolation gowns can result in significant cost savings. For example, the Ronald Reagan UCLA Medical Center has saved over $1.1 million in 3 years after implementing 3.3 million reusable gowns (see Case Studies section for more details) (21). In another case study, the Carilion Clinic, a healthcare system encompassing over 195 hospitals and clinics saved over $850,000 over 3 years after transitioning to reusable isolation gowns (22). After comparing the net investment costs with incremental savings, Carilion Clinic calculated a return on investment (ROI) period of only 6 months in a pre-COVID world. They estimated a cost savings of nearly 50% per gown use, with \$0.79 per use for disposable compared to \$0.39 per use for reusable gowns. Though few peer-reviewed studies have been published on the cost-savings of reusable isolation gowns, myriad studies have found similar cost-savings or cost-equivalence in the context of surgical gowns (23–26).

One study found that a single 100-day COVID-19 wave would require an additional 321,000,000 isolation gowns in the U.S. healthcare system (8). Assuming proportional cost savings to those for Carilion Clinic, reusable gown use would save healthcare systems an estimated \$128,400,000 in surge gowns over that 100-day period alone. These savings may be greater during large-scale crises when competition over limited single-use supplies drive up costs. Researchers at the Society for Healthcare Organization Procurement Professionals found that the COVID-19 pandemic has led to a 2000% price increase for isolation gowns, from \$0.25 to \$5 per gown (27). With new disposable gowns required for every provider and every provider requiring multiple gowns per day, the demand and therefore cost of gowns has skyrocketed. Reusable gowns provide not only a baseline cost savings but also price and supply stability during times of high PPE demand.

ENVIRONMENTAL SUSTAINABILITY

Reusable isolation gowns offer a tremendous opportunity to reduce environmental impact across their lifetime. Life cycle inventory (LCI) studies consistently find that, while initial manufacturing of reusable gowns might be more energy-intensive than disposable gowns over their lifetime, reusable isolation gowns use less energy, produce less waste, and generate less greenhouse gas emissions compared to disposable gowns (10, 15, 28, 29).

In a systematic evaluation of isolation gowns that included the impacts of manufacturing, packaging, and landfill disposal of disposable gowns compared to reusable gowns, reusables were found to consume 28% less total energy over the cradle-to-grave product life cycle (10). In addition, reusable gown use led to a 30% reduction in greenhouse gas emissions and a 93–99% reduction in solid waste generation at the studied healthcare facility (**Figure 1**). Finally, blue water consumption in reusable gown systems was found to be half the consumption level typical to disposable gown systems (10).

A Life Cycle Inventory (LCI) of reusable vs. disposable isolation gowns, commissioned by the Textile Rental Services Association of America, found that even the best case scenario of disposable gowns (polypropylene, spunbond nonwoven with more efficient manufacturing and transportation) had higher global warming potential than the worst case for reusable gowns (polyethylene with less efficient manufacturing, transportation, and washing) at 61 kg CO_2 compared with 41 kg CO_2, respectively. In addition, the best case of disposable gowns had substantially higher acidification potential, eutrophication potential, smog creation potential, and primary energy demand, and similar-to-higher ozone depletion potential, compared to the worst case of reusable gowns. The impacts of disposable gowns were primarily linked to raw materials (polypropylene) and manufacturing, while impacts of reusable gowns were dominated by washing (29).

A cradle-to-use comparison of reusable medical patient gown (55% cotton/45% polyester with a halamine antimicrobial surface) to a disposable gown (polypropylene Spunbond-Meltblown-Spunbond fabric) found that the reusable gown consumes 71% less energy than the disposable gown (65,049 MJ compared to 225,947 MJ, respectively, per 75,000 gown uses), assuming 75 reuses per reusable gown. In addition, the reusable gown produces significantly less air, water and solid chemical emissions. The reusable gown uses fewer raw materials overall, excluding water. Even assuming only ten reuses, the reusable gown achieves lower energy usage than the disposable gown (28).

We emphasize that the results must be contextualized based on the unique fabric (e.g., 100% cotton vs. cotton/polyester mix), manufacturing process, and laundering process of the gowns, as well as the antimicrobial finish and application process. For example, nanoscale Silver (nAg) is an attractive antimicrobial product used in many consumer textiles. A comparison of nAg enabling processes found substantial variation in environmental impacts (30). Environmental impacts from silver must be addressed, for example, through textile wastewater treatment (31).

Acknowledging the relative scarcity of studies on isolation gowns, we compared our findings to the literature on surgical gowns and drapes in the OR. A recent cradle-to-end-of-life analysis, including natural resources, creation, use and reuse, laundering, sterilization, and transportation, and end-of-life disposal of reusable surgical gowns against disposables found that using reusable gowns reduced natural resource energy consumption by 64%, greenhouse gas emissions by 66%, blue water consumption by 83%, and solid waste generation by 84% when compared with disposable gowns (32). This is consistent with earlier studies of reusable vs. disposable surgical textiles: across six large life-cycle studies, researchers found that, compared with reusable textiles, disposable textiles require 200–300% more energy and 250–330% more water, generate 750% more solid waste and generate a 200–300% larger carbon footprint (24).

CASE STUDIES

Reusable isolation gowns have been in widespread use at many medical sites, including Carilion Clinic and Ronald Reagan UCLA Medical Center.

Carilion Clinic has been using reusable isolation gowns since 2011, when clinics experienced gown quotas from the H1N1 outbreak. Short gown supply, combined with dissatisfaction over the waste from disposables, drove the project's initiation. Reusable gowns were assessed based on clinical performance (i.e., safety), cost, environmental impact, and user experience. Gowns were designed and deployed in a manner that received full approval from the infection control committee, and several

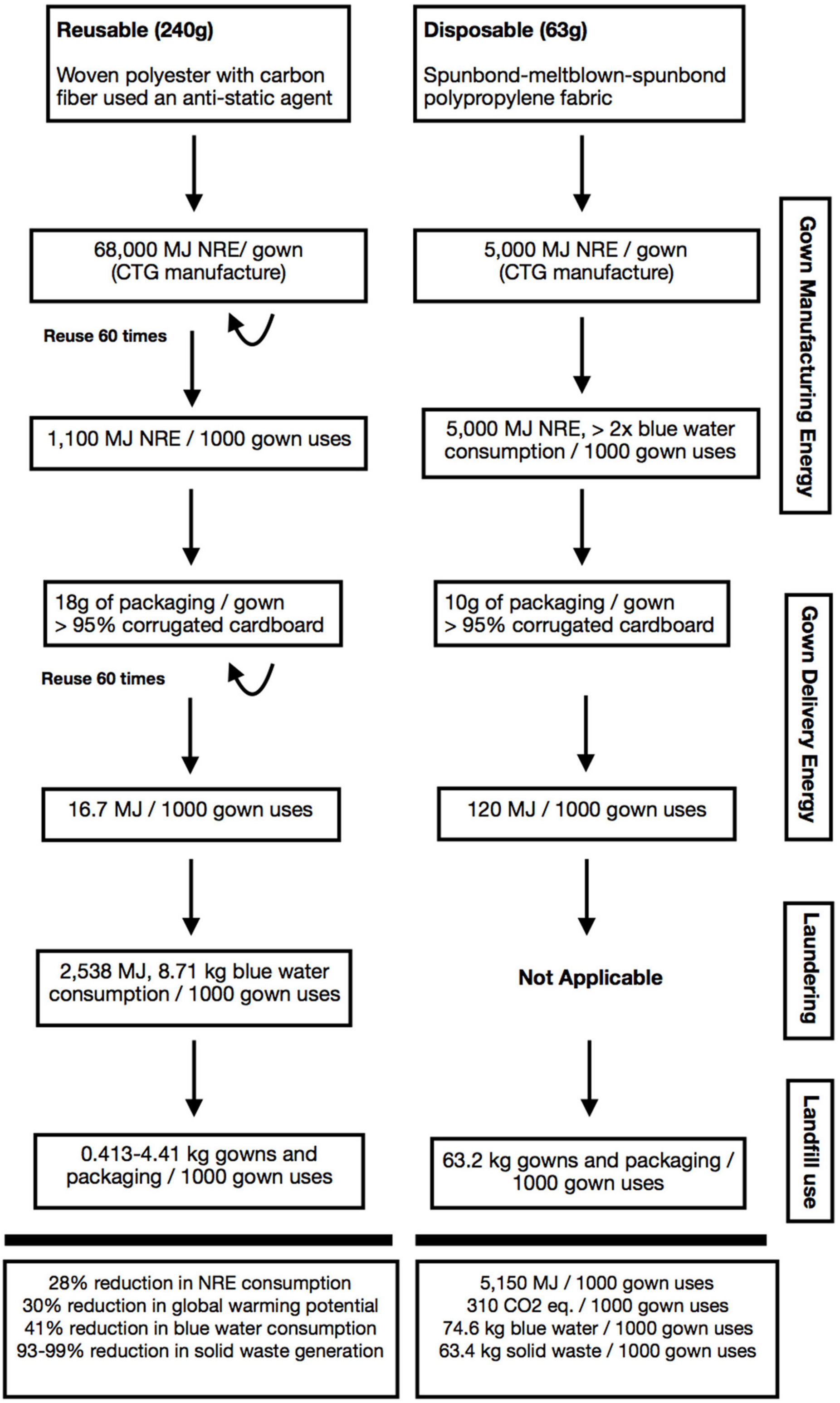

FIGURE 1 | Life cycle inventory of reusable vs. single-use isolation gowns. Environmental costs of each step of a life cycle inventory (LCI) as reported in Vozzola et al. (10). *Environmental considerations in the selection of isolation gowns: A life cycle assessment of reusable and disposable alternatives.* While reusable gowns exhibit higher footprints in manufacturing and delivery energy expenditure, re-calculated footprints based on gown use reveal significant reductions across all four categories of environmental indicators. Vertical boxes on the right indicate stage of life cycle inventory. CO_2 eq, carbon dioxide equivalent; MJ, megajoules; NRE, natural resource energy.

safety measures were taken with each use. First, gowns were inspected for stains and tears before repackaging. Second, for each inspection, a quality control grid on the isolation gown was marked with a symbol unique to the employee, which allowed both tracking of the gown's useful lifetime as well as tracing of any quality control problems. Finally, the isolation gown was re-rinsed with a barrier re-treatment product (22).

Carilion Clinic has now been using reusable gowns for over 9 years. They found that the deployment addressed all considerations from infection control and resulted in a savings of $851,984 over the initial 3 years. This deployment also eliminated 514,839 pounds of waste, and end users appreciated the increased comfort, coverage, barrier protection, storage space, and decreased environmental impact (22). Notably, during the COVID-19 pandemic, Carilion Clinic did not experience any isolation gown supply disruptions (33).

The UCLA reusable isolation gown pilot project began in 2012 and was aimed at reducing waste. Reusable gowns were designed through a multi-stakeholder effort including vendors and infection control staff. Reusable gowns were piloted at the liver transplant unit, which had the highest turnover of 1,000 disposable gowns used per day. While some staff members voiced concerns on gown comfort and washing with patient linen, these concerns dissipated over time with education efforts and steady cultural shift. Following the pilot study, the medical center introduced reusable gowns on a unit by unit basis, achieving full conversion over a 4-year period. More than 3.3 million reusable gowns have been used since 2012, saving over $1.1 million. Tracking reusable gown lifespan is currently done by inspection, but the institution is considering more formal tracking by RFID-type scanners. Over a 3-year period (2011–2015), this program diverted 297 tons of waste from the landfill (34).

DISCUSSION

We have discussed how reusable gowns are safer, more cost-effective, and more sustainable than disposable gowns. Still, reusable gowns remain widely unused due to several concerns. The first is safety: although reusable gowns are available in several layers of protection, all of which meet or exceed the AAMI safety standards (35), institutions may still worry that reusable gowns could lose protective capacity with repeated laundering (13). Several studies have shown this concern can be addressed by adding layers to aid in repellency. Ronald Reagan UCLA Medical Center has found their reusable isolation gowns to have a lifespan of 75–100 washes (21). Carilion Clinic's reusable isolation gowns had higher coverage and protection than their isolation gowns, in part due to their barrier retreatment product (22). Thus, the protective capacity of reusable gowns can be addressed and need not be a barrier to adoption.

Another potential barrier is patient and staff thermal discomfort with reusable isolation gowns compared to disposable alternatives (13). At UCLA, initial complaints that the gowns were uncomfortably hot eventually dissipated as staff became accustomed to wearing reusable gowns (21). A separate study found that the type of gown (disposable or reusable) played little to no role in patient and staff compliance (36). Another reported that reusable gowns engineered using microfiber technology and 100% polyester material both met protection standards and were more comfortable than disposable gowns (35).

Successful transition to reusable gowns requires both initiative and consideration of institutional needs. A proper workflow includes engagement of all stakeholders, especially infection control, and education on the superior protective properties of reusables. Practice Greenhealth provides an example workflow to adopt reusable gowns (tailored for surgical gowns, but easily applicable to isolation gowns) (37). This can be used to quickly track new deployment.

A key determinant of reusable gown adoption is market forces, especially affecting cost and supply. For example, during the pandemic, UCSF substantially increased its use of reusable gowns in response to the increased demand and shorter supply for disposable gowns. Carilion Clinic made their initial switch to reusables during the H1N1 outbreak to achieve a robust supply of gowns (22). However, these supply strains of disposable gowns are not confirmed by quantitative analysis; further research is warranted to evaluate whether increased reusable isolation gown use provides supply chain stability that would not otherwise be provided by disposable isolation gowns.

FUTURE DIRECTIONS

Winter is approaching, and with it an expected spike of infectious disease cases like COVID-19. At the same time, steady offshoring of PPE to other countries has left the U.S. vulnerable to supply chain disruptions (38). Countries like Spain and India also suffered severe PPE shortages that placed frontline healthcare workers at risk (39). To adequately protect healthcare providers, we must address key vulnerabilities in our PPE supply chain and current practices.

First, we advocate for increased funding for multidisciplinary, clinically translatable research on sustainable PPE practices. Though isolation gowns are among the better studied items of reusable PPE, shortages of masks and face shields must also be addressed. At present, there are only two groups in the U.S. that we are aware of who are actively pursuing research in this area, with one studying the efficacy, supply, environmental impact, and usage of reusable PPE and the other developing biocidal air filters for reusable PPE (40, 41). Both groups are funded by the NSF RAPID grant. Researchers outside of the U.S. are similarly investigating the feasibility and/or impacts of transitioning to reusable materials in light of pandemic-driven PPE shortages particularly as they related to readily accessible materials and ensuring reliability in the reusable PPE supply chain (42–44). While these individual examples are important, more dedicated research funding toward reusable PPE is needed to support prompt translation for healthcare systems during this urgent time. Specifically, further research is needed to understand how public policy can incentivize sustainable PPE adoption and facilitate healthcare system transitions at scale. Research and deployment should engage all relevant stakeholders, including end users (healthcare workers), vendors, infection control, and linen services. Open data on sustainable PPE should be published and collected, similar to how the N95DECON consortium has gathered resources for decontamination of N95 masks (45). Public-private partnerships can further support reusable PPE deployment; Hanes and other clothing brands have already been working with FEMA to increase reusable PPE production (46).

Second, we call for the rapid adoption of evidence-based sustainable PPE into clinical practice across the U.S. This will require buy-in by hospital leaders, infection control, departmental advocates and supply chain; as well as concurrent public policy to incentivize sustainable PPE. Our presented data on cost and safety, together with case studies from medical centers who have successfully used reusable isolation gowns for years, should address common concerns about reusable PPE. Policymakers can aid by ensuring a robust supply chain for reusable PPE, designing incentives for reusable PPE production and usage, and educating staff toward transitioning to reusable PPE practices.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Weather Conditions and COVID-19 Incidence in a Cold Climate: A Time-Series Study in Finland

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Background: The current coronavirus disease 2019 (COVID-19) is spreading globally at an accelerated rate. There is some previous evidence that weather may influence the incidence of COVID-19 infection. We assessed the role of meteorological factors including temperature (T) and relative humidity (RH) considering the concentrations of two air pollutants, inhalable coarse particles (PM_{10}) and nitrogen dioxide (NO_2) in the incidence of COVID-19 infections in Finland, located in arctic-subarctic climatic zone.

Methods: We retrieved daily counts of COVID-19 in Finland from Jan 1 to May 31, 2020, nationwide and separately for all 21 hospital districts across the country. The meteorological and air quality data were from the monitoring stations nearest to the central district hospital. A quasi-Poisson generalized additional model (GAM) was fitted to estimate the associations between district-specific meteorological factors and the daily counts of COVID-19 during the study period. Sensitivity analyses were conducted to test the robustness of the results.

Results: The incidence rate of COVID-19 gradually increased until a peak around April 6 and then decreased. There were no associations between daily temperature and incidence rate of COVID-19. Daily average RH was negatively associated with daily incidence rate of COVID-19 in two hospital districts located inland. No such association was found nationwide.

Conclusions: Weather conditions, such as air temperature and relative humidity, were not related to the COVID-19 incidence during the first wave in the arctic and subarctic winter and spring. The inference is based on a relatively small number of cases and a restricted time period.

Keywords: COVID-19, cold climate, weather, Finland, air pollution

BACKGROUND

In Finland, the first case of COVID-19 was identified in the Helsinki Metropolitan Area on January 29, 2020. Since then, the SARS-CoV-2 pandemic has spread to other regions of the country via travelers from Helsinki or foreign countries. To supplement other major mechanisms promoting public safety during the pandemic, on March 12 the Finnish government declared the Emergency Powers Act, which was approved in the Parliament and came into effect on March 16. This Act enabled the Government to decide about several recommendations and orders aiming at controlling the SARS-CoV-2 pandemic. Among the actions, schools and day-care centers were closed, the province of Uusimaa, including the Helsinki metropolitan area, was isolated from the rest of the country and several restrictions and recommendations were made for unnecessary travel.

Several epidemiological studies in an early phase of the pandemic suggested that weather may influence the incidence of SARS-CoV-2 virus infection (1–4). The first results from Wuhan reported an association of COVID-19 mortality with diurnal temperature range and low humidity (2). In a study of 17 Chinese cities, COVID-19 incidence was inversely related to an increase in temperature and diurnal temperature range (4). Two studies conducted in subtropical cities of Brazil both provided evidence that an increase in temperature is related to a decrease in COVID-19 incidence (1, 3). This is consistent with previous evidence on the associations between weather and temperature *per se* for several other viral diseases, including SARS-CoV (5), *h. influenza* (6), and *rhino* viruses (7). A Chinese study based data from Wuhan and XiaoGan from Jan 26th to Feb 29th reported a positive correlation of COVID-19 incidence with daily air quality index, $PM_{2.5}$, NO_2 concentrations, but a negative correlation with temperature (8). There is also recent evidence from a US nationwide study that long-term exposure to air pollutants is related to an increased risk of COVID-19 infection at a community level, indicating that air pollution may increase susceptibility to COVID-19 infections (8, 9). Environmental factors may influence function of the virus itself, but it is also likely that these factors predispose individuals to infection by pathophysiological and immunological responses to the environmental challenges (6). However, the independent effect of environmental factors on the incidence of COVID-19 in Finland has not been studied.

Based on previous evidence on COVID-19 (1–4) and other viral pathogens (5–7) and the substantial evidence on the influence of cold weather to human health and immunology (10, 11), we hypothesized that cold temperature and low relative humidity increase the incidence of COVID-19 infection in the cold climate. We tested this hypothesis by assessing the relations between meteorological factors, including daily ambient temperature (T) and relative humidity (RH), and daily counts of COVID-19 cases in Finland adjusting for air pollutants (PM_{10} and NO_2) during the first 5 months of the pandemic.

METHODS

Study Area

The study area comprised the whole Finland, located between latitudes 60° and 70°N, and longitudes 20° and 32°E, with a population of 5.5 million (**Figure 1A**). The Capital city of Helsinki and the surrounding cities comprise the Helsinki Metropolitan area with altogether 1.1 million inhabitants. Finland is located between the Baltic Sea and the Eurasian continent and has characteristics of both maritime and continental climates. The mean annual temperature is 6.6°C and the mean annual and monthly precipitation in July are 655 and 63 mm, respectively (Finnish Meteorological Institute; http://ilmatieteenlaitos.fi/).

COVID-19 Data

The National Institute for Health and Welfare of Finland (https://thl.fi/en/web/thlfi-en) maintains the registry of infectious diseases in Finland, and the law requires that health care personnel report all cases of selected infectious diseases including COVID-19. Thus, selection bias by underreporting is minimal. We retrieved the daily count data of the confirmed coronavirus cases (COVID-19) from January 1 to May 31, 2020 from the official website of National Institute for Health and Welfare of Finland (https://experience.arcgis.com/experience/92e9bb33fac744c9a084381fc35aa3c7).

Meteorological and Air Quality Data

The daily contemporaneous meteorological data, including daily average temperature (T, °C), average relative humidity (RH, %), dew point (°C), wind speed (m/s) and pressure (KPa) was retrieved from the Finnish Meteorological Institute (https://en.ilmatieteenlaitos.fi/). These data are based on continuous measurement of the weather stations across the country. For each hospital district, we calculated an average value from the stations closest to the provincial hospital. We calculated daily temperature range as a difference between the daily maximum and daily minimum temperature. Data on daily concentrations of air pollutants, including NO_2 ($\mu g/m^3$) and PM_{10} ($\mu g/m^3$), were also retrieved from the Finnish Meteorological Institute and were treated as potential confounders in the sensitivity analyses.

Statistical Analysis

Time-series methods were used to assess the associations between daily meteorological factors and daily count of COVID-19 cases. A standard two-stage approach was applied to obtain the region-specific and nationwide incidence rate ratios (IRRs) as measures of effect. In the first stage, a quasi-Poisson generalized additional model (GAM) was fitted to estimate the relations between region-specific meteorological factors and COVID-19 incidence rate (IR). Considering the reliability of the models, only regions with >100 cases ($N = 9$) were included in the analysis and 12 other districts were excluded from the study. The nine regions produced 93% of the COVID-19 cases. Spearman correlation coefficient matrix was calculated for meteorological factors in each region, and the correlation matrices were pooled

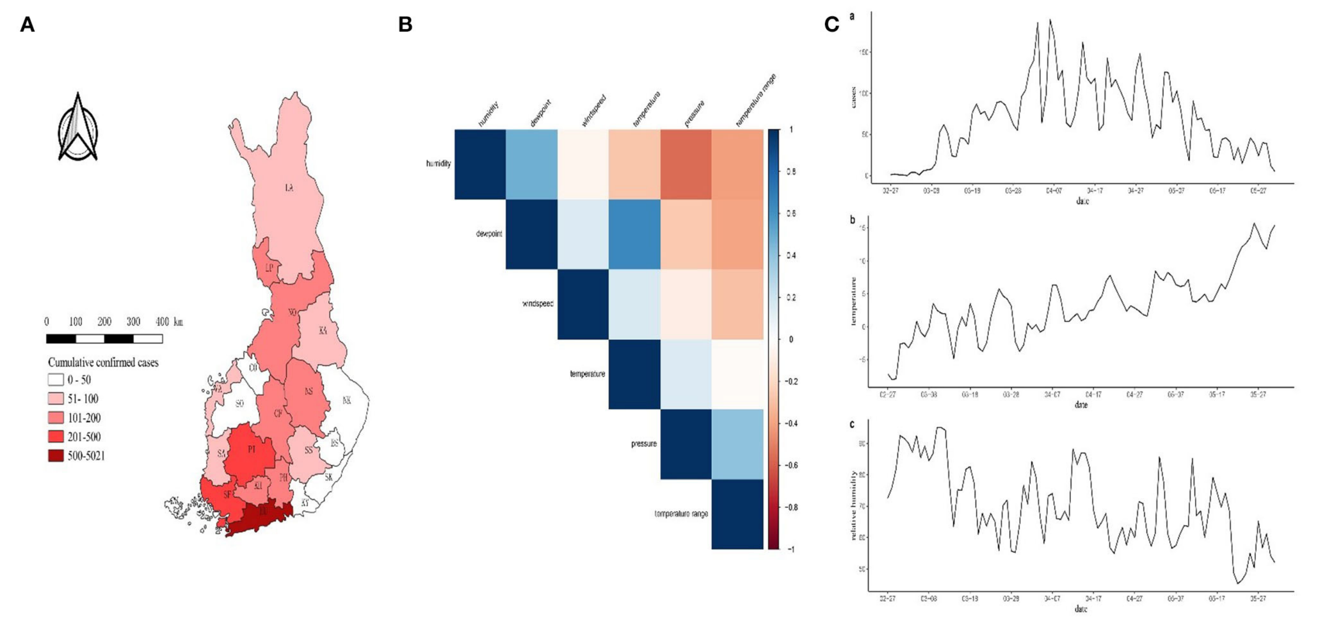

FIGURE 1 | (A) Number of confirmed COVID-19 cases in the hospital districts. **(B)** Plot of correlation coefficient matrix. Darker blue colors indicate higher correlation between the two variables. **(C)** Time series plot of (a) COVID-19 cases, (b) temperature (T), and (c) relative humidity (RH). The hospital districts are Helsinki and Uusimaa (HU), Soutwest Finland (SF), Pirkanmaa (PI), Länsi-Pohja (LP), Northern Ostrobothnia (NO), North Savo (NS), Central Finland (CF), Kanta-Häme (KH), Päijät-Häme (PH), Lapland (LA), Kainuu (KA), Vaasa (VA), Satakunta (SA), South Savo (SS), South Ostrobothnia (SO), Kymenlaakso (KY), North Karelia (NK), South Karelia (SK), Central Ostrobothnia (CO), East Savo (ES) and Ahvenanmaa (AL).

by averaging the region-specific correlation coefficients. To avoid multicollinearity, the threshold of correlation coefficient was set as 0.6. We applied the backward elimination algorithm for selection of variables to the final model in each district. Wald test was used for testing statistical significance. The effects of meteorological factors were expressed with a 14-day exponential moving average (EMA) (12). To control the short-term temporal trend, the natural splines of time with 2 degrees of freedom was applied. The model is given by:

$$\begin{aligned} E\left(y_t\right) &= \mu_t \\ \log \mu_t &= \beta_0 + \beta_1 \times matem\ p_t + \beta_2 \times mahm\ d_t \end{aligned}$$

Where, y_t is the daily count of COVID-19 at day t, μ_t is the expected value of daily count at day t, β_0 is the intercept, β_1 and β_2 denote the effect of moving average of temperature and relative humidity, and β_3 and β_4 are the regression coefficients of natural splines of time with two degrees of freedom.

In the second stage, a meta-regression model with random effects was used to obtain national average effect estimate between COVID-19 and meteorological factors. I^2 statistics and Cochran Q test were used to quantify inter-regional spatial heterogeneity. To estimate the overall relationship of the association between meteorological factors and COVID-19, exposure-response curves were plotted using the GAM with natural spline's knot setting at its median ($df = 2$).

Sensitivity Analyses

Sensitivity analyses were performed by modifying the parameter of EMA from 14 days to 10 and 12 days, respectively, and including the two air pollutants (PM_{10}, NO_2) into the above model as potential confounders to assess their possible influence on the associations between meteorological factors and COVID-19 incidence. The R4.0.1 software (R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses. ArcGIS10.1 software (Environmental Systems Research Institute Inc, Redlands, CA, USA) was used to draw the geospatial map.

RESULTS

Characteristics of the COVID-19 Pandemic in Finland

A total of 6,831 cases of COVID-19 were confirmed in Finland during the study period January 1 to May 31, 2020. The cumulative number of confirmed cases appears to have a gradually decreasing trend from south to north (**Figure 1A**).

Region-Specific Analysis

Regions with >100 cases were Helsinki and Uusimaa (HU), Southwest Finland (SF), Pirkanmaa (PI), Länsi-Pohja (LP), Northern Ostrobothnia (NO), North Savo (NS), Central Finland (CF), Kanta-Häme (KH), and Päijät-Häme (PH) districts in our analysis shown in **Figure 1**. Dewpoint was excluded from the correlation coefficient matrix (**Figure 1B**) and temperature range, wind speed and pressure were excluded from the univariate GAM model. Only average temperature and relative

TABLE 1 | Nationwide associations between temperature and relative humidity and COVID-19 incidence in Finland.

Variable	Estimate (95% CI)	I^2 (%)	Cochran Q test	
			Statistics	*P-value*
Temperature	−0.03 (−0.11, 0.05)	<0.01	6.14	0.63
Relative humidity	−0.02 (−0.04, 0.0001)	65.11	22.93	<0.01

humidity were selected in the final model, which ranged from −8.03 to 15.70 (°C), and from 45.31 to 95.16%, respectively (**Figure 1C**). The COVID-19 incidence rate gradually increased until a peak around April 6 and then decreased to May 31 (**Figure 1C**,a), while temperature had a visibly upward trend (**Figure 1C**,b) and relative humidity had a downward trend in the same time period (**Figure 1C**,c).

Overall, there was no association between temperature or relative humidity and nationwide incidence rate of COVID-19, although both showed a tendency of negative association (**Table 1**). However, there was a spatial heterogeneity in the associations between relative humidity and COVID-19 across regions (I^2 65.11%). In Central Finland (CF) and North Savo (NS), relative humidity was negatively correlated with COVID-19, but in other regions it was not. Temperature was not associated with COVID-19 in any of the regions (**Figure 2**).

Exposure-Response Curves

The exposure-response curves depicted the slightly decreasing linear tendency for the association of relative humidity with COVID-19 incidence (**Figure 3**).

Sensitivity Analysis

The sensitivity analysis indicates the results are robust under the situations of changing the EMA parameter or including the air pollutants as potential confounders (**Table 2**).

DISCUSSION

Main Findings

On the basis of previous knowledge about weather and COVID-19 incidence (1–4) and several other viral diseases, including SARS-CoV (5), *h. influenza* (6), and *rhino* viruses (7), we tested the hypothesis that low temperature and low relative humidity increase the incidence of COVID-19. We evaluated the relations between weather conditions and the daily number of COVID-19 cases in Finland during the first 5 months of the pandemic. In the nationwide analysis, temperature and relative humidity were not associated with the incidence of COVID-19. However, in two hospital districts located inland there was a negative association between relative humidity and COVID-19 incidence i.e., consistently with our hypothesis, the incidence rate of COVID-19 was greater in the dry air.

Validity of the Results

We used data from the meteorological stations located in the same city with the provincial hospital. This approach assumes that the spatial distribution of exposure is homogeneous. This assumption is reasonable for temperature and relative humidity but results in measurement error in air pollution concentrations. Exposure assessment was made at population-level, which means that there was no information on individual-level exposure.

The infectious disease law required reporting of all COVID-19 cases to the National Institute of Health and Welfare of Finland. The identification of severe cases of COVID-19 was likely to be complete, but the percentage of non-diagnosed mild cases is unknown. Further, the percentage may have changed over time. The diagnostic practice was changing over the course of the pandemic producing uncertainty to the incidence rate estimates. However, misclassification or underdiagnosis of COVID-19 was not likely to be related to prevailing weather and thus any systematic error was not likely. There is a possibility that some cases were first identified outside their own hospital district. This would cause bias if their exposure was based on the conditions in their home district. Due to common public patient information databases, the information could be in most cases seen both hospital districts, which would have reduced the potential bias.

The population producing the COVID-19 cases remained relatively constant. Air pollution was the most obvious potential confounder, because weather, especially temperature is for several reasons associated with air pollution concentrations. We were able to adjust for PM_{10} and NO_2, but as stated before the concentrations at the monitoring stations may not be representative of the whole hospital districts. However, the concentrations at the monitoring stations give reasonable estimates of the relative levels of air pollution over time. Inclusion of PM_{10} and NO_2 did not influence the associations between weather parameters and COVID-19 incidence.

We applied a statistical approach, a quasi-Poisson generalized additional model, commonly used in chronic disease epidemiology where the assumption of the independence of individual observations is reasonable. The dynamics of COVID-19 pandemic is new and unknown which is a source of uncertainty when assessing the effects of weather on disease incidence. For example, the emergence of the COVID-19 pandemic took place from early winter to late spring during which there is a strong time-trend of both temperature and relative humidity. Never-the-less, we think it was important to make a fast attempt to model the associations between the main weather parameters and the incidence rate of COVID-19 regionally and nationwide. In reality, the incidence rate of COVID-19 declined fast after the intensive intervention on March 16, which definitely played a role in the reduction. This intervention may have masked the influence of increasing ambient temperature in the course of changing season from winter to summer. Further, we were not able to take into account any population movements related to tourism or immigration, which were likely to influence the COVID-19 incidence.

Synthesis With Existing Knowledge

We identified several previous studies which had assessed the role of weather in the COVID-19 incidence (1–4, 12–23), but only few studies were conducted in a cold climate with large temperature variations. A synthesis of the present and previous findings faces

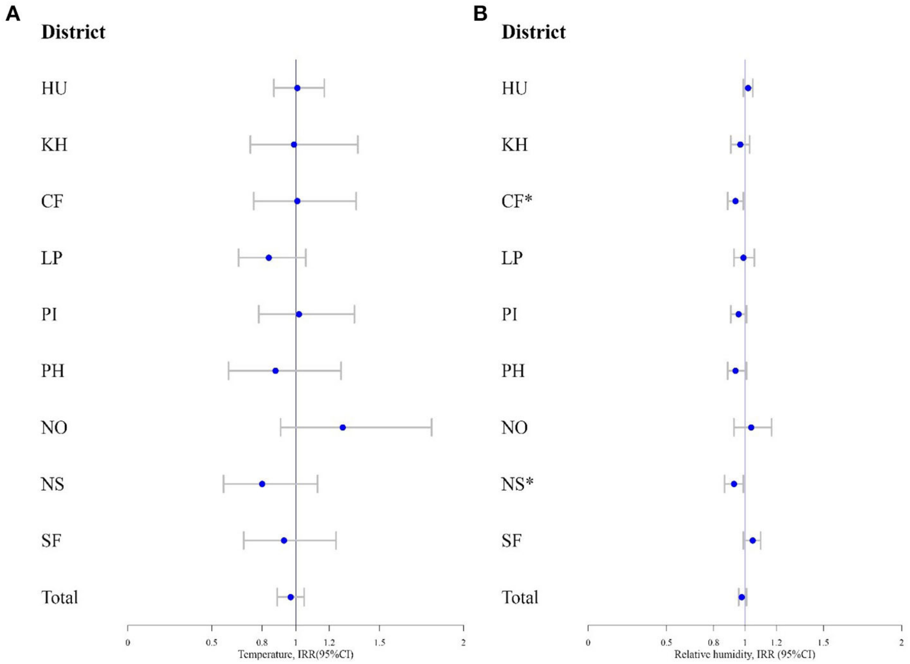

FIGURE 2 | (A) The incidence rate ratio (IRR) and 95% confidence interval (95% CI) for COVID-19 by temperature and **(B)** relative humidity. * indicates statistical significance.

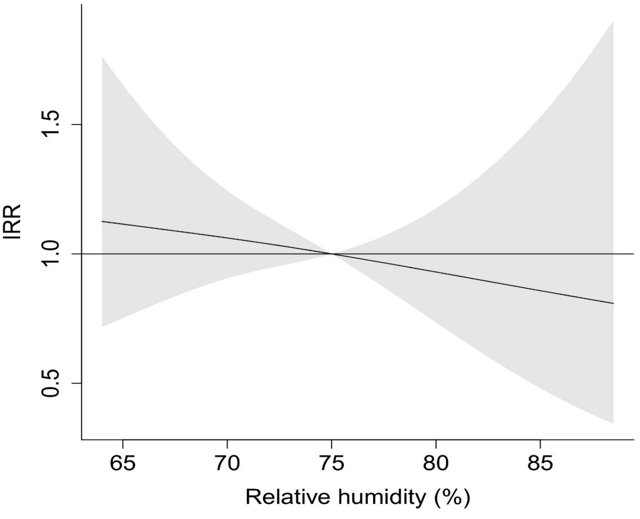

FIGURE 3 | Exposure-response curve of IRR for COVID-19 by relative humidity. Ninety-five percentage confidence interval is shown shaded.

thus several challenges. The studies were conducted in different climatic zones, the relations between weather parameters and COVID-19 incidence rate were estimated in different ranges of temperature and relative or absolute humidity, and there were substantial differences in the statistical modeling approaches.

One of the studies by Bashir et al. (15) was conducted in New York City with a climate and temperature range closest to Finland, two Chinese studies covered several climatic zones (16, 18), the Brazilian study by Prata et al. (3) included all the 27 state capitals all in subtropical and tropical climates and the study in New South Wales, Australia by Ward et al. was conducted in subtropical climate (12). Another study by Pramanik et al. was conducted in the Russian climatic regions with a similar range of climate and temperature as in Finland, including a total of 101 primarily selected cities classified into two climatic regions (79 cities in the humid continental and 22 cities in the sub-arctic climate) (19).

We did not find any overall or regional association between daily temperature and incidence rate of COVID-19 during the study period with a temperature range from −8.0 to 15.7°C. Bashir et al. (15) reported significant correlations between daily average and minimum temperatures and the daily count of COVID-19 in New York City. The range of temperature was from −1.8 to 15.7°C, which partially overlaps with the temperature range in the present study. The statistical analysis was based on calculation of Kendall and Spearman correlation between daily air quality parameters and counts of COVID-19 cases during March 1 – April 12, 2020. In the Russian study, the temperature seasonality (29.2 ± 0.9%) had the strongest effect on incidence of COVID-19 in the humid continental region. The authors reported that the diurnal temperature range (26.8 ± 0.4%) and temperature seasonality (14.6 ± 0.8%) had the greatest contribution for incidence in the sub-arctic region (19). On the other hand, the effects of diurnal temperature range, wind speed, and relative humidity on the intensity of the COVID-19 incidence were observed in the

TABLE 2 | Sensitivity analyses on the associations between temperature and relative humidity and COVID-19 incidence in Finland [Estimate (95% CI)].

Variable	**EMA (*df*)**		**Air pollutants**
	10	**12**	**($PM_{10} + NO_2$)**
Temperature	−0.02 (−0.08, 0.04)	−0.02 (−0.1, 0.06)	−0.04 (−0.13, 0.05)
Relative humidity	−0.01 (−0.03, 0.01)	−0.01 (−0.03, 0.01)	−0.01 (−0.05, 0.02)

sub-arctic region. The temperature was relatively low (<2°C) which overlaps with the temperature range in our study. Pramanik et al. (19) reported that COVID-19 risk was lower in the temperate and subtropical regions when the temperature remains <10°C.

Berumen et al. analyzed the effects of temperature and humidity on the doubling time of COVID-19 cases in 67 countries grouped by the climate zone (20). This study suggested that the behaviors of the growth curve and doubling time in the first stage of the epidemic were related to the ambient temperature but the magnitude of this effect was different between countries located in temperate and tropical/subtropical areas (20). Two studies in tropical climate provided controversial results of the association between temperature and COVID-19 risk. In the Brazilian study, there was a 4.9% decrease in COVID-19 risk per 1°C increase in temperature ranging from 16.8 and 27.4°C, i.e., in a different range compared with that in Finland (3). In the study conducted in New South Wales, Australia there was no association between temperature and COVID-19 in a subtropical climate with a temperature ranging from 16 to 24°C (9 a.m.) and 16 to 34°C (3 p.m.) (12). In the Chinese study of 122 cities in different climatic zones, a non-linear association was reported between temperature and COVID-19 incidence (21). The incidence rate of COVID-19 increased by 4.9% per 1°C increase up to −3°C, but there was no association in warmer temperature range. In the other Chinese study of 80,981 COVID-19 cases in 31 provinces with 344 cities, the incidence rate of COVID-19 decreased by increase in temperature in the range of −22 to 26°C (22). The association between temperature and COVID-19 incidence appears to be non-linear with the highest risk in temperatures around zero. Although in the Finnish nationwide analysis there was no association between relative humidity and COVID-19, there was evidence of a negative association in two inland provinces. The range of RH was from 45.31 to 95.16%. Consistently with this observation, the New York study reported a negative association between relative humidity and COVID-19 incidence (15). Interestingly, a negative association between relative humidity and COVID-19 incidence was reported also in the subtropical climate of New South Wales, with a 6.11% risk increase by 1% reduction in relative humidity (12). The large Chinese study of 31 provinces in different climate zone found no association between relative humidity and COVID-19 incidence (23).

In summary, there seem to be differences in COVID-19 transmission between different climate zones (22), and these differences could be partially explained by weather. However, there are several population-level alternative explanations for the observed difference in COVID-19 transmission between geographical regions, including climate zones. Potential determinants are population density, age distribution, levels and differences in socioeconomic conditions, and any cultural and behavioral differences that could modify the actual exposures to weather conditions, such as differences in housing stock, heating infrastructures, and risk perception. It is also too early to elaborate the role of seasonality itself in this context, as not all seasons have been experienced in the COVID-19 pandemic yet. The associations between weather and COVID-19 transmission require further research. Our own results provide some preliminary evidence that low relative humidity may play a role in COVID-19 transmission.

CONCLUSIONS

This nationwide time-series analysis of the Finnish COVID-19 cases during the early pandemic months did not provide evidence that ambient air temperature and relative humidity affected the COVID-19 incidence in the arctic and subarctic winter and spring. We provide suggestive evidence that dry air may increase the incidence of COVID-19. The inference is based on a relatively small number of cases and a restricted time period covering the first wave of the pandemic in Finland. Most of the previous studies were conducted in very different climates and ranges of temperature and relative humidity. However, the evidence of the role of temperature and relative humidity is controversial even in studies from similar climatic conditions. A non-linear association between temperature and COVID-19 risk could partly explain the controversial observations, whereas the complex dynamics of COVD-19 pandemic and radical social interventions may complicate the inference. Further studies are needed to elaborate on the complex associations between weather and COVID-19 in different climates and seasons. The emerging second wave of the pandemic in Finland will offer an opportunity for further assessment of these relations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was based on anonymous registry data.

AUTHOR CONTRIBUTIONS

BH: data collection, writing—original draft, writing—review and editing. WW: conceptualization, methodology, and formal analysis. NR: writing—review and editing. AD and FD: review and editing. ZZ: review and editing and supervision. JJ: supervision, writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2020.605128/full#supplementary-material

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Vitamin Nature: How Coronavirus Disease 2019 Has Highlighted Factors Contributing to the Frequency of Nature Visits in Flanders, Belgium

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Visiting nature is positively associated with physical and mental well-being. The role of nature became more pronounced during the coronavirus outbreak in the spring of 2020. Countries all over the world implemented confinement measures to reduce the transmission of the virus. These included but were not limited to the cancelation of public events, schools, and non-essential businesses and the prohibition of non-essential travels. However, going outside to exercise was recommended by the Belgian government. During this period, we conducted an online survey to determine if people visit nature more frequently than before and to identify the factors that contribute to this. The results are based on data from 11,352 participants in Flanders, Belgium. With the use of a bivariate and multiple regression analysis, results indicate that people visit nature more frequently than before and that nature helped to maintain social relationships during the coronavirus period. Gardens were reported to be the most popular place, followed by parks. More than half of the people experienced nature in a more positive way, and the belief that nature visits are important for general health increased. In addition, we found a positive association between nature visits and home satisfaction, as well as a positive association with subjective mental and physical health. Lastly, we identified several demographic factors contributing to the frequency of nature visits such as age, gender, and socioeconomic status. Our findings indicate the importance of nature visits for general well-being and highlight the need for nearby green infrastructure.

Keywords: COVID-19, confinement measures, green space, nature, ecosystem service, citizen perceptions

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INTRODUCTION

It is widely acknowledged that nature affects human health (1–3). Increasing empirical evidence demonstrates a positive relationship between nature and well-being (4–6), such as improved relaxation and restoration, enhanced immune function, improved air quality, social connectedness, and increased physical activity (7). These findings have led to more health-care research exploring the value of nature's contributions to (primary) health care (8, 9). The importance of contact with nature for human health became clear during the coronavirus pandemic (10). Previous research highlighted that contact with nature may be an effective strategy to cope with stress (11, 12) and emotion regulation (13). During the pandemic, a trend of people visiting nature more often could be observed in western countries (14–17).

There are different views regarding the interpretation of contact with nature in the literature. Frumkin et al. (7) argue that there are different ways of contact with nature: "varying by spatial scale, proximity, the sensory pathway through which nature is experienced (visual, auditory, etc.), the individual's activities and level of awareness while in a natural setting, and other factors" [as cited in Frumkin et al. (7)]. First of all, Frumkin and Fox (18) refer to contact with nature in buildings. These are plants, photos, or videos of natural environments as well as looking out on nature. This type of contact with nature is indirect (19). However, research shows that this type of contact with nature is also associated with improved health and well-being (7, 18, 20). Secondly, neighborhoods with a green environment such as trees and plants are also subject to contact with nature (18). This can be classified under incidental contact (19). A third and last type of contact with nature is the conscious search for a green environment such as a park, garden, forest, or nature reserve (18). The latter is described as intentional contact with nature (19).

This study focused on the intentional seeking of nature, and thus, we refer to "nature visit" instead of contact with nature. Nature was broadly defined: ranging from a green terrace/balcony or garden to nature in the environment such as a (city) park, nature reserve, forest, field, meadow, pond, river, sea, and beach. This definition was opted based on previous research that showed how benefits can differ based on the type of nature (21, 22).

The Coronavirus Disease 2019 Pandemic: Confinement Measures in Belgium

The coronavirus was first reported in Wuhan, China, on December 31, 2019 (23, 24). On March 11, 2020, the WHO characterized the coronavirus disease as a pandemic (25, 26). To reduce the transmission of the virus, governments worldwide imposed exceptional confinement measures (27–29), which affected our daily life (30) and psychological health (31, 32). These regulations had a negative effect on people's social participation, life satisfaction, and sedentary behavior (33, 34).

Furthermore, changes in eating pattern were observed (35), including, among others, an increased consumption of unhealthy foods (34).

In Belgium, the measures implemented to deal with the first coronavirus outbreak took effect on March 14, 2020. These included, but were not limited to, keeping physical distance from other people; the prohibition of all recreational activities and public gatherings; closing of non-essential stores, bars, and restaurants; and mandatory working from home, where applicable. Going outdoors was only allowed for essential reasons. However, outdoor exercise was allowed and even recommended by the government. No restrictions were imposed in terms of distance from home. These regulations were gradually phased out starting May 3 (36).

With a growing body of evidence of proven health benefits from visiting nature (6, 8, 37), the current study aimed to investigate to which extent people visit nature (more often) when the first confinement measures where applicable in Flanders, Belgium, and how this contributes to their perceived general well-being and their perception of nature and health.

In sum, the key research questions of this study were as follows: (1) Do people visit nature more often than before the coronavirus disease 2019 (COVID-19) confinement measures? (2) Which factors influence the frequency of nature visits during the COVID-19 confinement measures in Flanders, Belgium? Due to the exceptional situation of the coronavirus, we started this research with an open mind. We focused on the presented research questions and the hypothesis that there would be a noticeable increase in nature visits due to the COVID-19 confinement measures.

To ensure clarity and consistency in this paper, we will refer to C19CM (COVID-19 confinement measures) to indicate the period in which confinement measures were imposed by the Belgian Government and the online survey was conducted. More specifically, this concerns the period between April 9 and 19.

MATERIALS AND METHODS

Study Design and Sample

Data were gathered through a cross-sectional survey design. An online survey was launched using Socratos Survey Software. This study was conducted by the Chair of Care and Natural Living Environment of the Faculty of Medicine and Health Sciences of the University of Antwerp. The chair is funded by the Province of Antwerp. The Department of Environment, subdivision Sustainable Environmental and Nature Policy, and the PIH of the Province of Antwerp also contributed to the realization of this study. Participants were recruited by convenience sampling (38). The authors distributed the online survey in the network of the Chair, the University of Antwerp, and the Province through press announcements, email, and social media. Respondents were asked to complete the survey and subsequently distribute the survey further into their own network. Additionally, in the days and weeks after the initial launch, the survey call was communicated by Flemish newspapers and several radio and television networks.

A total of 11,352 participants completed the survey. The sample is not representative for the Flemish population, as there is a significant overrepresentation of female respondents, highly educated people, respondents living in the Province of Antwerp, and respondents reporting feeling healthy. An overview of the demographic factors can be found in **Figure 1** (gender), **Figure 2** (age) and **Figure 3** (educational level).

Ethics

Ethical approval was obtained from the Committee for Medical Ethics (CME) of Antwerp University Hospital (study

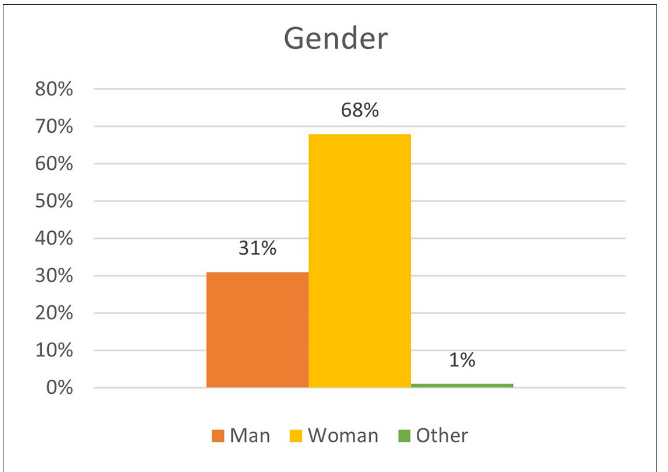

FIGURE 1 | Overview of distribution by gender.

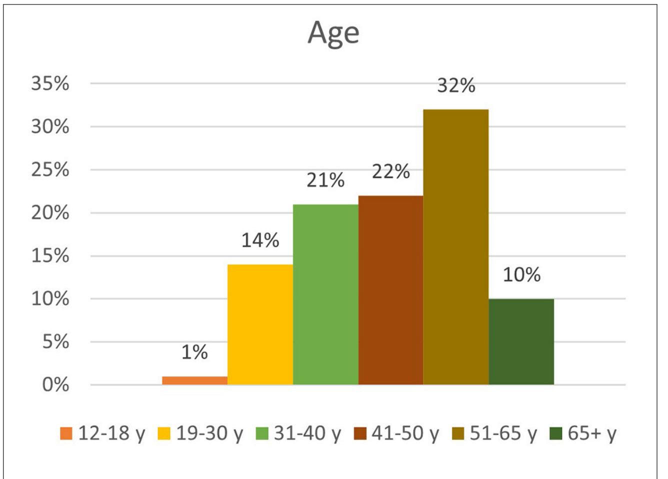

FIGURE 2 | Overview of distribution by age.

20/15/182/B3002020000062) on April 6, 2020. Prior to the start of the survey, participants had to confirm their informed consent. No incentives were promised for completing the survey. Participation was voluntary, and all respondents had the right to leave the survey at any point.

Measurements

A pretest was conducted by 15 people. After their feedback was received, a few questions and response options were adjusted to precise questions and formulation in order to avoid misunderstandings. The questionnaire was structured in five sections: demographic information, housing situation, residential area, nature (visit), and health. Mainly closed-ended questions were used to explore the above-mentioned objectives. For a detailed overview of the questionnaire, see **Supplementary Data 1**: **questionnaire**.

Demographic Information

Participants answered questions regarding age, gender, nationality, living situation (number of roommates), highest obtained educational degree (elementary school, secondary education, university of applied sciences bachelor's, university bachelor's, university master's, or post-university), work situation (working, student, retired, temporarily unemployed due to corona crisis, unemployed, job seeker, disabled, and sick), and remote working before and during C19CM (never, once a week, part of the time, always, and not applicable).

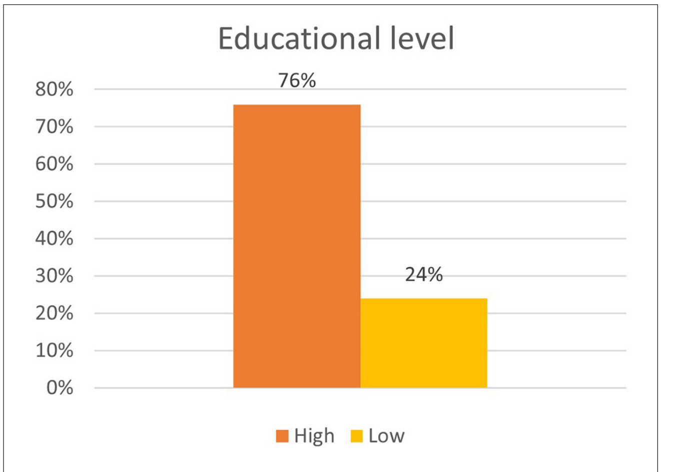

FIGURE 3 | Overview of distribution by educational level.

Housing Situation—Satisfaction and Characteristics

Questions were asked about the respondent's current housing situation. These were developed in cooperation with the department of housing from the Flemish government. Participants were asked about the type of housing they currently live in (open building, semi-detached building, closed building, apartment low-rise/high-rise, room, and studio), the belonging facilities (garden private/communal, courtyard, balcony, garage, or private parking), the size of the different rooms in the house (too small, small, medium, large, and too large), and their housing satisfaction before and during C19CM (very satisfied, satisfied, rather satisfied, rather dissatisfied, dissatisfied, and very dissatisfied).

Residential Area—Satisfaction and Infrastructure

In addition to questions about the housing situation, participants were asked to indicate their satisfaction about the residential area—before C19CM and at the present time. Questions were asked based on statements that were answered on a 6-point scale (1 = totally agree, 6 = not agree at all).

Nature—Frequency and Experience

Participants were asked about the presence of nature in their life. Nature was broadly defined: ranging from a green terrace/balcony or garden to nature in the environment such as a (city) park, nature reserve, forest, field, meadow, pond, river, sea, to beach. Respondents who went into nature were asked questions about the frequency (several times a day, once a day, several times a week, once or twice a week, and less than once a week) and motives (to hike/sport, the

TABLE 1 | Variables overview of frequencies ($N = 11{,}352$).

Variable	Categories	*N*	%	Cum. %
Frequency of nature visit (during COVID-19)	Not	550	4.8	4.8
	Less than once a week	166	1.5	6.3
	Once or twice a week	742	6.5	12.8
	Several times a week	2,442	21.5	34.4
	Once a day	3,534	31.1	65.5
	Multiple times a day	3,918	34.5	100
Gender	Man	3,568	31.4	31.4
	Woman	7,742	68.2	99.6
	Other	41	0.4	100
Age (in years)	12–18	81	0.7	0.7
	19–30	1,563	13.8	14.5
	31–40	2,356	20.8	35.2
	41–50	2,569	22.6	57.9
	51–65	3,642	32.1	89.9
	65+	1,141	10.1	100
Education level	Low	2,685	23.7	23.7
	High	8,562	75.4	99.1
	Other	105	0.9	100
Work situation (during COVID-19)	Working	7,361	64.8	64.8
	Not working	3,991	35.2	100
Housemates < 12 years	Yes	2,403	21.2	21.2
	No	8,949	78.8	100
Home satisfaction (during COVID-19)	Satisfied	10,678	94.1	94.1
	Not satisfied	674	5.9	100
Neighborhood satisfaction (during COVID-19)	Satisfied	10,556	93	93
	Not satisfied	796	7	100
Physical health	Healthy	10,263	90.4	90.4
	Unhealthy	1,050	9.2	99.7
	Missing	39	0.3	100
Mental health	Healthy	9,628	84.8	84.8
	Unhealthy	1,655	14.6	99.4
	Missing	69	0.6	100
Access to private garden	Yes	8,978	79.1	79.1
	No	2,374	20.9	100
Access to communal garden	Yes	446	3.9	3.9
	No	10,906	96.1	100
Sufficient green in neighborhood	Yes	8,965	79	79
	No	2,372	20.9	99.9
	Not applicable	15	0.1	100
Green and squares in neighborhood well-maintained	Yes	9,081	80	80
	No	131	12.3	92.2
	Not applicable	880	7.8	100

COVID-19, coronavirus disease 2019.

silence, social contact, boredom, etc.) before and during C19CM. Additionally, questions were presented about how important they find nature for their health (ranging from very important to not at all). Finally, participants were asked how they felt after their nature visit. Eleven statements were presented with seven answer options ranging from "totally agree" to "totally disagree." Respondents who did not go into nature were introduced questions about their possible use of nature indoors (houseplants, green view, nature images/documentaries, nature sounds, and nature books).

Health

To obtain an indication of how respondents felt at the present time, questions were asked regarding their mental and physical health containing six respond categories (very healthy, healthy, rather healthy, rather not healthy, not healthy, and not at all healthy).

Data Analysis

The data were analyzed using the software program SPSS. A number of steps were taken to obtain the results. To explore the data, a univariate analysis was carried out based on frequency tables. An overview of the variables used can be found in **Table 1**. Next, a multiple regression analysis was carried out. Based on an ordinal logistic regression, several independent variables (gender, age, educational attainment, mental and physical health, private garden, satisfaction with home and living environment, and sufficient green space in the living environment) were associated with the dependent variable "frequency of nature visit during C19CM." In this way, we were able to detect to what extent the independent variables explain how often the participants visit nature. The results in **Table 2** are presented using the Exp(B) coefficient or odds ratio, with a 95% confidence interval.

RESULTS

Descriptive Analysis

Of the respondents, 95.1% went into nature during C19CM in Belgium. More than one third (36.3%) went several times a day. Of the respondents who visit nature during C19CM, 59.5% do so more often than before. Having more time due to the confinement measures (76.3%) appears to be the most important reason followed by an alternative to sitting inside (71.2%) and to exercise (68.5%). Contrary to this, the presence of too many people in nature was reported as the main reason (31.4%) for not going into nature, followed by being afraid of a possible contamination with the coronavirus (19.5%).

The most popularly reported places for nature visits were people's own garden or terrace (84.2%), followed by parks or forests (66.5%). Walking was the most practiced activity in nature (90%).

Remarkably, nature receives a higher value during C19CM. Hence, 51.6% of the respondents who go into nature during C19CM experience nature in a more positive way than before. An overview of the main reasons can be found in **Table 3**. Only 7% of all respondents experience nature more negatively than before C19CM. An overview of the main reasons to experience nature in a more negative way can be found in **Table 4**. A significant difference was found with respect to educational level ($X^2 = 49.695$; $p < 0.05$). More positive feelings toward nature were reported among higher-educated respondents.

TABLE 2 | Ordinal logistic regression "frequency of nature visit during C19CM" ($N = 10{,}267$; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).

Variable	Exp(B)	Lower (95% CI)	Upper (95% CI)
(Ref = man)			
Woman	1.345***	1.246	1.452
(Ref = 65+ years old)			
12–18 years	0.652*	0.427	0.996
19–30 years	0.847*	0.722	0.993
31–40 years	1.010	0.858	1.190
41–50 years	0.999	0.856	1.166
51–65 years	1.055	0.918	1.211
(Ref = low education level)			
High education level	1.513***	1.386	1.651
(Ref = not working during C19CM)			
Working	0.884**	0.810	0.965
(Ref = housemates < 12 years old)			
No housemates < 12 years	0.776***	0.700	0.861
(Ref = dissatisfied with home during C19CM)			
Satisfied with home	1.366***	1.166	1.600
(Ref = dissatisfied with neighborhood during C19CM)			
Satisfied with neighborhood	1.133	0.974	1.319
(Ref = physically unhealthy)			
Physically healthy	1.458***	1.283	1.657
(Ref = mentally unhealthy)			
Mentally healthy	1.312***	1.180	1.458
(Ref = access to private garden)			
No access to private garden	0.454***	0.412	0.499
(Ref = access to communal garden)			
No access to communal garden	0.854	0.708	1.030
(Ref = insufficient green in neighborhood)			
Sufficient green in neighborhood	1.708***	1.556	1.874
(Ref = green and squares in neighborhood poorly maintained)			
Green and squares in neighborhood well-maintained	1.107	0.995	1.232
Coefficient of determination = pseudo R^2(Nagelkerke)	10%		

C19CM, coronavirus disease 2019 confinement measures.

Multiple Regression: Ordinal Logistic Regression

Since 95% of the respondents went into nature, the analysis investigated the variables related to the frequency of nature visits. An overview of these variables can be found in **Table 2**. Consequently, we identified three different themes associated with frequency of nature visit.

Firstly, frequency of nature visits is associated with the living environment. The analysis showed that respondents who are satisfied with their own home are more likely to go into nature several times a day than those who are dissatisfied with their home ($X^2 = 1{,}366$; $p < 0.05$). However, satisfaction with one's home neighborhood does not appear to have a significant effect on the frequency of nature visits. Subsequently, respondents with a private garden are more likely to visit nature several times a day than respondents without a garden. This correlation is statistically significant according to the chi-square test ($X^2 = 584.154$; $p < 0.05$). However, it should be noted that nature was broadly defined in this study, including own garden. Therefore, one may spend time in one's own garden when indicating visiting nature several times a day. Lastly, results showed that

TABLE 3 | Main reasons to experience nature in a more positive way than before C19CM ($N = 5,856$).

Reason	% that named as reason
Thankful for being able to go outside instead of constantly staying inside	88.2
Being able to go into nature for a longer period of time	42.4
Newly discovered stimuli or elements in nature	30.9
Grown connection with nature	30.7

C19CM, coronavirus disease 2019 confinement measures.

TABLE 4 | Main reasons to experience nature in a more negative way than before C19CM ($N = 759$).

Reason	% that named as reason
Too crowded outside	67.8
It's no longer allowed to sit on a bench or in the grass	37.2
Fear of getting infected with COVID-19	34.9

C19CM, coronavirus disease 2019 confinement measures.

respondents who are satisfied with their residential area are more likely to visit nature several times a day (37.1%), compared with respondents who are dissatisfied (24%). This association was significant ($X^2 = 107{,}540$; $p < 0.05$).

Secondly, we could identify three different demographic factors associated with frequency of nature visit: age, sex, and educational level. Regarding age, 7.4% of the respondents over the age of 65 do not go into nature during the C19CM. This is a significant lower percentage than among the younger age groups, of which a larger percentage does visit nature. However, people over the age of 65 who go into nature go more frequently than the age group 12–30 years. The other age categories do not appear to differ significantly from this reference group. Furthermore, women visit nature more often than men, though it must be acknowledged that our sample had an overrepresentation of women. Lastly, the analysis indicated that lower-educated people go into nature less frequently than higher-educated people ($X^2 = 133.316$; $p < 0.05$). Of the lower-educated respondents, 91.1 went into nature during C19CM as compared with 96.5% of the higher-educated ones. Even after verification for age and sex, this association was still found to be significant [Exp(B) = 1,513; 95% CI = (1,386; 1,651)].

Lastly, subjective mental and physical health are associated with frequency of nature visits. The chi-square test indicates that respondents who feel mentally healthier are more likely to go into nature than those who indicate that they feel "not at all healthy"; 44.7% of the "very healthy" respondents go into nature several times a day, while only 23.1% of those who indicate that they feel "not at all healthy" do so ($X^2 = 207.405$; $p < 0.05$). In terms of physical health and nature visits, we see a rather small but significant difference between physically healthy and non-healthy people ($X^2 = 71{,}687$; $p < 0.05$). Of the respondents who feel physically healthy, 36.7% go into nature several times a day, compared with 31.9% of the people who do not feel healthy. However, our sample contained an overrepresentation of people indicating feeling healthy. An important difference was found considering health and level of education. Less-educated people reported feeling less physically healthy (88.5% compared with 91.5%) and slightly less mentally healthy (82.7% compared with 86.2%) than highly educated people.

DISCUSSION

We explored to which extent people visit nature (more often) during C19CM and which factors contribute to this. Half of the participants indicated going into nature more often than before C19CM. These findings complement research elsewhere in Europe (17, 39) and Asia (16).

This study can be embedded in the broader definition of nature contact from Frumkin (7). This study focused on one dimension of contact with nature, namely, visiting and going into nature. The results show a significant relationship between the frequency of nature visits and home environment, age, gender, socioeconomic status, and health.

Having more time due to the C19CM seems to stimulate respondents to visit nature more often than before (14, 30, 39). In line with previous research, gardens were reported as the most popular place, followed by parks (17). In addition, respondents with a private garden were more likely to visit nature several times a day.

More than half of the people experienced nature more positively during C19CM than before. Participants reported feeling less anxious, more relaxed, positive, fitter, and happier after visiting nature. The benefits of exposure to nature are well-highlighted in some previous work for reducing stress and anxiety (40) and improving physical and mental health (6, 41) and the general well-being (5, 42).

The majority of the respondents consider visiting nature important for their health, and this seems to have increased during C19CM. This is in accordance with the research from Lopez et al. (43). Nature helps to maintain social relationships during C19CM, as the younger respondents reported visiting nature more often than before to walk together with friends. It is known that spending time with others in nature can build social capital and also improve social cohesion (44). In this way, visiting nature may mitigate the negative effects of social isolation on mental health (45, 46), an effect that may have been especially important during lockdown (44, 47).

The level of high educated respondents in our sample was significantly higher than in the general population. Despite this response bias, the results show that less-educated people are less likely to go into nature during the C19CM and experience nature as less positive. In addition, we found a positive association between home satisfaction and nature visits that may also be explained by more favorable housing facilities for better-educated people. People with low levels of education are more likely to live in small dwellings (48) where the quality of access to nature may wane (49), and they report more often feeling unhealthy (50).

The present study is subject to several limitations. Firstly, a key limitation was that we did not detail enough in the questions which type of nature the respondents were visiting; hence, we could not clearly see whether this was, e.g., public (park, forest, field, etc.) or private nature (garden and green terrace/balcony). Perhaps, nature was defined too broadly. Due to the questioning and data analysis, we cannot specify how often people visit a particular place. This would have been an added value since previous research has shown how benefits can differ based on the type of nature (22). Secondly, our sample is not representative for the general population of Flanders. Therefore, results mainly apply within the characteristics of the sample. Generalization to a wider population remains speculative. There is an underrepresentation of low-educated and vulnerable groups who feel less healthy and a small underrepresentation of men. Future research should seek to achieve a more diverse sample. A mixed-method research design could be used to achieve this, in which qualitative research is necessary to reach more vulnerable groups. Furthermore, we must take the weather conditions into account. At the time of the survey, there was exceptionally good weather in Belgium, which may have possibly influenced the frequency of nature visits. Finally, we can question whether the behavior toward nature persists or whether this was only the case at the start of the confinement measures. A follow-up survey could verify this.

In sum, this study investigated the frequency of nature visits during the C19CM in Belgium and explored how people experienced nature. The results from this study are in accordance with previous studies who highlight the benefits of visiting nature for human health. People went into nature more often and reported positive feelings afterwards. The frequency of visiting nature was associated with several variables such as educational level, age, health, and living environment. Respondents with a higher educational attainment, who felt mentally and physically healthy, and were satisfied with their living environment went into nature more often.

This study highlights the importance of nearby green infrastructure. These findings show implications for policy makers to create more accessible green spaces and to keep these places accessible during C19CM, as it is considered a significant contribution to the general well-being and could serve as a coping strategy for emotion regulation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

AL: conceptualization and design of the study, coordination and supervision of the questionnaire distribution, data cleaning, analysis of results and interpretation, creation of figures and tables, and editing manuscript. SH: drafting and editing manuscript. AD: editing questionnaire, collaboration in survey distribution, data cleaning (conversion of online survey data into dataset), support with analysis, and editing manuscript. AS, LL, and RR: editing questionnaire, collaboration in survey distribution, and editing manuscript. HB: editing questionnaire and collaboration in survey distribution. HK: conceptualization and design of the study, coordination and supervision of the questionnaire distribution, data cleaning, analysis of results and interpretation, and editing manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.646568/full#supplementary-material

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Epidemiology, Biodiversity, and Technological Trajectories in the Brazilian Amazon: From Malaria to COVID-19

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The Amazon biome is under severe threat due to increasing deforestation rates and loss of biodiversity and ecosystem services while sustaining a high burden of neglected tropical diseases. Approximately two thirds of this biome are located within Brazilian territory. There, socio-economic and environmental landscape transformations are linked to the regional agrarian economy dynamics, which has developed into six techno-productive trajectories (TTs). These TTs are the product of the historical interaction between Peasant and Farmer and Rancher practices, technologies and rationalities. This article investigates the distribution of the dominant Brazilian Amazon TTs and their association with environmental degradation and vulnerability to neglected tropical diseases. The goal is to provide a framework for the joint debate of the local economic, environmental and health dimensions. We calculated the dominant TT for each municipality in 2017. Peasant trajectories (TT1, TT2, and TT3) are dominant in ca. fifty percent of the Amazon territory, mostly concentrated in areas covered by continuous forest where malaria is an important morbidity and mortality cause. Cattle raising trajectories are associated with higher deforestation rates. Meanwhile, Farmer and Rancher economies are becoming dominant trajectories, comprising large scale cattle and grain production. These trajectories are associated with rapid biodiversity loss and a high prevalence of neglected tropical diseases, such as leishmaniasis, *Aedes*-borne diseases and Chagas disease. Overall, these results defy simplistic views that the dominant development trajectory for the Amazon will optimize economic, health and environmental indicators. This approach lays the groundwork for a more integrated narrative consistent with the economic history of the Brazilian Amazon.

Keywords: biodiversity, Amazon, ecosystem service, technological trajectory, epidemiology, COVID-19, neglected tropical diseases

1. INTRODUCTION

The Amazon basin is home to the largest tropical forest in the world, covering eight South American countries and one of France's overseas territories. The maintenance of this biome is mandatory for planetary health (1) and is invaluable to the world due to its unique biodiversity, human culture, climate regulation, gene banks and freshwater reservoirs, to name but a few social and ecosystem services (2). Approximately two thirds of the Amazon basin are located within Brazilian territory. In Brazil, there are two official boundaries for the so called Amazon region: the Legal Amazon[1], a political-administrative definition that encompasses 58.9% (ca. 5 million km^2) of Brazilian territory and the Amazon biome, corresponding to a biogeographic area covering ca. forty-nine percent of the country's territory (4.2 million km^2) (3). The Legal Amazon is home to a wide diversity of cultures, languages and types of human settlements, including indigenous, quilombola and riverine communities, towns and industrialized urban centers. About 30 million people currently inhabit the Legal Amazon, ~12.5% of the total Brazilian population (4). From this total, 72.4% live in urban areas varying from small towns displaying different rurality degrees to large metropolitan regions, such as Belém and Manaus (5). In addition, 355 thousand Indigenous individuals inhabit 383 demarcated Indigenous lands (6). Forest maintenance requires understanding and caring for cultural and productive practices that seem to have established a healthy balance between direct or indirect Amazon forestry activities, having co-evolved in the Amazonian context and remained resilient until now.

Since 2012, after the lowest deforestation rate observed in three decades, a strong upward trend in Legal Amazon deforestation rates are now being witnessed, reaching 11,088 km^2 in 2020 (7). This forest suppression is mainly driven by land demands for the implementation and expansion of new pasture areas. Large-scale agriculture also causes indirect pressure on the forest, as pastures are converted into agricultural lands. This process promotes the creation of new pasture areas by further deforestation (8–10). The rural economy of the Legal Amazon in 2018 was ca. R$ 65 billion[2], corresponding to 12% of the region's total Gross Domestic Product (GDP). Large-scale agriculture, illegal logging and mining activities are characterized by intense conflicts during land accumulation processes, as land is one of the most valued social assets in the Amazon biome (12). Large-scale agricultural and mining projects are supported by high economic, technological and financial incentives as well as investments in large infrastructures prioritizing road building, hydroelectric dam construction, as well as freight railways and berth and bulk port terminals for commodity exports. On the other hand, rural production systems based on agroextractive and smallholder livestock activities that have persisted through the last centuries still exhibit a strong presence in the Amazon agrarian economy (13, 14). Although these sectors lack economic and fiscal incentives when compared to the agribusiness sector, they remain an important way of life for a large portion of the population that strongly relies on provisional ecosystem services and natural capital.

Deforestation and habitat fragmentation lead to several negative effects on ecosystem services, such as loss of biodiversity, soil and water quality and increased abundance of disease reservoirs and vectors in contact with human communities (15–17). Leishmaniasis, malaria, Chagas disease, leptospirosis and dengue, are all neglected tropical diseases prevalent in the Amazon region and are indicative of social and environmental vulnerability, including poverty, poor sanitation, and lack of clean water supplies.

In 2020, the vulnerability of the Amazon region to directly transmitted diseases became evident during the COVID-19 epidemic. This emergent viral disease was discovered in December 2019 in China and was declared a pandemic by the World Health Organization on 11 March 2020. On 13 March 2020, the first case was confirmed in Manaus, rapidly evolving to a large epidemic with 32259 confirmed cases and 1957 deaths in 4 months (18–20). Initially present in cities, COVID-19 rapidly spread to rural and forest communities, causing large indigenous and riverine community losses. This disease exacerbated the inequality gap and brought to light regional precarities, mainly associated with the uneven distribution of access to collective consumption goods, sanitation, and basic health services, directly impacting the living conditions of the Amazon population.

We advocate that, in order to maintain the forest and its planetary services, we must move beyond disciplinary knowledge and consider that epidemiology, economy and ecosystem services are intertwined components of the complex Amazon biome system, affecting biodiversity and the well-being of local populations. Assessments on how the state of this adaptive complex system is affected by economic development pathways, in particular, those related to the local agrarian economy, which comprises one of the main forces driving the future of the region, are paramount. We, therefore, seek to determine proper wealth, health and environmental integrity measurements that take into account the singularities of the Brazilian Amazon region. The need for new measures for wealth characterization, as well as new economic indicators concerning well-being, is now at the center of discussions regarding economic development models and policies (21–23). Using a series of indicators, we characterized the environmental and epidemiological states of municipalities following different techno-productive trajectories (TT) in the Amazon region. TT is a concept derived from a framework developed by Costa (12) and Costa (14) to model the agrarian economy of the Brazilian Amazon. This framework describes the rural reality of the Amazon region according to its structural historical-geographical diversity (13). With this approach, a more integrated and consistent narrative is produced to explain the scenarios that create or maintain ecosystems and human health in the Amazon.

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[1] The Legal Amazon or the Brazilian Amazon is the administrative area operated by the Superintendence of Amazon Development (SUDAM), created in 2007. The Amazon biome includes the Amazon Rainforest formations and associated ecosystems subject to the Rain Forest Protection Law 11.428, 2006.

[2] All figures are corrected for 2018 Brazilian Real values. Based on an average commercial exchange rate of the Brazilian-Real/US-Dollar in 2019 of 3.6542 (11), the values for the rural Gross Production Value (GPV) in US$ was of about US$ 18 billion.

In the following sections, we introduce the concept of techno-productive trajectories and describe their distribution in the Amazon. Then, we present how environmental and epidemiological indicators are associated with these trajectories forming a co-evolving system.

2. THE BRAZILIAN AMAZON TECHNO-PRODUCTIVE TRAJECTORIES

Until the 1920's, the agricultural frontier advancing within the Brazilian Amazon established productive structures that alternated predominantly between those based on compulsory labor and those based on relatively autonomous agriculture and extractive work (13). This historical context concerning the agrarian Amazon economy is reflected today in the presence of two main microeconomic rationalities and their interactions, as follows: (i) family centrality in decision-making processes, subordinating the marginal efficiency of the capital to the logic of family and life reproduction and (ii) an economy where production essentially depends on wage labor, where economic agents behave predominantly guided by assessments concerning the marginal efficiency of the capital, i.e., oriented by profit. These two microeconomic rationalities synthesize the strategies and contexts in which economic agents make their decisions in the agrarian Amazon and are associated with the Amazon's Peasants and Farmer and Rancher economic agents (13, 14, 24, 25).

These two distinct rationalities are guided by two major technological solution patterns, comprising Technological Paradigms (14, 26), within different rural production systems. The Agricultural Paradigm, herein represented by intensive temporary crop systems, large scale cattle raising, large permanent crops, planted forests and technified silviculture, defines a production process based on technologies targeting the efficient mechanical, chemical and biological control of nature to achieve large-scale production. The other is the Agroextractivist Paradigm, defined from the Peasant's form of production that has persisted and evolved over the centuries, characterized by the structural diversity of their production systems, which presuppose Amazon biome diversity maintenance and coexistence.

Techno-productive Trajectories or Technological Trajectories (TTs) emerge from the combination of these two rationality patterns and their corresponding paradigms (Agricultural and Agroextractivist) regarding the relationship between economic agents and nature, expressed in their production systems. To identify these TTs, Costa (14) developed a complete operational method consisting of four steps. The method applies multivariate regressions and principal component and factor analysis techniques to data collected by the Brazilian 1995, 2006, and 2017 agricultural censuses. Using this approach, six[3] different technological trajectories were identified and characterized. **Table 1** presents a synthetic description of these trajectories as well as the footprints they have left on the biome's landscape. We also qualitatively described each landscape footprint based on forest-nonforest spatial patterns left by economic trajectories and observed by satellite images (27). The percentage shares of the TTs in relation to the agrarian component of Amazon's gross domestic product were determined by Costa (14). **Figure 1** presents a map of the dominant technological trajectories per municipality using the most recent 2017 national agrarian census data (14).

To calculate the dominant technological trajectory for each municipality, we computed which of the six TTs was responsible for over 50% of the municipal Gross Agricultural Product Value, that is, the total contribution value derived from the rural economy to the Municipal Gross Domestic Product in 2017. We observed that Peasant trajectories (TT1, TT2, and TT3) are dominant in ca. fifty percent of the Amazonian territory, mostly concentrated in areas covered by continuous forest. On the other hand, a strong presence of TT4, a non-peasant trajectory, linked to large cattle raising, is noted in the Southern and Eastern portion of the biome. This activity is expanding toward areas that still exhibit large amounts of forest cover. It is important to note that TT4 trajectories appear in many municipalities that also present TT3 trajectories. These two trajectories, one based on peasant rationality and the other on profit-oriented rationality, can interact through competition or cooperation. Presently, the TT4 trajectory is more likely to become the dominant trajectory in these municipalities, given current institutional arrangements. TT7 is dominant in the Southern and Northern Amazon, mainly associated with grain production, i.e., soybean and rice. Finally, non-peasant trajectories TT5 and TT6 are located at the boundaries between continuous forest and pasture.

3. BIODIVERSITY TRAJECTORIES

The main biodiversity threats in the Brazilian Amazon ecosystem include deforestation and the expansion of livestock and industrialized monocultural agriculture activities over new areas. This follows a hasty industrialization process since the 1950s and, more recently, a nationwide attempt to adapt Brazil to economic globalization. In this sense, the distinct technological trajectories found across the Amazonian landscape are the primary drivers shaping the environment and its biodiversity (28).

There is unequivocal evidence that environmental change and the unsustainable use of natural resources decrease biodiversity by causing local extinctions, increasing the dominance of few species and homogenizing biotas through species introduction (29, 30). These biodiversity changes can potentially affect the occurrence of infectious diseases in humans and other taxa, including wildlife and domesticated animals (31). For instance, deforestation and habitat fragmentation increase the likelihood of contact between humans and zoonotic pathogens (15–17). This connection between environmental degradation and disease emergence has already been demonstrated for several diseases and environments (32). However, the precise mechanisms

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[3] As the Technological Trajectory associated to the silviculture systems run by non-peasant agents, (TT6) only displays a small and local contribution to the regional agrarian economy, it was combined with TT5 (TT5 and TT6). It is important to note that TT5 and TT6 merge two distinct non-peasant TTs. TT5 consists of permanent crops (for example, palm oil) and specific agroforestry systems (such as Açaí palm with pepper) while TT6 is associated with silviculture systems.

TABLE 1 | Technological Trajectories and their contemporary empirical forms of expression in the Amazon biome and their associated landscape structures.

Technological trajectories (TT)			**Landscape footprints description**
Peasant Systems	TT1	Production systems that converge to the agriculture of permanent (cocoa, pepper, coffee) and temporary (manioc, corn, rice and beans) crops with varying compositions and diversity, but still maintaining a level of structural diversity in their operation.	*Land Mosaics with Forests.* Heterogeneous land cover mosaics composed of small temporary and permanent crops, secondary vegetation in different stages, small pasture and large continuous forest areas.
	TT2	*Agroforestry production systems.* Agroforestry production systems. Mainly comprising two types: One based on non-timber extraction (acai, nuts, waxes, rubber, oils - andiroba, copaíba, etc.) and the other based on agroforestry with permanent crops (cocoa mainly). Both are deeply rooted in structural diversity as an essential ecological context for production.	*Forest Dominant.* Predominance of large continuous forest areas, which may or may not contain small patches of secondary vegetation and permanent crops in association to the forest cover.
	TT3	Productive systems that converge to small/medium cattle ranching with the production of dairy products or beef cattle often associated with temporary (manioc, rice, beans, corn) and/or permanent crops (cocoa, peeper, coffee).	*Grassland Dominant.* Predominance of small and medium pasture areas, which may contain shrubs and trees (unmanaged pasture) associated with small cultivation areas, secondary vegetation in early stages and fragmented forests.
Farmers and Ranchers systems	TT4	Productive systems that converge almost exclusively to livestock for beef production. These systems may present crops comprising foraging species for livestock, like corn and sugarcane.	*Grassland.* Homogeneous landscapes produced by the dominance of large clean (managed) pasture areas with small patches of fragmented forests.
	TT5 and 6	Productive systems based on the cultivation of permanent crops (TT 5), such as palm oil (dendê) or upland irrigated acai, and silvicultural systems (TT 6), with the cultivation of exotic and native forest species and the extraction of products like wood, firewood, nuts, waxes and gums, among others.	*Cultivated Forest.* Homogeneous landscapes generated by the dominance of large patches containing one or few species of planted trees and shrubs. In the case of forestry, some recent wood harvest areas may occur. The landscape may or may not present forest remnants.
	TT7	Productive systems oriented to temporary crops presenting the strong use of mechanical and/or chemical technologies, primarily for grain cultivation (soybeans, rice, corn, etc.).	*Crop Landscape.* Homogeneous landscape generated by the dominance of large patches of a single crop with or without few and small forest remnants.

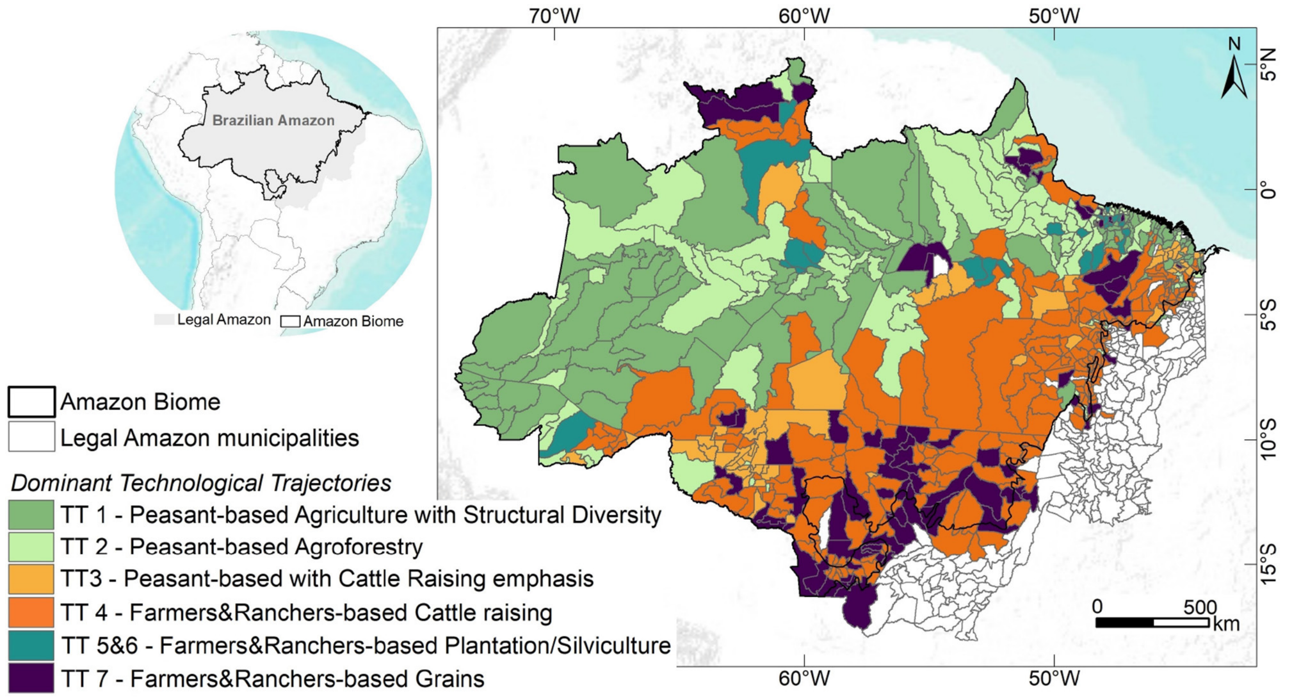

FIGURE 1 | Dominant Technological Trajectories (TT) in Amazon biome municipalities in 2017. The inset highlights the limits of the Brazilian Amazon (Amazon Biome and Legal Amazon).

of increased disease transmission following anthropogenic environmental impacts are still poorly investigated and understood, especially in the Amazon.

The conservation status of an ecosystem is often assessed through biodiversity indicators, such as species richness and composition, endemism areas, phylogenetic composition and species conservation status (33). These metrics may correlate with the potential products and services provided by biodiversity, such as decreased or increased risks of disease (34). However, despite the Amazon's importance and huge geographic area, its biodiversity is still poorly known (35) and biodiversity data on short temporal and local spatial scales are still scarce for this region. Furthermore, biodiversity is a complex multifaceted concept that includes space and time scales and entities such as species, traits and evolutionary units (36). Thus, estimating the consequences of biodiversity loss and the erosion of ecosystem function and services on planetary health greatly depends on the considered biodiversity indicator and scales. We argue that a broad evaluation of the processes driving the structure and dynamics of biodiversity on multiple spatial and temporal scales is key to model and better understanding the ecological and evolutionary mechanisms linking landscape change to zoonotic disease emergence.

Due to a lack of better Amazon indicators, landscape degradation and deforestation are adequate proxies that may be applied to characterize the temporal and spatial environmental trajectories induced by the different uses of biodiversity and its natural resources. Peasant systems are predominantly characterized by mosaics of heterogeneous agropecuary use, secondary forest fragments and large portions of continuous forest remnants, leading to a highly diverse landscape that may sustain higher biodiversity. In contrast, Farmer and Rancher systems are dominated by homogeneous landscapes with the predominance of generalist habitat and synanthropic species, harboring lower biodiversity. The temporal dynamics of TT dominance and transitions leave landscape imprints on short and long-term time scales, and alteration patterns of these landscape footprints are used to characterize environmental trajectories.

Herein, we considered remote sensing indicators regarding vegetation cover and deforestation for each Brazilian Amazon municipality (**Table 2**, **Supplementary Figures 1, 2**, and **Supplementary Table 1**), in order to characterize environmental trajectories and their association with TTs. First, we computed the proportion of municipalities with original forest physiognomies and with non-forest physiognomies (savanna, grasslands and wetlands, among others), as the Legal Amazon presents other physiognomies besides the tropical rainforest. Second, using deforestation data (7), we computed the percentages of remaining forest area until 2017 (Remn forest), deforestation from 2006 to 2017 (Def 2006–2017) and the percentage of the total deforested area until 2017 (Def by 2017) for each municipality. A detailed description of these indicators is found in the **Supplementary Table 1**.

Forest conversion is considered an important biological change driver and a meaningful proxy for habitat loss (37). Recent studies have demonstrated the importance of habitat amount (38), landscape and within-forest disturbances (39), and landscape configuration (40) to explain biodiversity declines following deforestation. A survey of multiple agricultural areas (landscape scale) in the Amazon indicated that overall local biodiversity dropped steeply when forest cover fell below 30–40% and when forest patches reached 50% of undisturbed forest (41). Studies also underline the importance of old secondary vegetation, managed forests, and tree plantations in the maintenance of local species richness for different groups of plants and animals (39, 42).

4. EPIDEMIOLOGICAL TRAJECTORIES

The Twentieth century is characterized by an overall transition from infectious to chronic diseases as the main causes of death in several countries. This epidemiological transition is attributed to the discovery of etiological agents and transmission cycles, city sanitization and more effective prevention and health promotion strategies, as well as more effective treatments. Many diseases have been eliminated or controlled, such as measles, polio and tuberculosis, among others (43). Meanwhile, we are witnessing the emergence and reemergence of new infectious diseases triggered by demographics, transportation and environmental changes.

In Brazil, life expectancy improvements and decreased death rates by communicable diseases, especially diarrhea, lower respiratory infections, tuberculosis, meningitis, and vaccine-preventable diseases are noted (44). However, compared to other Brazilian regions, the Amazon region has maintained the worst health indicators. The median age at death was 60 years in 2008 and remained the same until 2013, while other Brazil regions gained at least 5 years of life. Neglected tropical diseases are an important morbidity and death cause in the Amazon, and the median age of death by infectious diseases was 50 years old in 2013 (45). This region also displays the highest infant mortality rate in the country (21.8 deaths per 1,000 births) and the second lowest life expectancy at birth (72.43 years) (46).

Neglected tropical diseases (NTDs) are infectious diseases presenting chronic and debilitating characteristics, prevalent in low-income countries and more concentrated in extremely poor populations (47). Poor housing and working conditions and a lack of access to preventive health services and assistance are social determinants for these diseases. Many NTDs are zoonotic diseases, and their dynamics also depend on environmental determinants, such as regulating and supporting ecosystem services (48). Herein, we collected data on zoonotic diseases reported to the Brazilian Ministry of Health (see details in the **Supplementary Material**) and analyzed their distribution among municipalities following different technological trajectories. The data comprise vector-borne NTDs (dengue + Zika + chikungunya, Chagas disease, visceral and cutaneous leishmaniasis, vivax malaria) and non-NTDs (spotted fever) as well as diseases directly associated with environmental degradation, including rodent- and water-borne diseases (leptospirosis, hantavirosis and schistosomiasis). These diseases follow a spectrum of urban to rural diseases, with varying degrees of association with biodiversity, land use and land cover. Finally,

TABLE 2 | The values correspond to the percentage (%) of municipalities following a techno-productive trajectory classified as presentng "high values".

Environmental descriptors	Proportion of municipalities with high values					
	TT1	**TT2**	**TT3**	**TT4**	**TT5&6**	**TT7**
Original phytophysiognomy						
Forest physiognomy	66.0	50.0	75.0	72.0	81.0	47.0
Non-forest physiognomy	1.0	5.2	0.0	7.6	4.8	20.3
Habitat and Habitat loss						
Deforestation 2006 - 2017	21.0	20.8	39.6	40.6	33.3	47.3
Deforested area up to 2017	25.0	13.0	38.0	41.0	24.0	16.0
Forest remnants in 2017	47.0	41.7	22.6	18.3	38.1	20.3
Diseases						
Environmental borne						
Hantavirus (2009-2013)	0.0	0.0	0.0	2.5	0.0	6.8
Schistosomiasis (2010-2014)	4.5	0.0	13.2	2.5	0.0	4.1
Leptospirosis (2013-2017)	10.0	16.7	15.1	6.6	9.5	5.4
Vector borne						
Spotted fever (2008-2013)	0.0	0.0	0.0	0.5	0.0	0.0
Chagas disease (2014-2018)	7.3	14.6	0.0	0.0	9.5	0.0
Visceral Leishmaniasis (2014-2018)	5.5	8.3	3.8	18.3	4.8	8.1
Malaria (2014-2018)	39.1	45.8	24.5	14.2	28.6	8.1
American cutaneous Leishmaniasis (2014-2018)		28.1	30.2		28.6	32.4
Aedes-borne diseases: dengue, Zika and chikungunya (2014-2018)	9.1	11.5	24.5	31.5	14.3	50.0
COVID-19 (2020)	25.0	37.5	3.8	22.4	33.3	24.0

A "High value" is defined as belonging to the top quartile of the frequency distribution. Color intensity is illustrative for ease of viewing and is proportional to the values as represented on the scale.

we also analyzed the spatial distribution of COVID-19 that invaded the Amazon region on March 13th 2020 and spread quickly into a large epidemic.

We calculated the accumulated incidence for each disease in a time window of 5 years (**Supplementary Table 1**). The specific time window varied to accommodate data availability differences. The population in 2015 was used as the denominator. For COVID-19, we calculated the accumulated incidence in 2020, using surveillance data collected up to April 1st 2021. The estimated population in 2019 was the denominator. Municipalities within the top 25% of accumulated incidence were classified as "high risk." This indicator is robust when applied to data varying from highly prevalent endemic diseases to more focal diseases with episodic outbreaks.

4.1. Vector Borne Diseases (VBD)

Supplementary Figure 3 displays maps concerning the accumulated incidence of Aedes-borne diseases (dengue + Zika + chikungunya), american and visceral leishmaniasis, Chagas disease, and spotted fever in the Brazilian Amazon. A map of the annual parasite index (API) for malaria is also shown. **Figure 2A** displays the municipalities where one or more of these VBDs co-occur at higher sintensities.

Malaria (MAL) is still an important cause of years of life lost to disability, particularly in children and young adults (49). It is also associated with preterm birth and low birth weight in women lacking access to prenatal care (50). Most malaria cases in the Amazon are caused by *Plasmodium vivax*, an NTD (51, 52). Malaria vectors breed in shaded clean and still water, like lakes, the borders of rivers and streams, and small transient puddles formed in flooded forests. Roads and canals that create artificial pools, as well as fish tanks close to flooded forests, are examples of human constructions that may amplify mosquito populations (53). *Anopheles darlingi*, the most important malaria vector in the region, has adapted well to these artificial environments but other *Anopheles* species displaying different vector competence degrees and habitat preferences are also found in the region (54–57).

Aedes-borne diseases (ABD). The Brazilian Amazon was the port-of-entry of DENV-2 in 1982 (58), DENV-4 in 2010 (59) and chikungunya in 2014 (60). Urban centers in the Amazon suffer from poor garbage collection services and piped water. These factors create environmental conditions that facilitate the maintenance of a high abundance of *Aedes* spp. Approximately 58 thousand cases are reported each year, mostly dengue (76%), followed by chikungunya (15%) and Zika (9%). Other ABD, such as Marburg, although detected, are not monitored by routine epidemiological surveillance efforts.

American cutaneous leishmaniasis (LTA) and visceral leishmaniasis (VL) are diseases caused by protozoans belonging to the *Lutzomyia genus*. Sandfly vectors are abundant in humid forests (61) but have adapted to secondary forests, tree plantations and green spaces in rural and urban areas (62). In the past, LTA was a major cause of illness in extractivist communities, alongside malaria. As ruralization and urbanization progressed, the LTA transmission cycle also adapted which is evident in the homogeneous distribution of this disease along all TTs (**Supplementary Material**). An average of 7,000–11,000 LTA cases are reported per year. Although its displays low lethality,

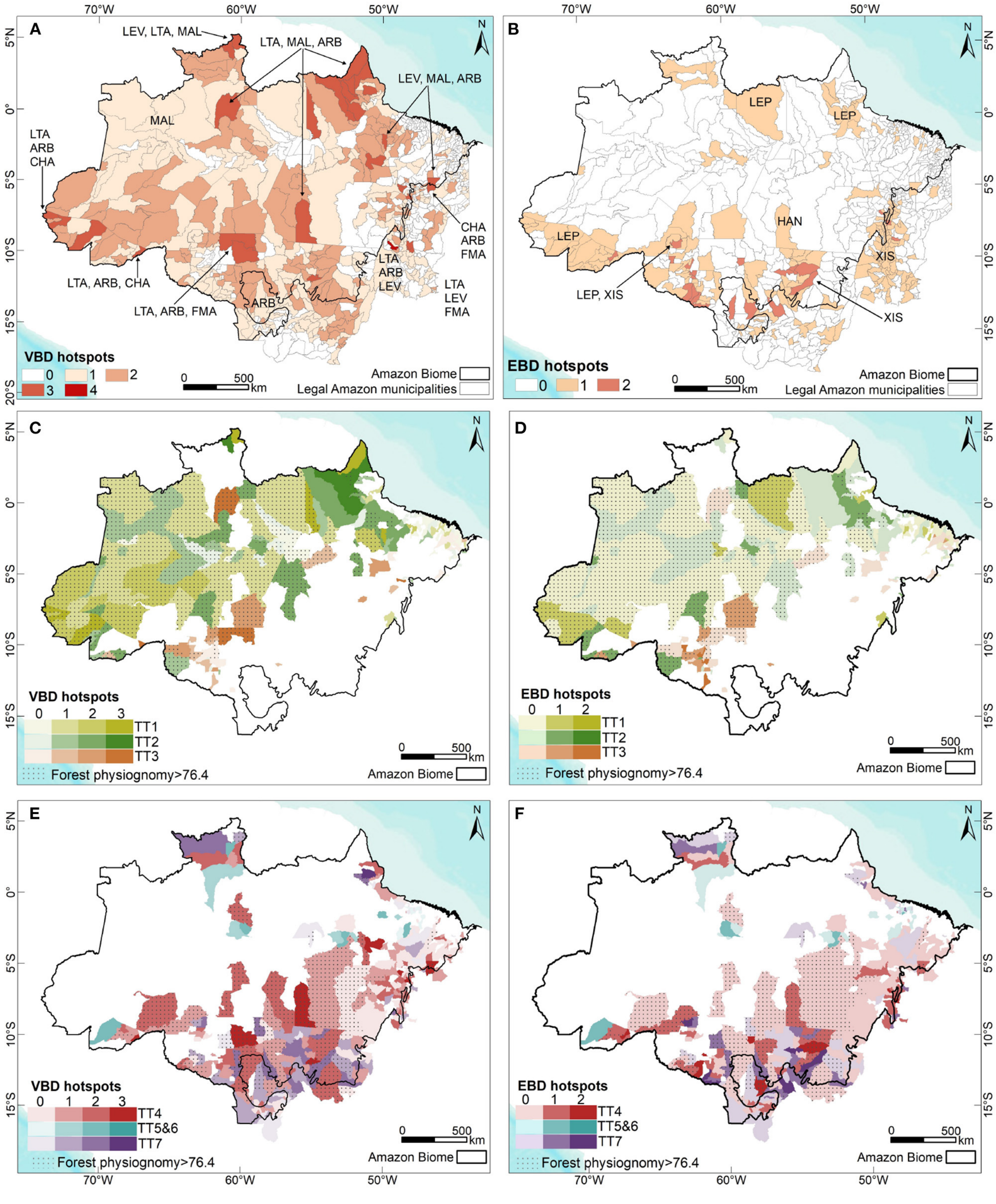

FIGURE 2 | (A) Municipalities presenting the occurrence and co-occurrence of Vector-borne diseases (VBD); **(B)** Municipalities presenting the occurrence and co-occurrence of schistosomiasis, hantavirosis and leptospirosis (EBD); Municipalities dominated by Peasant Trajectories (colors), forest physiognomy (hatch) and the occurrence of VBD **(C)** or EBD **(D)** (color intensity); Municipalities dominated by Farmer and Rancher Trajectories (colors), forest physiognomy and occurrence of VBD **(E)** or **(F)** EBD (color intensity).

this neglected tropical disease is a cause of social stigma. Cure depends on aggressive treatment since spontaneous cure occurs in only 6% of all cases (63). The ecological plasticity of LTA is explained by the diversity of potential vertebrate hosts, including both wild and domestic *Canidae*, rodents, and marsupials, as well as a vector adaptation to feed on humans and peridomestic animals (64). In the Amazon, new leishmaniasis foci have been associated with deforestation followed by farming (65). VL, the visceral form of leishmaniasis is more concentrated on the eastern part of the Amazon and north of Roraima, in the transition region between the forest and non-forest biomes. From 900 to 1,500 cases on average are reported each year, with a lethality rate ranging from 5 to 7%.

Chagas Disease (CHA) is an endemic disease with an enzootic cycle involving wild mammals (Marsupialia, Chiroptera, Rodentia, Edentata, Carnivora and Primata) and forest-dwelling triatomine vectors. Two to three hundred new cases are reported each year. Higher incidence areas are concentrated in Pará, around the city of Belém, and in the state of Acre. Oral transmission is also detected, associated to the consumption of açaí and other palm fruits.

Spotted fever is a bacterial disease caused by the *Rickettsia* genus, usually transmitted by ticks. In Brazil, most cases are reported in the Southeast region, with capybaras and horses as the main animal reservoirs. Although not endemic in the Amazon region, 10–20 cases have been reported each year in the transition area in Tocantins and Mato Grosso states. Diseases caused by *Rickettsia* spp. are likely to be highly under-diagnosed in the Amazon region, in part due to the lack of awareness (66). Recently, the disease was described as being caused by *Rickettsia typhi* in the Amazon, transmitted to humans by fleas. In 2009, a rickettsiosis outbreak was investigated in an indigenous population in the state of Mato Grosso (67). Better tools for monitoring rickettsioses should, therefore, be a priority in the Amazon.

4.2. Other Environmentally Borne Diseases (EBD)

Supplementary Figure 4 presents accumulated incidence maps for leptospirosis, hantavirus and schistosomiasis. **Figure 2B** displays the municipalities where one or more of these EBDs co-occur at higher intensity.

Leptospirosis (LEP) is an acute febrile illness caused by bacteria belonging to the *Leptospira* genus, transmitted to humans through contact with water contaminated with urine from infected rodents. *Leptospira* can remain viable in water for several months (68) and is considered a doubly neglected disease due to the lack of awareness of the Brazilian population regarding its severity (69). Endemicity is associated to urban areas with poor sanitation and open sewers or rural areas where agricultural practices lead to water contamination with animal urine. In agricultural settings, pigs and cattle can also act as reservoirs for *Leptospira*. Large leptospirosis outbreaks often occur after flooding events, common during the heavy rain months in the Amazon. For example, a molecular study carried out in the Peruvian Amazon reported heavy contamination of river water with rat urine (70). Cases are likely highly under-reported due to difficulties concerning Leptospirosis diagnoses.

Hantavirus infections (HAN) comprise zoonotic infections that have wild rodents as reservoirs. In the Americas, hantaviruses cause Hantavirus Pulmonary Syndrome (SPH). Human infection occurs through the inhalation of secretions or excreta from wild and synanthropic rodents from different species, predominantly in grain production settings that concentrate a large density of rodents. In the Amazon, the number of reported hantavirus infection cases is small compared to other areas in Brazil, concentrated in Mato Grosso and Southern Pará (71, 72). On the other hand, a serological survey in municipalities with forest economies (73) reported a low prevalence of hantavirus infections. Studies have demonstrated that the transmission of hantavirus is sensitive to biodiversity, although specific mechanisms may differ between places (74).

Schistosomiasis (XIS) is a helminthic disease caused by *Schistosoma mansoni*, whose intermediary hosts are aquatic snails belonging to the *Biomphalaria* genus. The transmission cycle involves contamination of snail-inhabiting lakes by infected human feces. The receptivity of the Amazonian limnological environment to the introduction of *S. mansoni*, and the risk posed by the arrival of migrants from endemic areas of the country to work in rubber plantations was already known in the 1950's (75). XIS is found in higher prevalence in municipalities located in the southern border of the Amazon (**Table 2**). These areas have attracted immigrants from endemic regions that end up inhabiting areas with poor sanitation infrastructure where the XIS transmission cycle has a high probability of becoming endemic (76). There is evidence that the acidic water in part of the Amazon region has acted as a barrier against XIS expansion, although, more studies are required to identify other hosts that may participate in the transmission of this disease in the region (77).

4.3. COVID-19

Supplementary Figure 5 displays the accumulated incidence of COVID-19 in the Brazilian Amazon during 2020. This period encompasses the first epidemic wave and the inter-epidemic period, with 1.2 million cases reported, 26,349 confirmed deaths, and a lethality rate of 2.1%. In the absence of measures to reduce mobility and increase social distancing, the disease spread at full speed. The health system collapsed in April in the large city of Manaus (78). Several municipalities were intensely affected (**Table 2**). COVID-19 also moved very quickly into the forest, brought by chains of contacts involving health and social assistants coming from the cities or by the flow of forest dwellers fleeing from towns back home. Entire communities were hit at once (79). **Supplementary Figure 5** indicates the ubiquity of COVID in this region.

5. INTERACTIONS AMONG ECONOMIC, ENVIRONMENTAL AND EPIDEMIOLOGICAL TRAJECTORIES

Figure 3A synthesizes the conceptual framework applied herein. We depart from the perspective that the changing land use

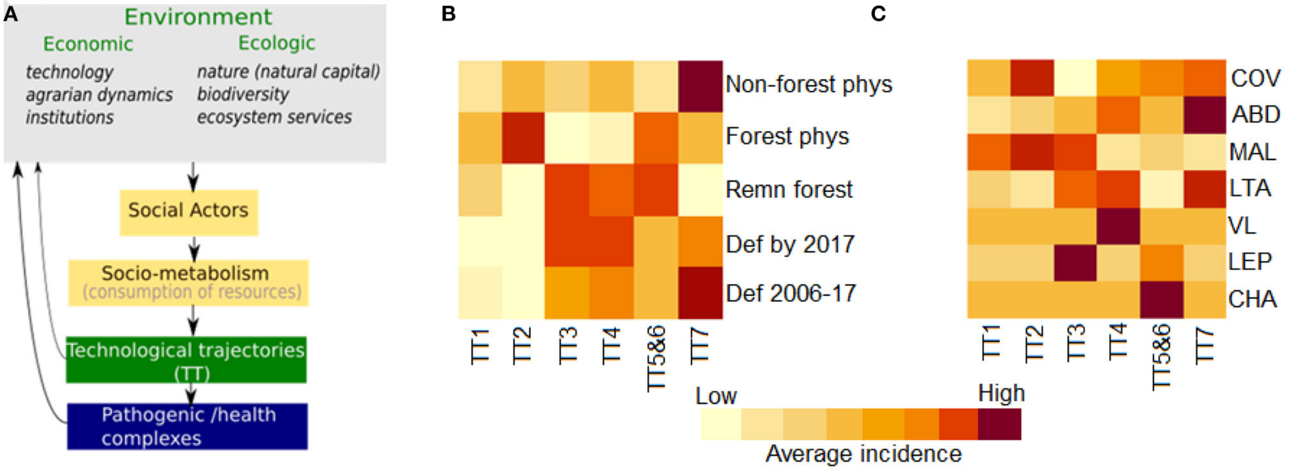

FIGURE 3 | Theoretical model for the system comprising the technological, ecological and epidemiological trajectories in the Amazon region. **(A)** Diagram presenting links between economic and ecological context variables and pathogenic/health complexes mediated by the technological trajectories. **(B)** Heatmap of the median environmental and disease indicators in municipalities following different technological trajectories (see **Table 1** for trajectory description, TT-1 to TT-7). Ecological indicators: recent deforestation (def 2006-2017); total deforestion prior to 2017 (Def by 2017); amount of forest remnant areas in 2017) (remn forest); forest physiognomy as the original biome (forest phys); non-forest physiognomy-savanah, rocks, natural grassland and wetland (non-forest phys). **(C)** Median disease incidence in municipalities following the assessed technological trajectories: schistosomiasis (SCH), leptospirosis (LEP), Chagas disease (CHA), visceral leishmaniasis (VLE), malaria (MAL), american cutaneous leishmasis (ACL), *Aedes*-borne diseases (ARB), COVID-19 (COV).

and land cover mosaics observed in the Brazilian Amazon landscape are driven by the local agrarian economic dynamics. This process can be described in ecological and socio-economic terms. From a socio-economic perspective, this dynamic is well characterized by Techno-productive Trajectories (TTs). Different TTs can coexist and interact via competition or cooperation strategies, determining changes in the forested landscape. The specific relationship between production and nature in each setting will vary depending on the producers' logic, knowledge and technology, which may or may not incorporate an ecological context in their processes. Concerning the landscape, this is seen as loss of forested areas with a direct impact on habitat loss. Habitat loss is associated with biodiversity impacts (80, 81). As the natural environment is anthropized, landscape transformations create conditions for the (re)emergence of diseases and persistence of endemic cycles with varying degrees of dependence on the sylvatic environment and TT predominance (**Figures 2C–F**).

Figures 3B,C present heatmaps with colors proportional to the median value of each environmental indicator and disease in the assessed municipalities classified by TT type. **Table 2** presents the percentage of municipalities with top values for each indicator according to TT type. Together, these indices illustrate the associations between economic and ecological trajectories in the Amazon region and the burden of selected diseases. Among the municipalities dominated by Peasant economies, those with TT2 trajectories are most concentrated in originally forested regions that underwent more intense land conversion prior to 2006, indicating older colonizations. Agroforest activities are an important component of this economy, which may explain the lower rate of recent change. Higher deforestation rates are observed more recently in TT3-dominated municipalities, which are found in both forest and non-forest physiognomies. A historical association is noted between Peasant TT3 and Farmer and Rancher TT4 trajectories with strategies of cooperation or assimilation of the trajectory TT3 by the TT4 (82). During the 2006-2017 period, municipalities dominated by TT3 and TT4 ranked in first places concerning deforestation rates. This intense conversion of forested landscapes into grassland formations followed by the establishment of cattle ranching and other agriculture activities has impacted the amount of available forest habitat, leading to biodiversity consequences. In this context, deforestation is associated with conflicts and pressure from non-peasant economies. Meanwhile, municipalities where TT1 dominates maintain larger forest remnants and lower change rates.

The distribution of vector-borne diseases among TT1, TT2, and TT3 trajectories is heterogeneous (**Figure 2C**). Malaria is the main cause of disease burden in all three, although more intense in TT2. Individual risk factors include working within or close to the forest, living at the border of the forest, being an immigrant from a non-endemic area, living in houses made of wood and lacking nets and scarce access to treatment (52, 83). American cutaneous leishmaniasis is concentrated in TT3 (and TT4) municipalities, characterized by the presence of large livestock herds. Chagas disease has a low median incidence in Peasant-dominated municipalities. However, some TT2 and TT1 municipalities are also located within the most affected areas (**Table 2**). Exposure to wild triatomines attracted by light or peridomestic animal blood meals are risk factors for forest dwellers living in TT1 municipalities. A second scenario is related to palm extractivism, such as acai and piassava, where workers are bitten by triatomines that live in the palm leaves in both TT1 and TT2 (84). A total of 24.5% of the municipalities displaying

TT3 also presents a high burden of dengue and chikungunya. These municipalities are mostly located in non-forested areas in the southern border of the Amazon region, in the transition are between the forest and cerrado biomes. Higher urbanization rates in this region can explain the presence of dengue in this landscape.

Municipalities dominated by Farmer and Rancher trajectories present high deforestation rates. One-quarter of the TT5- and TT6-dominated municipalities are among the municipalities with the highest percentages of deforested areas by 2017. Forest conversion in these municipalities is often performed by the substitution of the original forest by forest plantations. The newly planted forests are merged with the forest remnants areas, but the ecosystem is ecologically different, characterized by lower biodiversity, among others.

Of all trajectories, TT7 presents the highest number of municipalities displaying Aedes-borne diseases and American cutaneous leishmaniasis (**Figure 3**). These municipalities, located in areas with original non-forest physiognomy, were the first to cultivate grains in the Brazilian Amazon, expanding into the forested areas after the 2000s (85). Despite the fact that most non-forest physiognomy areas are located in municipalities associated with dominant TT7 trajectories, 47% contained originally over 78% of forest physiognomy (**Table 2**). From 2006 to 2017, municipalities with dominant TT7 trajectories presented the highest contribution to deforestation in the Legal Amazon, followed by TT4 and TT3 (**Table 2**). Regarding TT5 and TT6, acai monocultures are associated with reduced biodiversity and increased abundance of parasite-amplifying hosts such as marsupials (86). The high incidence of Chagas disease in TT5 and TT6 may be associated to the consumption of uncooked foods, like acai, contaminated by the feces and urine of wild triatomines (87).

Municipalities presenting high incidences of leptospirosis are observed in all technological trajectories (**Table 2**), from forest to urban, particularly in areas susceptible to flooding, such as the states of Acre and Pará (88, 89). Despite this overall distribution, the leptospirosis burden is higher in TT3 and TT5 and TT6. TT5 and TT6 municipalities also exhibit high malaria incidence. These areas display relatively less forest cover, where malaria is likely associated to specific rural activities. For example, (90) found a strong association between acai production and increased malaria incidence by *P. falciparum*, higher than associations to nut extraction and agricultural activities.

6. LIMITATIONS OF AVAILABLE METRICS AND INDICATORS

Despite its importance and huge geographic area, the Brazilian Amazon biodiversity is still poorly known (35). Recent studies demonstrate that biodiversity distribution is highly heterogeneous at both local and regional scales. A lack of studies on ecological interactions involved in the control of vector and reservoir species, as well as in pathogen virulence is noted. Adding to the challenge, the complex ecological interactions related to disease transmission and their interplay with other variables (e.g., landscape, economy, demography) form a complex system that defies causal relationships. This highlights the urgent need for understanding biodiversity dynamics and ecosystem functioning in the rapidly changing Amazon landscape.

Deforestation and forest fragmentation have already been applied as proxy indicators for habitat loss in studies addressing the relationship between environmental degradation and human health in the Amazon. A strong positive correlation between the number of malaria cases, deforestation and forest degradation in the Brazilian Amazon forest frontier has been reported, for example (91). The expansion of techno-productive trajectories linked to more intensive land uses (large areas for cattle raising and intensive agriculture) in the Amazon has resulted in an intense loss of forest habitat. However, the identification of biodiversity metrics that reflect anthropogenic disturbances relevant for epidemiology remains a challenge. Many of the metrics commonly applied to quantify biodiversity do not necessarily directly reflect the ecosystem service of disease regulation. For instance, species richness and abundance, the most basic biodiversity measures, naturally vary among distinct environments, and are not necessarily able to account for the regulatory role that ecosystems play in parasite transmission cycles. Another important biodiversity indicator used in ecological studies is endemism, although the relationship between endemic patterns and their potential contribution to the amplification or dilution of parasite transmission is not yet clear. In a local study, (92) reported that a reduced biodiversity of mammalian reservoirs led to increased *Trypanosoma cruzi* infection rates in domestic animals. This indicates that the identity of host species or even local trait distribution may better measure ecosystem functions played by certain species. This is noteworthy, as traits related to the epidemiology of parasite-host interactions determine the potential of ecological communities to amplify or dilute parasite transmission (31).

Although an increasing availability of global biodiversity data is observed, the Amazon is still poorly represented, with vast knowledge and sampling gaps. The global impacts of the COVID-19 pandemic brought forth the need to understand the direct effects of biodiversity changes on disease risk in the Brazilian Amazon. To address such a challenge, broad-scale studies aiming to describe biodiversity patterns and understand how they correlate with ecosystem services are required. Further studies in the biodiversity and health interface with the aim of surveying and monitoring the dynamics of infection rates in vectors and reservoirs are also paramount.

Furthermore, public health data limitations are also noted, as only a small set of diseases comprise mandatory notification and the surveillance system is not tailored for detecting new diseases. By measuring some separate diseases at a time and relying on clinical criteria for disease classification, a low sensitivity and low specificity surveillance system is established. This issue must be handled in order to study the association between disease and biodiversity. Moreover, incidence counts do not provide sufficient information.

Peasant trajectories with lower biome impacts, although still very present, are losing strength in the Amazon. These economies are invisible to standard economic indicators, despite the fact that they effectively contribute to the composition of the municipal GDP and are spatially distributed throughout the biome. The economic development agenda for this biome has supported and favored technological trajectories linked to the Agricultural paradigm (TT4, TT5, TT6, and TT7). The expansion of these trajectories into areas where Peasant trajectories are still strongly present is of concern (**Supplementary Figures 6A,B**). The fact that these regions comprise the largest continuous forest cover areas must be acknowledged. In particular, the spatial distribution of municipalities with dominant TT3 and TT4 trajectories is of special concern, as these trajectories are associated with cattle raising, one of the main deforestation-causing activities (**Supplementary Figure 6C**). To reach an inclusive, socially just and environmentally responsible development agenda for the Amazon, the real economy associated with the Peasant trajectories cannot be forgotten in the debate. The choices that will be made in this field will be decisive for the complex interactions between forest cover, biodiversity and disease development and emergence. We defend that novel economic indicators are required, because either the standard economic indicators contain problems and must be changed, or we will have to choose between saving economic indicators or saving the forest and the people who live in it.

7. CONCLUSION

This study groups economic, environmental and life health dimensions in the Brazilian Amazon. We demonstrate herein how environmental and health indicators differ among different technological trajectories, creating specific environmental and disease landscapes. While some diseases, like malaria and dengue, are dependent on specific socio-biodiverse complexes, this paper demonstrates that other diseases associated with specific TTs, such as LVA, have evolved to prevail in all TTs. As NTDs, these diseases comprise social and environmental vulnerability markers, and tracking these associations in other spatial and temporal scales, as well as other diseases and health outcomes, are paramount to validate this approach.

The ultimate goal of the planetary health initiative is the development of an ecosystem-human health index, combining biodiversity alteration, demographic and health and economic indicator patterns and how they change in response to different economic and social contexts. Some global indices have been proposed in the literature, such as a measure of global biodiversity intactness index by combining observational data regarding species richness and abundance, land use and land cover maps and human density maps (93), which should be properly assessed at the local and regional levels. Testing and validating or adapting these indices to local realities and devising new methodologies to adequately integrate them with health and economic dimensions is an urgent task. Understanding the role of biodiversity in regulating ecosystem services is paramount to reconstruct the barriers concerning the transfer of diseases from animals to humans in degraded environments (94). In this sense, it is crucial to consider the interdependence of ecosystem integrity and the strategies and policies deployed to develop local and regional economies. Land use and its impacts on Brazilian Amazon biodiversity will be determined by the outcome of the disputes among the different TTs present in the region. The local peoples resistance and resilient structures and production systems, although invisible by the conventional indicators, are an important part of the regional economy.

Health and well-being are not simply external environment outputs, but are strongly dependent on adaptation to local environments. Human culture, technology, genetics and physiology are aspects of this adaptation. While in the temperate zone many adaptations were required to avoid the cold and food scarcity during the winter, tropical forest dwellers evolved adaptations to support seasonal floods, heavy rains and rapid rotting. It is imperative that we abandon the notion of the forest as inhospitable for humans. What is inhospitable for one, is home for another. Solutions are local and diverse and must be acknowledged by adequate metrics. As an Amazonian poet once sang "*I don't want to be global, I want to be local*" (Eliakin Rufino).

DATA AVAILABILITY STATEMENT

Data is shared in the Zenodo repository. Access: DOI 10.5281/zenodo.5038657.

AUTHOR CONTRIBUTIONS

AD, AR, and ME organized the environmental dataset, while AD, RL, TN, and IR organized the epidemiological dataset. AM and DF organized the technological trajectories dataset. Maps were created by AD, AR, and IR. MB proposed the conceptual diagram. This synthesis resulted from a series of group discussions with all the authors. All authors contributed to the conception of the study and writing the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.647754/full#supplementary-material

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Integrating Health Systems and Science to Respond to COVID-19 in a Model District of Rural Madagascar

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There are many outstanding questions about how to control the global COVID-19 pandemic. The information void has been especially stark in the World Health Organization Africa Region, which has low per capita reported cases, low testing rates, low access to therapeutic drugs, and has the longest wait for vaccines. As with all disease, the central challenge in responding to COVID-19 is that it requires integrating complex health systems that incorporate prevention, testing, front line health care, and reliable data to inform policies and their implementation within a relevant timeframe. It requires that the population can rely on the health system, and decision-makers can rely on the data. To understand the process and challenges of such an integrated response in an under-resourced rural African setting, we present the COVID-19 strategy in Ifanadiana District, where a partnership between Malagasy Ministry of Public Health (MoPH) and non-governmental organizations integrates prevention, diagnosis, surveillance, and treatment, in the context of a model health system. These efforts touch every level of the health system in the district—community, primary care centers, hospital—including the establishment of the only RT-PCR lab for SARS-CoV-2 testing outside of the capital. Starting in March of 2021, a second wave of COVID-19 occurred in Madagascar, but there remain fewer cases in Ifanadiana than for many other diseases (e.g., malaria). At the Ifanadiana District Hospital, there have been two deaths that are officially attributed to COVID-19. Here, we describe the main components and challenges of this integrated response, the broad epidemiological contours of the epidemic, and how complex data sources can be developed to address many questions of COVID-19 science. Because of data limitations, it still remains unclear how this epidemic will affect rural areas of Madagascar and other developing countries where health system utilization is relatively low and there is limited capacity to diagnose and treat COVID-19 patients. Widespread population based seroprevalence studies are being implemented in Ifanadiana to inform the COVID-19 response strategy as health systems must simultaneously manage perennial and endemic disease threats.

Keywords: pandemic response, public health system, health system strengthening, data platform, COVID-19

INTRODUCTION

As of May 2021, COVID-19 has infected over 160 million people globally and killed more than 3 million, with the highest reported per capita tolls in Europe, North America, and South America in the first year, with the worst surge of the second year occurring in India (1). One of the great mysteries of the pandemic has been its relatively smaller impact on the World Health Organization (WHO) African Region, which endures high burdens of other infectious diseases, including respiratory infections, for reasons that are also relevant to COVID-19 epidemiology: crowding inside and outside of the home, inadequate water and sanitation infrastructure, and under-resourced health systems (2, 3). While Sub-Saharan Africa (SSA) is home to 16% of the world's population, its share of reported COVID-19 cases is 3% of the global case count, more than a year after the first COVID-19 cases were diagnosed in China (**Figure 1A**) (1). This could be explained by underlying differences in the effectiveness and timing of control measures, immunology, age distribution, contact structure, or low rates of testing and under-reporting (2, 3).

As the world works to roll out newly developed vaccines, the global health community and national governments lack data to guide action throughout most of Africa. This brings to the fore critical questions. Are vaccines especially needed in SSA because of high undetected burdens of COVID-19 that will go untreated? Or is COVID-19 less of a threat in SSA than in the rest of the world while the pandemic response disrupts delivery of health services for other diseases? The central challenge for answering this question is the same for global health equity in the management of most infectious diseases: to ensure that health systems integrate prevention, testing, and treatment of illness for everyone, with quality data that informs the response within a timeframe that matters. This is particularly challenging and important for remote communities, where the majority of the Madagascar population and most of Africa lives (4).

Here, we present the first year of a COVID-19 management and research strategy in the context of a model health district in Madagascar. Key features are the integration of programs across all levels of the local health system (community health, primary care health centers, district hospital), population based preventative efforts, and the array of testing and surveillance approaches necessary for responding to the complex situation. We share lessons learned, identify unresolved questions and show how such a platform can address such critical questions in an under-resourced rural African setting.

Madagascar is a large island nation across the Mozambique channel from mainland Africa, with a population of over 25 million. While its insularity confers advantages to controlling transmission across borders. Madagascar embodies much of the COVID-19 paradox of the rest of SSA: it is managing high burdens of other diseases, including the largest measles and plague epidemics of the past half century (5, 6), while reporting relatively low rates of COVID-19 infection per capita—ranked 27 out of 47 countries in the region (1) (**Figure 1A**). The first case was identified in the country's capital, Antananarivo, among travelers on 19 March 2020. Community spread was found a week later. Over the course of the first 4 months of the epidemic, cases were identified in localized clusters in three cities in three different regions: Antananarivo, in the central region of Analamanga; Toamasina, on the eastern coast in the region of Atsinanana, and Fianarantsoa, in the southern central region of Haute-Matsiatra. The disease then spread slowly throughout the country. By September 2020, all 22 regions of Madagascar reported active COVID-19 infections (ref). With low testing rates, the true dynamics of the disease are unknown, but there have been several efforts to model its spread based on available data (3, 7, 8). As of April 2021, Madagascar began experiencing a second documented wave of rising cases, which cumulatively total over 30,000 (∼1,000 cases per million population) and 520 deaths (18 deaths per million population) recorded in Madagascar (**Figures 1B,C**). Over 160,000 tests have been administered (∼6,000 per million population) with an

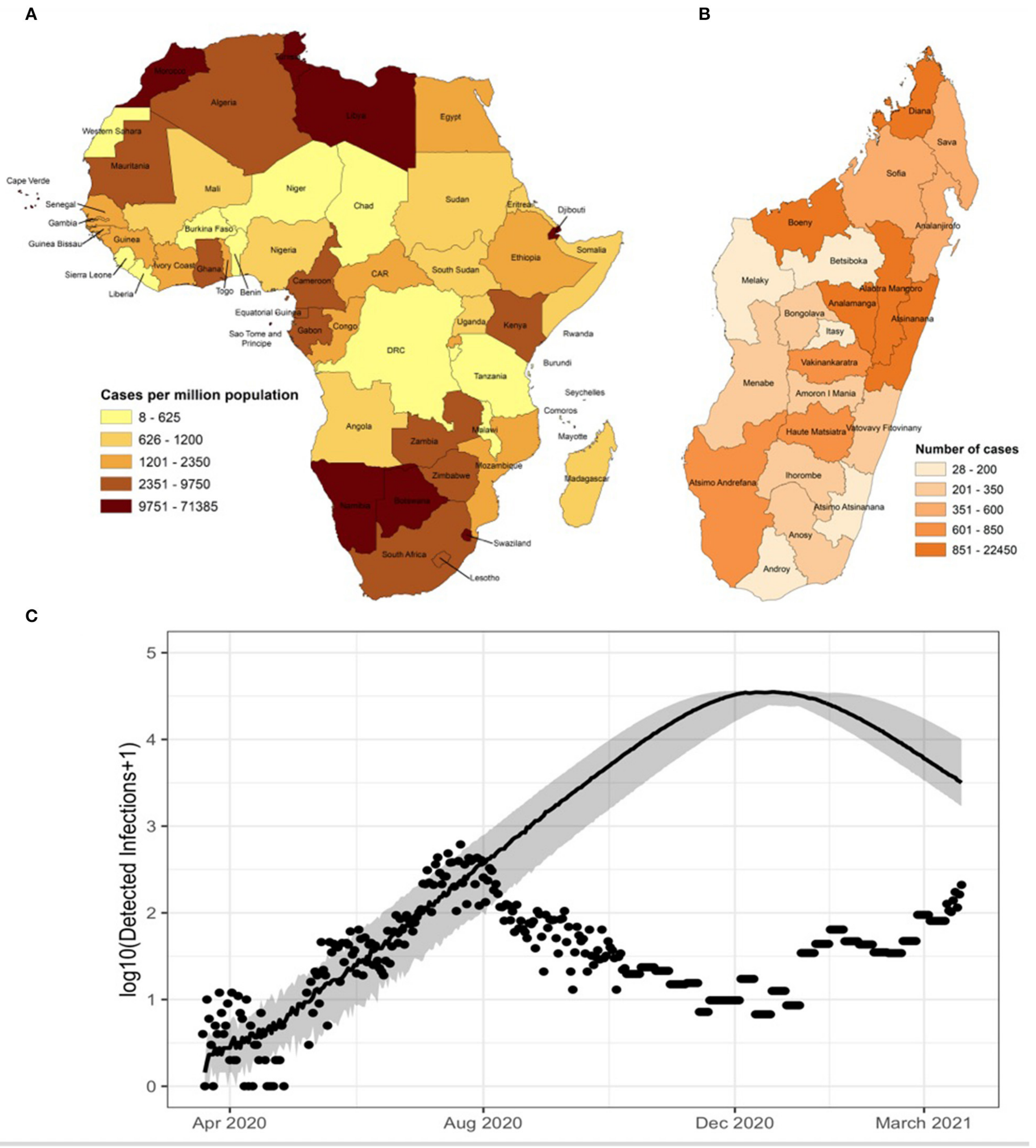


FIGURE 1 | (A) Cumulative total cases per million population for each country in the African continent as of April 21 2021 (1). **(B)** Cumulative total cases per region in Madagascar through April 21 2021 (1). **(C)** Updated estimate of COVID-19 dynamics (solid line) based on reported data and mathematical model for Madagascar shows that even conservative models predicted disease prevalence that is orders of magnitude greater than public case reports (dots) to date [for details on this model, see (3)].

average positivity rate of 18.75%. The crude case fatality rate of 1.7% is similar to global the average of 2.1%.

Strong health systems are essential for managing disease outbreaks, a lesson reaffirmed during the Haiti Cholera Outbreak in 2010 (9, 10), Ebola crisis in West Africa in 2014–2015 (11, 12), the Middle East Respiratory Syndrome experience in South Korea in 2015 (13, 14), as well as the COVID-19 pandemic in South Korea, Vietnam, Spain and Italy (15–19). To strengthen the

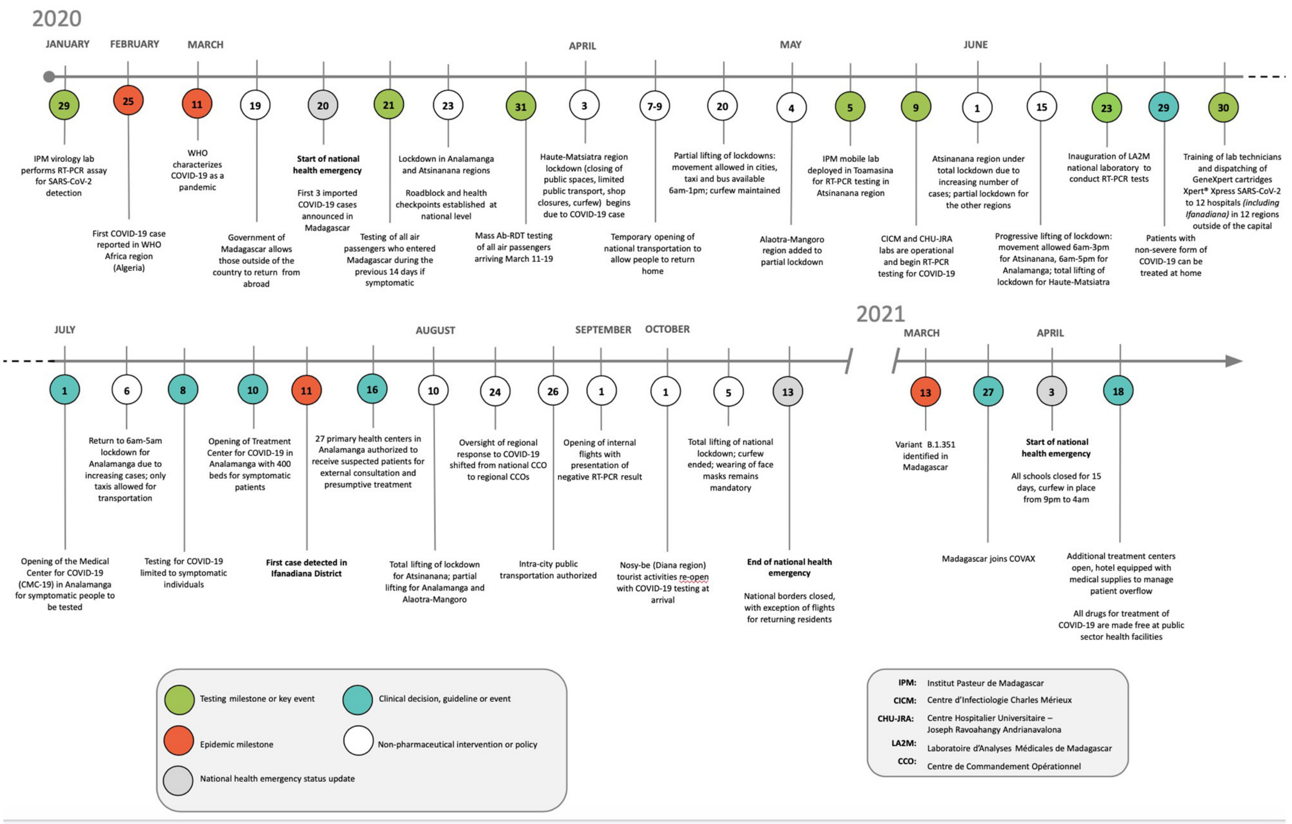


FIGURE 2 | Timeline of policies and interventions in response to COVID-19 in Madagascar.

local health system, the non-governmental organization, PIVOT, has partnered with the Government of Madagascar to establish a model system for universal health coverage (UHC) in Ifanadiana District (20). Ifanadiana is a rural district of ∼200,000 people in the Vatovavy-Fitovinany region in the southeast of Madagascar. This model has several pillars at all levels of the district health system (community health, primary care facilities, and the district hospital): improved system readiness (e.g., infrastructure, staffing, supplies, removal of financial barriers), clinical programs (e.g., infectious disease, maternal, and child health), and quality information systems. The result has been substantial increases in utilization rates of health facilities and community health, as well-progress in neonatal, infant and under-five mortality, and population-based improvements in the coverage of essential services such as antenatal care, delivery in health facilities, and vaccines. For more details on the MoPH-PIVOT model, history, and impact analyses, see (20, 21).

MADAGASCAR'S NATIONAL RESPONSE

The Government of Madagascar implemented non-pharmaceutical interventions (NPIs) nation-wide when the first cases of COVID-19 were detected (3). These included barrier measures (mandatory use of facemasks, hand-washing, and social distancing); bans on public gatherings; school closings; and lockdowns in major cities. The international airport was closed to commercial flights, beginning March 20 and continuing until the end of October 2020, and then closed again in April of 2021. Roadblocks were established on all national roads leaving the capital to prevent movement across regional boundaries and public transportation was suspended. NPI implementation and timing presented high variability for each region of the island based on case counts. By early September 2020, as reported cases dwindled and fears of an over-run health system diminished, many NPIs were lifted including restrictions on movement, though loosely enforced mask mandates remained in effect (**Figure 2**).

Testing is central to disease control, surveillance, and case management. Early in the epidemic, the Government of Madagascar focused testing on screening for possible imported cases. All passengers on international flights during the 2 weeks before the border closure were placed in quarantine for 14 days, after which they were tested for COVID-19. High priority was also placed on contact tracing for initial imported cases, as well as testing of patients with serious, unexplained respiratory illness. When COVID-19 was first introduced in Madagascar, there was one laboratory able to perform molecular testing for SARS-CoV-2. To meet the need for expanded testing, four molecular labs in the capital were made available for testing SARS-CoV-2 via

TABLE 1 | COVID-19 interventions across the levels of the health system in Ifanadiana District.

	Community	Health center	District hospital
Prevention	• Mask distribution • Door-to-door education campaign on COVID-19 risks and prevention • Community health posts equipped with buckets of water and soap to promote hand hygiene	• Pre-triage screening of all patients presenting for care • Construction of well-ventilated pre-triage areas • Video and education activities on COVID-19 risks and prevention	• Pre-triage screening of all patients presenting for care • Construction of well-ventilated pre-triage areas • Video and education activities on COVID-19 risks and prevention
Diagnosis	• Community health workers refer children under five diagnosed with fever or other COVID-19 symptom but negative malaria RDT to health center	• COVID-19 Ag-RDTs • Transfer of nasopharyngeal swab samples to district hospital or RT-PCR lab for NAAT	• COVID-19 Ag-RDTs • NAAT confirmation testing with Xpert or transfer of samples to RT-PCR lab
Treatment		• Symptom management • Isolation recommended for confirmed cases	• Symptom management • Confirmed cases with severe symptoms provided inpatient care on COVID-19 ward with enhanced ventilation and available oxygen • Isolation recommended for confirmed cases
Research activities		• Antibody serosurveillance in general patient population • Antigen and antibody testing of healthcare workers	• Antibody serosurveillance in general patient population • Antigen and antibody testing of healthcare workers

RT-PCR. These relied on the transport of nasopharyngeal swabs of suspected cases from health facilities around the country to Antananarivo. In addition, over time 12 district and regional hospitals that were already equipped with GeneXpert machines (routinely used for TB diagnosis) were supplied with specific SARS-CoV-2 cartridges in order to decentralize testing.

At the start of the epidemic, all Government of Madagascar COVID-19 response activities were managed by a national central-level Operations Coordinating Center (CCO in French). As the epidemic progressed, management authority shifted to regional CCOs. At the district level, a Vigilance Committee, including local authorities and partners, was established to manage COVID-19 response.

IFANADIANA DISTRICT RESPONSE

The first confirmed case of COVID-19 in Ifanadiana District was reported on July, 11 2020. As of May 2021, there have been 136 officially reported cases of COVID-19 in the district, including 12 severe cases and 2 official deaths. Administrative districts in Madagascar are similar to districts in much of Africa. As with many health districts in Africa, it has one district hospital. The district is divided into 15 communes (local administrative municipalities, each with at least one primary health center), which are further subdivided into fokontany—a cluster of villages, with a population of ∼300–4,400 individuals. Each fokontany has a community health site where community health workers provide treatment for sick children under-five, family planning counseling, and screening for tuberculosis (TB) and malnutrition in some locations.

As in other rural areas in the region, Ifanadiana District has limited water and sanitation infrastructure, necessary to reduce disease transmission. Approximately 15% of the population has access to clean water and <3% have access to a toilet or improved latrine (22). Under-five mortality, which is 89 per 1,000, is driven largely by malaria, diarrhea, and respiratory infections (19). The burden of TB in Madagascar (incidence of 233 per 100,000) is similar to many mainland African countries (23). The determinants of other infectious diseases, including the large and multigenerational structure of households (22, 24), are potential drivers of COVID-19 transmission in the community.

The response to COVID-19 in Ifanadiana District focused on: (1) preparing the community and delaying disease introduction; (2) bolstering the health system response through material support, direct clinical care, and support of patients; (3) expanding testing and lab capacity; and (4) information systems, surveillance, and modeling. Preparations were made at all levels of the health system (community, basic health center, and hospital) (**Table 1**).

Preparing the Community and Delaying Disease Introduction

District-wide COVID-19 preparedness activities began with multisectoral planning committees before the disease was first diagnosed in the district. Nationally and within Ifanadiana District, the initial government response focused on slowing the spread of COVID-19 throughout Madagascar by putting in place restrictions on movement and on screening travelers moving between towns and regions. The Government of Madagascar closed national roads to public transportation and established health checkpoints to screen for COVID-19 symptoms. Local partners, led by the gendarmerie (in charge of law enforcement), supported the health checkpoint established on National Road 25 (**Figure 3**); all passengers arriving by motor vehicle passed through this screening checkpoint before entering the district. From April 2 to August 9, all travelers along national road 25 were required to stop for a temperature check. Individuals with a temperature above 38°C (100.4°F) were questioned about their health status and their city of origin, in order to identify the risk of possible infection.

Several NPIs, including use of face masks, hand-washing, social distancing, and other barrier measures were implemented in the district to prevent and mitigate disease transmission. Community sensitization was carried out via radio and special informational programs broadcast by local radio stations, posters, and videos at primary care health centers and the district hospital. Additionally, sensitization campaigns were carried out in five communes via community education sessions and door-to-door visits by health promotion staff (**Figure 3**). Education sessions on COVID-19 prevention and detection of symptoms were conducted on market days and at schools. Approximately 40,000 facemasks were donated and distributed to the community.

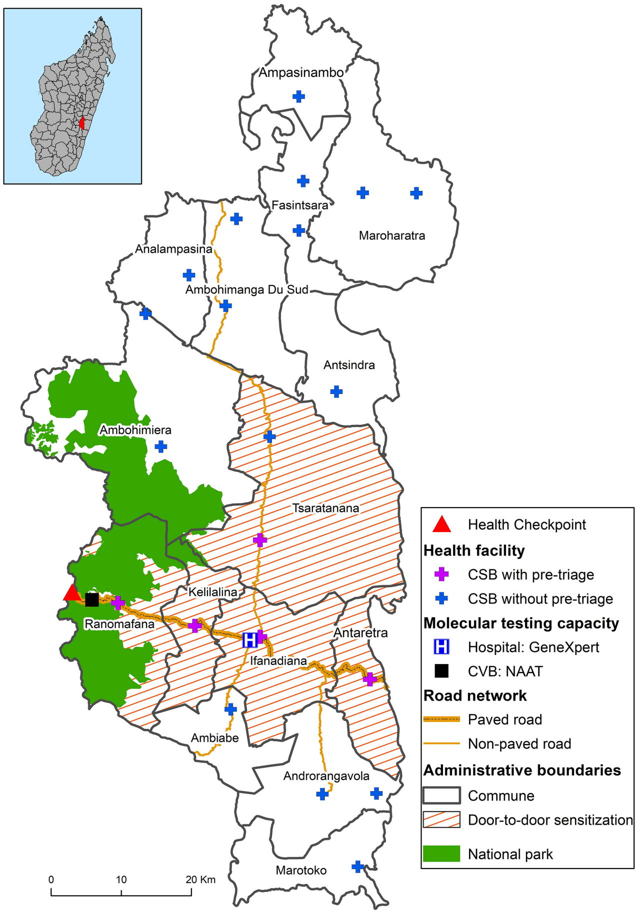


FIGURE 3 | Map of the COVID-19 response in Ifanadiana District with interventions, clinical care, testing capacity, and research activities across levels of the health system.

COVID-19 Clinical Care

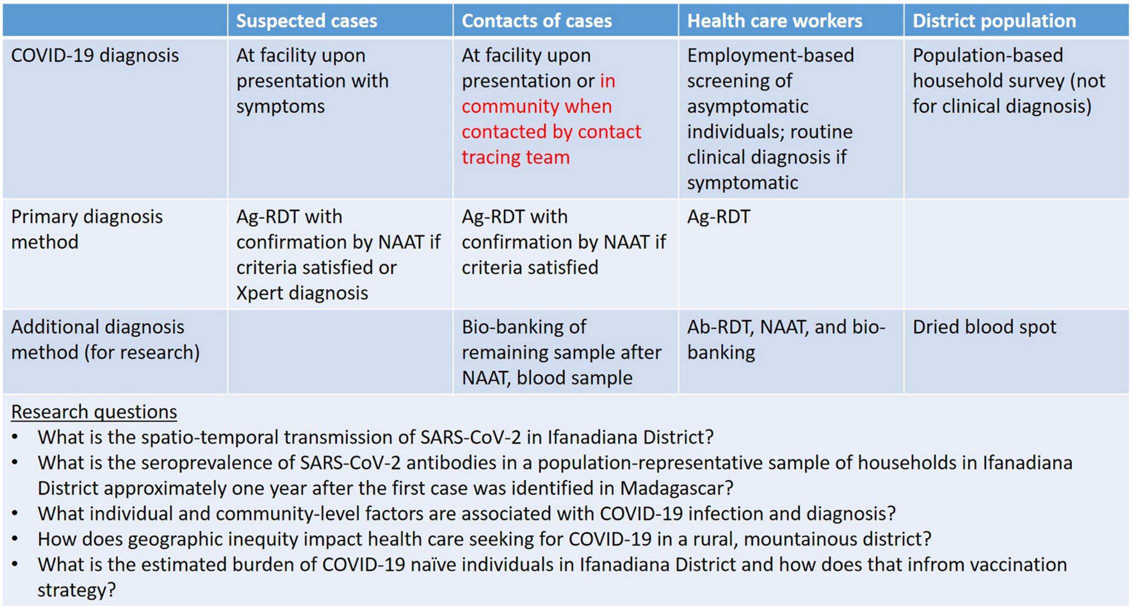
Comprehensive guidelines were developed for COVID-19 prevention, transmission, diagnosis, and management. The guidelines, available in French and English, were based on guidance from the WHO (25, 26), the US Centers for Disease Control and Prevention (27) and the international NGO, Partners In Health, and adapted for the local context of Ifanadiana District (16). They included basic information about the SARS-CoV-2 virus; reorganization of healthcare facilities for improved infection prevention and control; diagnostics and clinical care; data collection; and supply chain systems. Guidelines were made available to clinical staff at the district and national level. Prevention, diagnosis, and treatment measures were implemented across all levels of the health system.

At both health centers and the district hospital, pre-triage sites were established in well-ventilated spaces (such as gazebos) to screen for suspected COVID-19 cases and to prevent close congregation indoors. During pre-triage, each patient had their temperature taken and was asked about COVID-19 symptoms and about any potential recent exposures. Patients who screened negative for symptoms and exposure were directed to the service that they sought. Suspected cases and those who screened positive for COVID-19 exposure were directed to a specific area where a dedicated health care worker in personal protective equipment (PPE) evaluated them for COVID-19. If, after further evaluation, testing was deemed appropriate, a nasopharyngeal sample was collected for testing either by GeneXpert or rapid antigen test (Ag-RDT) (described below). Implementation of testing varied across the District with the majority of tests deployed at health facilities along the road. However, as of May, 2021, rapid antigen testing has been deployed to health facilities across the District.

Patients who tested positive for COVID-19 were advised to isolate. An isolation facility was set up away from the hospital grounds for people with mild COVID-19 who did not require hospitalization, but who could not safely isolate at home. Patients with severe symptoms were admitted for inpatient care at the district hospital. Patients with minor symptoms and asymptomatic cases were advised about disease progression, the need for isolation, and danger signs that would require a return to the health facility. Confirmed cases were provided with psychological support from PIVOT's social workers if they requested it.

Whenever possible, close contacts of confirmed cases were tested for COVID-19, instructed to quarantine, and followed for 14 days while monitoring for symptom development; contacts were tested if COVID-19 symptoms developed. To support individuals undergoing quarantine, food and toiletries were provided whenever possible.

The district hospital was reorganized to prepare for a surge of severely ill patients who might require isolation and/or oxygen. One section of the hospital—which had already been designated as an Infectious Disease Ward, and which is located away from the rest of the hospital wards and officers—was dedicated to receive severe COVID-19 patients and another tent-based structure nearby was prepared for patient overflow. Suspected cases were kept separate from confirmed cases. Procedures were put in place to minimize transmission from healthcare workers to patients: providers rounded on either COVID-19 patients or non-COVID patients, or saw patients without COVID-19 first, and then attended to patients with COVID-19 while in full PPE.



	Suspected cases	Contacts of cases	Health care workers	District population
COVID-19 diagnosis	At facility upon presentation with symptoms	At facility upon presentation or in community when contacted by contact tracing team	Employment-based screening of asymptomatic individuals; routine clinical diagnosis if symptomatic	Population-based household survey (not for clinical diagnosis)
Primary diagnosis method	Ag-RDT with confirmation by NAAT if criteria satisfied or Xpert diagnosis	Ag-RDT with confirmation by NAAT if criteria satisfied	Ag-RDT	
Additional diagnosis method (for research)		Bio-banking of remaining sample after NAAT, blood sample	Ab-RDT, NAAT, and bio-banking	Dried blood spot

Research questions

- What is the spatio-temporal transmission of SARS-CoV-2 in Ifanadiana District?
- What is the seroprevalence of SARS-CoV-2 antibodies in a population-representative sample of households in Ifanadiana District approximately one year after the first case was identified in Madagascar?
- What individual and community-level factors are associated with COVID-19 infection and diagnosis?
- How does geographic inequity impact health care seeking for COVID-19 in a rural, mountainous district?
- What is the estimated burden of COVID-19 naïve individuals in Ifanadiana District and how does that infrom vaccination strategy?

FIGURE 4 | Key populations for COVID-19 research activities and data collection to inform modeling.

Critical materials were obtained to meet the needs of patients with respiratory distress. These included additional oxygen concentrators, canisters, tubing, and masks, as well as pulse oximeters, blood pressure cuffs, vital sign monitors, ancillary medications (such as dexamethasone, and IV fluids. Plans were also made for possible delays in supply chain systems for critical items unrelated to COVID-19, such as malaria rapid diagnostic tests (RDTs) and medications. To reduce transmission by and to health care workers, PPE, including surgical masks, N95 masks, gloves, goggles, disposable gowns and foot-covers, were provided to the district health office, and then distributed to health facilities (19, 21, 22).

Increasing COVID-19 Testing Capacity in Ifanadiana District

One of the most fundamental steps to respond to COVID-19 is reliable testing data for patient diagnostics, planning, and research. The testing landscape is exceedingly complex and evolving in real time due to changes in technologies, their validation, clinical capacity and local and global supply chains. According to government policy, suspected cases are confirmed by a gold standard nucleic acid amplification test (NAAT)— RT-PCR or GeneXpert— to be included in the national COVID-19 statistics. Since the start of the pandemic, Madagascar has completed over 200,000 tests. There are four laboratories performing confirmation tests by RT-PCR, all of which are located in the capital city of Antananarivo.

Rapid technological advances led to several COVID-19 testing options, including the Xpert® Xpress SARS-CoV-2 cartridge, which relies on existing GeneXpert machines. This enabled rapid deployment of a test that can generate results within 45 min. As the disease spread to all 22 regions of the country, the Malagasy MoPH deployed thousands of Xpert® Xpress SARS-CoV-2 cartridges to twelve hospitals around Madagascar (including Ifanadiana District Hospital) that are equipped with this instrument in order to decentralize COVID-19 diagnostics. Under current national guidelines, diagnosis by GeneXpert is limited to suspected cases, although testing criteria continue to evolve. The MoPH defines suspected cases as (1) all people presenting with cough, sore throat, or dyspnea, with or without fever and having been in close contact with a confirmed case, (2) all people or clusters of people suffering for severe acute respiratory illness and having been in contact with a confirmed case. Though protocols were established by the MoPH for contact-tracing, they have not been implemented routinely throughout the country.

GeneXpert alone cannot adequately meet diagnostic demand in Madagascar due to insufficient availability of cartridges. In addition, there are limitations in the transportation of samples and communication of results. In order to improve COVID-19 diagnostic capacity, PIVOT and the MoPH implemented one of the only programs for COVID-19 antigen rapid diagnostic tests (Ag-RDTs) in the country, using the SD BIOSENSOR® STANDARD Q COVID-19. This point-of-care test can be administered provide results within 15 min, and does not require laboratory training for test administrators. It has good clinical performance, with sensitivity and specificity ranging from 58–89%, and from 92–99%, respectively (28–30); sensitivity is higher during the first 5 days after the symptom onset (28, 29). The Ag-RDTs were donated to the District Health Office, and distributed to various health centers and the district hospital (**Figure 3**).

In addition, the Ministry of Public Health, PIVOT, and Centre ValBio (CVB) partnered to increase RT-PCR capacity for COVID-19 NAAT outside of the capital. CVB is a conservation, education, and research organization located along the national highway near Ranomafana National Park in Ifanadiana District, with a biosafety level 2 laboratory. An RT-PCR machine was procured to allow for middle to high throughput molecular confirmation of COVID-19. The lab has been outfitted with needed equipment, reagents, and staff trained in accordance with MoPH protocols. The lab, launched in May 2021, following international procurement challenges, increases testing capacity not only for Ifanadiana District, but also for the region, extending access to vital diagnostic services for the rural population. It will also reduce the turnaround time for PCR test results, allowing for better management and mitigation of the spread of COVID-19.

COVID-19 Research Platform

What are the optimal strategies for COVID-19 control and how should that change over time? More than a year after the first reported case of COVID-19 in Wuhan, China, the answer to these questions remain unclear for many low and middle-income countries including Madagascar. Answers require accounting for epidemiological, molecular, and global health delivery considerations, and they vary across populations and social/political/epidemiological context. We highlight a few of the highest priority questions necessary to determine optimal control strategies (**Box 1**).

Since 2014, PIVOT and the MoPH have partnered to pioneer new ways of integrating field-based data analytics to improve health services. This combination of health systems and science presents unique opportunities for addressing the COVID-19 information crisis. For COVID-19, we collect data from a range of sources—no single one of which adequately captures the disease dynamics that are changing over space and time (**Figure 4**). Broadly, the main classes of quantitative data are from: (1) patients within the health system (e.g., health management information systems and patient diagnoses); (2) general population outside of the health system (e.g., household surveys that include biomarkers); and (3) the environment (e.g., environmental sampling and geographic information systems). These quantitative data are triangulated with other information sources: anecdotal reporting and programmatic updates from front line health workers, quantitative data on other indicators of the health system (availability of tests, health system utilization, geography, stock outs, and dynamics of other infections/health services), and analytical methods including mathematical modeling that are all material for assessing COVID-19 epidemiology. Such methods of combining complex data sources at different spatial and temporal scales for projecting dynamics of malaria ("nowcasting") have been recently employed for Ifanadiana District (31).

BOX 1 | Research questions.

Epidemiological

a) What is the burden of COVID-19 compared to other diseases and how is that changing over time?

b) What are the basic parameters of the disease: R_0, clearance, loss of immunity, fatality?

c) What are the primary risk factors for viral transmission, morbidity, and mortality?

Biological

a) What explains heterogeneity in immunological responses and clinical manifestations?

b) What is the duration of acquired immunity?

c) How does viral evolution affect transmission and disease, and how is fit influenced by acquired or vaccine-driven immune response?

Delivery/Implementation

a) What are the direct and indirect costs of various control measures?

b) What are their impacts on other dimensions of the health system?

c) Vaccines: for whom, where, which, how and how often?

Socio-economic

a) What individual and community-level factors are associated with infection and diagnosis?

b) How does geographic inequity impact health seeking for COVID-19 in a rural, mountainous district?

c) What is the impact of the disease on economic, social, emotional, and physical well-being?

One of the most important initiatives is a seroprevalence study, initiated in April 2021, which has been integrated into a pre-existing longitudinal cohort study designed to track general population health conditions (mortality rates, vaccine uptake, and access to care). The cohort consists of a representative sample of 1,600 households (∼9,000 people) in 80 geographic clusters across Ifanadiana District, for whom we currently have data from 2014, 2016, and 2018 (24). Questionnaires are based on the internationally-validated Demographic and Health Surveys, and include information on household composition, indicators of socio-economic status, recent illness for all household members, women's reproductive history, and mortality, as well as preventive and curative care seeking. The first three waves of the cohort study (2014–2018) included biometric measurements of all household members. In 2021, dried blood spot (DBS) tests were added to support a range of serological tests, including for SARS-COV-2 antibodies to be analyzed in partnership with the Pasteur Institute of Madagascar.

Point estimates of seroprevalence a year after introduction of the virus will provide a strong indication of the attack rate of COVID-19 in rural Madagascar. When combined with spatiotemporal data from patient diagnostics and mathematical modeling, this can be directly used for estimating effects of disease control strategies (i.e., vaccines) over time.

CONCLUSION

More than a year after the first case of COVID-19 was diagnosed in Wuhan, China, there remain enormous challenges for disease control globally, and unanswered questions that threaten strategies for prevention efforts, compromise strategic health system priority-setting, and undermine pandemic preparedness for the future. A unifying concept of global health is the "know-do gap"; known solutions are often not implemented because of break downs in the functioning of the health system itself. The system for responding to COVID-19 is the same as that for managing other diseases. It must be integrated, strong, and data-driven to be able to adapt dynamically to operational and epidemiological changes. But as a novel pathogen, COVID-19 also presents unique challenges due to acute information gaps that greatly confound disease control.

What explains the enormous heterogeneity in disease outcomes within countries and around the world? Biological factors, such as age and pre-existing conditions are clearly important, as are social determinants such as race and income. However, the impacts of COVID-19 on low-income countries, particularly those in the WHO African Region, are reportedly lower than high-income countries. This paradox suggests fundamentally different epidemiology, management, or rates of testing and reporting, with enormous implications for managing COVID-19 and preparing for future pandemics. To answer these questions, strong health systems are necessary, but not sufficient.

The need to strengthen health systems, generate reliable data, and make scientific advances to battle disease, are mutually reinforcing goals. In rural Ifanadiana District, COVID-19 management focused on integrated community preparedness, improvements to clinical infrastructure and processes, infection prevention, increased testing capacity, clinical care, and support for patients. These activities were designed to both ensure quality care for patients and reduce viral transmission. In responding to the pandemic, Madagascar drew from its experience with past national epidemics and from global recommendations for COVID-19 mitigation, which included early and widespread adoption of NPIs that were later relaxed before being enforced again during the second wave in March, April and May of 2021.

But there have also been many challenges to fully implement an emergency response, and to transition that response to a sustained level of vigilance. Due to a range of factors—including supply chain challenges, health system fatigue, economic constraints, sensitization and trust, and the complexity of evolving politics and policy—patients are still likely to be under-screened, under-tested, and cases are likely under-reported. Health workers, decision-makers, and communities, became fatigued from extensive and costly preparation for the early threat of the pandemic, leaving the health system exposed to the second major wave that started in March, 2021. PPE is under-resourced and health workers have become especially vulnerable in the second wave. The lack of adequate resources for isolation, accompaniment, and treatment of positive cases undermine incentives for logistically complicated screening and testing.

Our understanding of the effects of these efforts even on local areas like Ifanadiana District are not yet clear. Anecdotal evidence from front line health workers, combined with existing health system data, show high burdens of other infectious diseases such as malaria, pneumonia, and diarrheal disease, than of COVID-19. But suspected cases are not consistently tested. Two key sources of data continue to be critical moving forward: patient-based diagnostics and population-based serology. GeneXpert, RT-PCR, and validated Ag-RDTs are increasingly being relied on to ensure systems for tracking dynamics of disease but require sourcing that is reliable, protocols that are well-established and enforced, and patient buy-in. When complemented by seroprevalence studies on a representative sample of the population, our understanding of the current burden of disease will clarify quickly. Advances in modern serology and next generation sequencing, when combined with such integrated platforms, are within reach and could revolutionize disease surveillance to prevent the next pandemic and are within reach. Yet, there remains inadequate funding, forcing countries like Madagascar to face sharp tradeoffs for priority-setting for other diseases. International interest in transparent data and surveillance can conflict with domestic policy objectives and national sovereignty. Our platform shows the potential of having built-in epidemiological and health data systems, and that such efforts can be done in combination with government and non-governmental partnership, but these efforts also reveal complex challenges even in the best of circumstances.

As with Ebola, plague, measles, and other recent epidemics, COVID-19 has revealed fundamental weaknesses in existing health systems. The Malagasy public health system, like those throughout much of the world, can learn from the COVID-19 experience to be better prepared to confront future epidemics. We show how an integrated platform of strengthened health systems and research can be established in order to understand and control the pandemic.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: Data for Madagascar can be accessed through Madagascar Ministry of Public Health. Data were also obtained at: https://www.worldometers.info/coronavirus/.

AUTHOR CONTRIBUTIONS

The clinical intervention was designed by RR, HA, BRaz, ER-F, VR, FR, AT, LRah, LRak, JH, LC, GC, TL, MR, ARan, ER, GR, and AMa with laboratory and testing interventions designed by RR, LRah, LRak, LC, MK, PW, TG, MD, AMa, KF, and MB. HA, BRaz, ER-F, GR, JR, KF, and MB performed data collection and drafted the article. RR, HA, BRaz, ER-F, ME, FI, AG, AMa, KF, and MB conducted data analysis and interpretation. All authors contributed to the conception of the study initiative and critically reviewed the manuscript and approved the final version to be published.

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Optimal COVID-19 Vaccine Sharing Between Two Nations That Also Have Extensive Travel Exchanges

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Countries around the world have observed reduced infections from the SARS-CoV-2 virus, that causes COVID-19 illness, primarily due to non-pharmaceutical interventions (NPIs) such as lockdowns and social distancing measures designed to limit physical proximity between people. However, economies and societal interactions require restarting, and so lockdowns cannot continue indefinitely. Therefore, much hope is placed in using newly developed vaccines as a route back to normality, but this raises key questions about how they are shared. There are also emerging questions regarding travel. For instance, international business and trade necessitates at least some in-person exchanges, alongside restarting travel also for tourist purposes. By utilising a Susceptible-Infected-Recovered-Vaccinated (SIRV) mathematical model, we simulate the populations of two nations in parallel, where the first nation produces a vaccine and decides the extent to which it is shared with the second. Overlaying our mathematical structure is the virus-related effects of travel between the two nations. We find that even with extensive travel, nation one minimises its total number of deaths by simply retaining vaccines, aiming for full inoculation as fast as possible, suggesting that the risks posed by travel can be mitigated by rapidly vaccinating its own population. If instead we consider the total deaths i.e., sum of deaths of both nations, then such a policy of not sharing by nation one until full vaccination is highly sub-optimal. A policy of low initial sharing causes many more deaths in nation two than lives saved in nation one, raising important ethical issues. This imbalance in the health impact of vaccination provision must be considered as some countries begin to approach the point of extensive vaccination, while others lack the resources to do so.

Keywords: medical ethics, infectious travellers, disease transmission, epidemiology, SARS-CoV-2, COVID-19, vaccine, SIRV model

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1. INTRODUCTION

Through 2020, countries across the world have worked to diminish the impact of the SARS-CoV-2 virus and lower the related levels of COVID-19 illness (1). Initially, these control measures have included the implementation of non-pharmaceutical interventions (NPIs) to keep people apart, such as "social distancing" policies of limited socialising, or "lockdowns" whereby citizens are instructed to remain at home. Such measures have been found to be broadly successful (2). During the Northern Hemisphere Autumn period, there was a lifting of many aspects of lockdown across Europe, and societies were encouraged to reopen. Although some social distancing measures remained in place to lower transmission, in many instances the predicted possibility of additional waves of infection (3, 4) occurred. In addition, there is much confusion over whether it is safe to travel between nations, resulting in rapidly changing policies of country-specific travel restrictions because of concerns over importing infections. Yet in one of the first papers to consider this, Chinazzi et al. (5) find that restrictions on travel achieve only small reductions in infections without additional actions to limit transmission within countries. Travel remains essential in a world composed of tightly interwoven economies. Exchange visits remain important between nations that are trading partners, and hence restrictions are detrimental to business advancement. COVID-19, as expected, is proving especially harmful to businesses that support travel, whether for work or tourism purposes (6).

Toward the end of year 2020, multiple research centres performed advanced stage trials of potential COVID-19 vaccines [e.g., (7–9)]. In the United Kingdom for instance, approval has been given for the vaccines produced by Pfizer/BioNTech (10), AstraZeneca (11), and Moderna (12). However, vaccine availability also raises new questions. Should a country discover a safe vaccine, followed rapidly by mass production, a key question is how should it be distributed? A reasonable working assumption is that to reduce infections to levels that would promote herd immunity and fade-out of disease, a substantial fraction of inoculations will be given to citizens of the country that developed the vaccine. If during vaccine production and distribution, that country (nation "one") also implements measures to constrain infections while waiting for everyone to be vaccinated, then people travelling from another country (nation "two") may be a concern. Such concerns will be warranted if nation two places less emphasis on restricting the spread of COVID-19. Additionally, the infections of citizens of nation one are likely to increase as they visit nation two. Hence where extensive trade-related travel exchanges between nation one and nation two are critical, a fundamental question is whether it is prudent for nation one to share vaccines with nation two before nation one is fully vaccinated. A related question is whether more lives are saved overall (i.e., considering the combined effect on nation one and nation two) by the early sharing of vaccines. Here we use a mathematical representation of virus transmission, vaccine provision and sharing, and travel between two nations, to investigate these questions.

2. GOVERNING EQUATIONS

2.1. Infections, Deaths, Vaccinations, and Inter-Nation Exchange

Our aim is to provide a set of equations that are as simple as possible, yet retain sufficient complexity that they can describe three main effects of: (1) infection increases starting from low case numbers (e.g., after the lifting of lockdown measures), (2) travel between two nations and any related transfer of infections, and (3) the effects of different options for vaccine distribution. In our conceptual modelling framework, we consider two nations, "one" and "two" indexed by "1" and "2," respectively, and with populations N_1 and N_2 (people). Each nation has a virus transmission rate β (new infections per day caused by an infected individual in a completely susceptible population), and an infected case fatality rate α, which is a fraction of those currently infected. To account for travel between the two nations, variable f_2 is the fraction of the population of nation two visiting nation one at any given time. Similarly, for opposite travel, f_1 is the fraction of nation one visiting nation two. Variables f_1 and f_2 are considered invariant. The assumption is that the exchange of people between the two countries, characterised by f_1 and f_2, is continuous and so all people will be available in their own nation at some point to receive any vaccine. We list all model parameters in **Table 1**. The simulation framework has some similarities to modelling different communities within a single country and during lockdown, such as those who have essential roles and continued to work, vs. those isolating [e.g., (13)]. Here, we are concerned with continuous travel-based exchange between communities (i.e., two nations) and in parallel with vaccine introduction.

We utilise a form of bulk compartmental model to describe COVID-19 transmission. Such models have proven effective in modelling the spread of infectious disease for almost a century, since e.g., (14). Our first equation characterises the number of susceptibles, S (people) in nation one (S_1). The rate of change of S_1 in time t (specified as days since the start of vaccine production), is given by Equation (1), and has four terms on the right-hand side. The first describes the number of citizens of nation one who become infected while located in nation one, and this includes the impact of increased infection rates due to visitors from nation two (i.e., the $f_2 I_2$ term). These people leave the susceptibility group and enter the infectious group. The second term is those from nation one, but visiting nation two, and who become infected while overseas. The third is the re-entry of those who have recovered from the illness, characterised by rate of waning immunity, σ (day^{-1}), and where R (people) is the number who have recovered from COVID-19. A value of $\sigma = 0$ is valid if it is found that those who have recovered from the virus also have long-term complete immunity. We assume in our main calculations full immunity (i.e., $\sigma = 0$), although below in numerical results, we also perform a factorial simulation with a small value $\sigma > 0$, based on emerging literature. The last term is the impact of vaccination. Variable Q (vaccines day^{-1}) is the total number of vaccinations produced each day, available for use in either nation one, nation two, or sharing between the two countries. Available vaccines are assumed to be used immediately, and distributed according to the fraction of susceptible people and those who have recovered, R. Hence, despite strong immunity, we additionally assume that out of caution, the recovered group is offered and accepts vaccines. Critically, for the analysis here, quantity $\nu_1(t)$ is the fraction of vaccines retained for use by nation one, and that may vary in time. It is different time histories of this variable, $\nu_1(t)$, that we test for their impact in our simulation framework. These equation

TABLE 1 | Parameters and initial conditions used for our governing Equations (1)–(4) and (7)–(10), and in **Figure 1**.

Parameter symbol	Parameter name	Value	Units
β_1	Daily transmission rate, nation one	0.25	Day^{-1}
β_2	Daily transmission rate, nation two	0.25	Day^{-1}
f_1	Fraction of nation one visiting nation two	0.2	
f_2	Fraction of nation two visiting nation one	0.2	
γ	Recovery rate	0.2	Day^{-1}
σ	Rate of waning immunity (zero implies continued full immunity)	0.0	Day^{-1}
α	Infected case fatality rate	0.005	Day^{-1}
Q	Total vaccines produced per day	1×10^6	Vaccines day^{-1}
$V_1(0)$	Initial number of people vaccinated, nation one	0	People
$V_2(0)$	Initial number of people vaccinated, nation two	0	People
$S_1(0)$	Initial number of people susceptible, nation one	49×10^6	People
$S_2(0)$	Initial number of people susceptible, nation two	49×10^6	People
$I_1(0)$	Initial number of people infected, nation one	0.2×10^6	People
$I_2(0)$	Initial number of people infected, nation two	0.2×10^6	People
$R_1(0)$	Initial number of people recovered, nation one	0.8×10^6	People
$R_2(0)$	Initial number of people recovered, nation two	0.8×10^6	People

*Perturbations to these parameters are that $f_1 = f_2 = 0.05$ is tested and presented as a sensitivity analysis to less travel in **Figure 2**. Then in **Figures 3B,D**, we set $\beta_2 = 0.5$ as a sensitivity estimate of nation two having a far higher transmission rate. Further perturbations are made in **Supplementary Figures 1–6**.*

terms combine, respectively, to give for nation one:

$$\begin{aligned}\frac{\mathrm{d}S_1}{\mathrm{d}t} &= -\beta_1 \frac{(1-f_1)S_1}{(1-f_1)N_1 + f_2N_2}\left[(1-f_1)I_1 + f_2I_2\right] \\ &\quad -\beta_2 \frac{f_1S_1}{f_1N_1 + (1-f_2)N_2}\left[(1-f_2)I_2 + f_1I_1\right] \\ &\quad +\sigma R_1 - \nu_1 Q \frac{S_1}{S_1 + R_1}. \qquad (1)\end{aligned}$$

As susceptible people are infected, they move to the infected group, I (people). People leave the infected group by recovery as described by a rate γ (day^{-1}), or by dying and corresponding to a mortality rate α (day^{-1}). Hence, for nation one, these changes to infections (I_1) are given by:

$$\begin{aligned}\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta_1 \frac{(1-f_1)S_1}{(1-f_1)N_1 + f_2N_2}\left[(1-f_1)I_1 + f_2I_2\right] \\ &\quad +\beta_2 \frac{f_1S_1}{f_1N_1 + (1-f_2)N_2}\left[(1-f_2)I_2 + f_1I_1\right] \\ &\quad -\gamma I_1 - \alpha I_1. \qquad (2)\end{aligned}$$

The inverse of γ is the period, in days, that a person is infectious. From the value presented in **Table 1**, this gives a period of 5 days (15). Others suggest longer infection periods of a median of 8 days (16), or a range of 7–14 days (17). Very early during the emergence of the COVID-19 illness, it was realised that approximately one third of infected people show no signs of illness (18) yet these people can still infect others (19). Such asymptomatic individuals are included in our I_1 and I_2 groups, and so these quantities are not simply people who are unwell.

The recovery group, R, increases in size based on those who were previously infected and survive. People return to the susceptible group if there is no lifelong immunity effects or that immunity is time-limited, as characterised by parameter σ. People also leave the recovered group if vaccinated. For nation one, the number of recovered individuals (R_1) is:

$$\frac{\mathrm{d}R_1}{\mathrm{d}t} = \gamma I_1 - \sigma R_1 - \nu_1 Q \frac{R_1}{S_1 + R_1}. \qquad (3)$$

Again, it is the last term on the right-hand side of Equation (3) that captures the assumption noted above, that even when full immunity is assumed (i.e., $\sigma = 0$), a cautious approach is taken of vaccinating those who have recovered. Finally, the group of people vaccinated, V, for the first nation (V_1) satisfies:

$$\frac{\mathrm{d}V_1}{\mathrm{d}t} = \nu_1 Q. \qquad (4)$$

In the set of governing equations for nation one, we assume that all people are in one group: S, I, R, or V, and so:

$$N_1 = S_1 + I_1 + R_1 + V_1. \qquad (5)$$

In Equations (1)–(4), there is a final implicit assumption that births and non-COVID-19 deaths balance. Hence these equations, when combined additively, give $\mathrm{d}N_1/\mathrm{d}t = -\alpha I_1$, which is the excess death rate due to COVID-19 illness. The total number to have died from COVID-19, D (people), in nation one and after time t is, therefore:

$$D_1(t) = \int_0^t \alpha I_1(t')\mathrm{d}t'. \qquad (6)$$

For the second nation, then the governing equations are very similar to those of Equations (1)–(4); the indices are swapped, and the fraction of vaccines ν_1 is now replaced by $1 - \nu_1$. For completeness, we write these equations out below:

$$\begin{aligned}
\frac{\mathrm{d}S_2}{\mathrm{d}t} &= -\beta_2 \frac{(1-f_2)S_2}{(1-f_2)N_2 + f_1 N_1}\left[(1-f_2)I_2 + f_1 I_1\right] \\
&\quad -\beta_1 \frac{f_2 S_2}{f_2 N_2 + (1-f_1)N_1}\left[(1-f_1)I_1 + f_2 I_2\right] \\
&\quad +\sigma R_2 - (1-\nu_1)Q\frac{S_2}{S_2+R_2} \qquad (7) \\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= \beta_2 \frac{(1-f_2)S_2}{(1-f_2)N_2 + f_1 N_1}\left[(1-f_2)I_2 + f_1 I_1\right] \\
&\quad +\beta_1 \frac{f_2 S_2}{f_2 N_2 + (1-f_1)N_1}\left[(1-f_1)I_1 + f_2 I_2\right] \\
&\quad -\gamma I_2 - \alpha I_2. \qquad (8) \\
\frac{\mathrm{d}R_2}{\mathrm{d}t} &= \gamma I_2 - \sigma R_2 - (1-\nu_1)Q\frac{R_2}{S_2+R_2}. \qquad (9) \\
\frac{\mathrm{d}V_2}{\mathrm{d}t} &= (1-\nu_1)Q. \qquad (10)
\end{aligned}$$

and with:

$$N_2 = S_2 + I_2 + R_2 + V_2. \qquad (11)$$

There is substantial flexibility in the selection of parameters in our model. Here we restrict the degrees of freedom by holding most parameters fixed, and as given in **Table 1**. These values correspond to similarities in the size of the two nations, relatively low initial infection rates, and similar death rates. For the analysis presented here, we primarily focus on the effects of changing the extent of travel, by altering f_1 and f_2, alternative transmission rates β_1 and β_2, and importantly the impacts of different time-evolving policies for vaccine sharing, as defined by $\nu_1(t)$.

2.2. Provision of Vaccines and Their Sharing

We assume that at time $t = 0$ a vaccine becomes available, and a capability exists in nation one to mass produce it from then onwards. The production rate for $t \geq 0$ is Q (vaccines day^{-1}). The first nation then has a choice, which might evolve in time, as to the fraction $\nu_1(t)$ of vaccines to keep for its own country rather than offering to the second country. The total number vaccinated at time t is a simple integration in time of Equations (4) and (10):

$$V_1(t) = \int_0^t \nu_1(t')Q\mathrm{d}t' \qquad V_2(t) = \int_0^t \left[1 - \nu_1(t')\right]Q\mathrm{d}t'. \qquad (12)$$

Reaching a time when $V_1 = N_1$ causes $\nu_1 \equiv 0$ for all times after. This situation is where nation one becomes fully vaccinated, and all vaccines are made available for nation two thereafter. Similarly, if $V_2 = N_2$, then $\nu_1 \equiv 1$ for times after. At time $t = \tau$ (days), then everyone is vaccinated in both nations, i.e., the first time when both $V_1 = N_1$ and $V_2 = N_2$. At $t = \tau$ we stop the simulations and total deaths in nation one, $D_1(\tau)$, is noted. For the values of **Table 1**, then $\tau \sim 100$ days.

Many strategies can be envisaged for vaccine provision, and here we initially search for those that minimise the total number of COVID-19 related deaths for the first nation. That is we look for vaccine sharing pathways, $\nu_1(t)$, that satisfy or get near to satisfying, the condition:

$$\min D_1(\tau). \qquad (13)$$

Two approaches to searching for optimum solutions are possible. The first is noting that the solution of Equations (1)–(4) and (7)–(10) and discovery of the path $\nu_1(t)$ that satisfies Equation (13) is a formal problem in optimal control. This requires derivation of the adjoint to the governing equations, following the optimisation approach of Pontryagin's Maximum Principle (20), and subsequent calculation of solution for $\nu_1(t)$, while also satisfying any constraints. Such constraints include that $0 \leq \nu_1(t) \leq 1$, along with further constraints that ensure physical realism e.g., that all S, I, R, and V values are positive, and $V \leq N$. The second approach is to instead iterate over possible pathways in $\nu_1(t)$, subject to the same constraints, and determine for each the $D_1(\tau)$ value. This latter approach is far less elegant, and cannot guarantee an overall minimum solution is found. However, there are some advantages. The iterative approach may bring more intuition as to which solutions are particularly sub-optimal, and is easier to implement when there is a necessity of speed in understanding a research problem of concern. Furthermore, a single minimum solution does not necessarily represent an enactable strategy, and of more practical use can be an understanding of the potential outcomes of a range of vaccination strategies. We adopt the second numerical approach, and in particular consider changes to ν_1 at discrete intervals, which may reflect how policy is enforced.

3. NUMERICAL RESULTS

3.1. Effect of Delay Before Vaccine Sharing

We start by considering a policy where nation one retains all vaccines until a threshold, X (%) of its population are vaccinated. At that stage, all further vaccines are given to nation two until they too have X% of their population inoculated. Following this, all vaccines are used again in nation one until everyone is vaccinated, after which all further vaccines are given to nation two. We present numerical calculations for $X = 20\%$ in **Figure 1**. In **Figure 1**, the left-hand side panels are time-evolving quantities for nation one, and the right-hand side for nation two. The top row shows this policy choice regarding vaccine sharing (i.e., $X = 20\%$), and the second row is cumulative deaths. This policy results in $\sim$25% fewer deaths in the first nation (annotations in second row in **Figure 1**) as calculated at $t = \tau$ when both nations are fully vaccinated. In the next four rows, left column are the solutions to Equations (1)–(4), and right column to Equations (7)–(10). In many circumstances, it is the projected number of infected people (row four of **Figure 1**) that is of most interest to health planners, who need to know if the number of severely ill people may exceed hospital or intensive care unit capacity. The setting of $f_1 = f_2 = 0.2$ (**Table 1**) corresponds to extensive inter-nation levels of travel, and this large value is taken to provide an outer bound in our analysis. Some travel exchanges have historically been especially large, including for

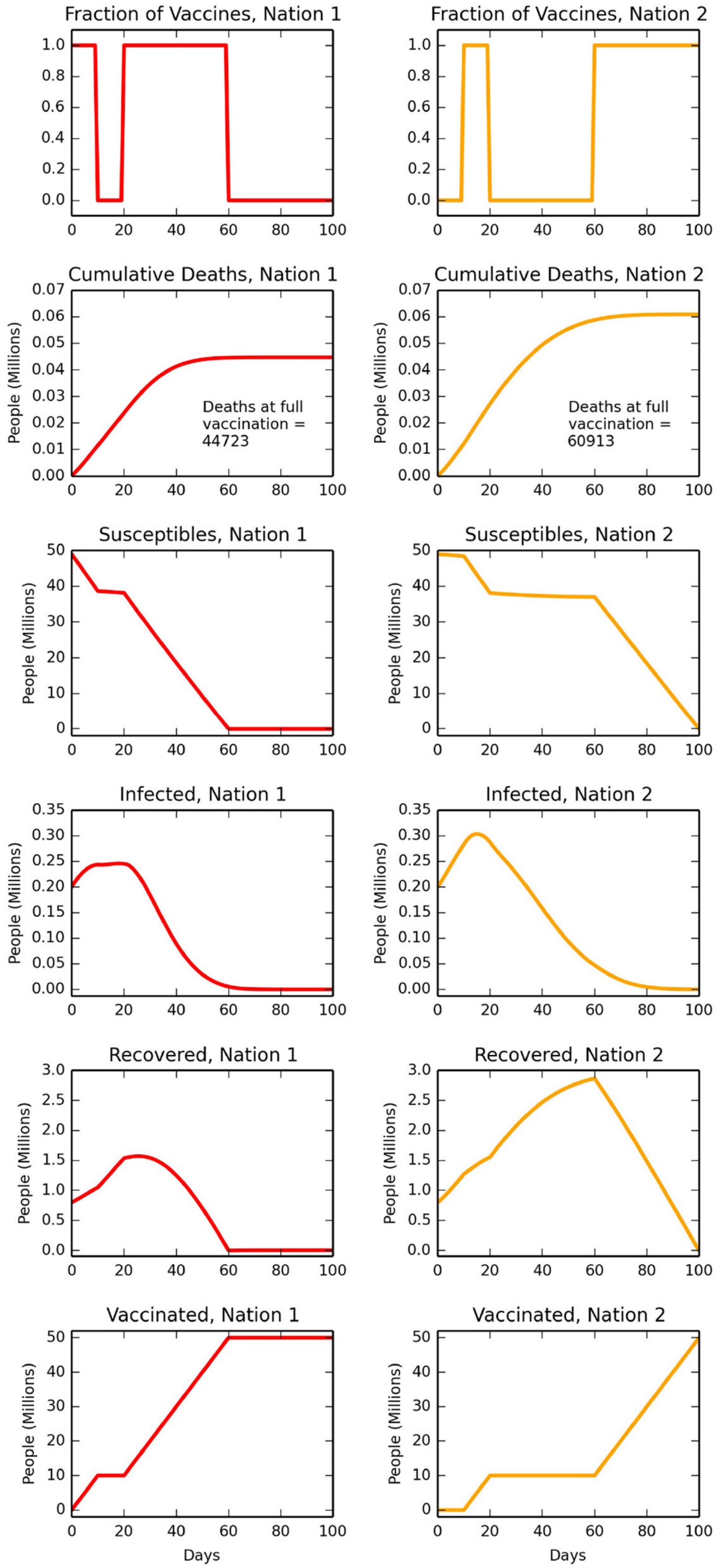

FIGURE 1 | Calculations with parameters and initial conditions as given in **Table 1**, and including for extensive travel with $f_1 = f_2 = 0.2$. The left-hand column are time-evolving projections for nation one and that has developed the vaccine, and right-hand column are for nation two. After 20% of the population of nation one

(Continued)

FIGURE 1 | are vaccinated, the vaccine is instead used exclusively in nation two. In nation two, 20% of that population is then vaccinated, before returning to fully vaccinate nation one, and then on to fully vaccinate nation two. The top row presents these vaccine sharing decisions, of ν_1 and $1 - \nu_1$. For this scenario, the second row is cumulative deaths (D_1 and D_2), and with annotations of final death count when both countries are fully vaccinated. The next rows are, respectively, the numbers of people susceptible to COVID-19 (S_1 and S_2), infected (I_1 and I_2), recovered (R_1 and R_2) and vaccinated (V_1 and V_2). For each row, the vertical scales are identical to allow comparison between nation one and nation two.

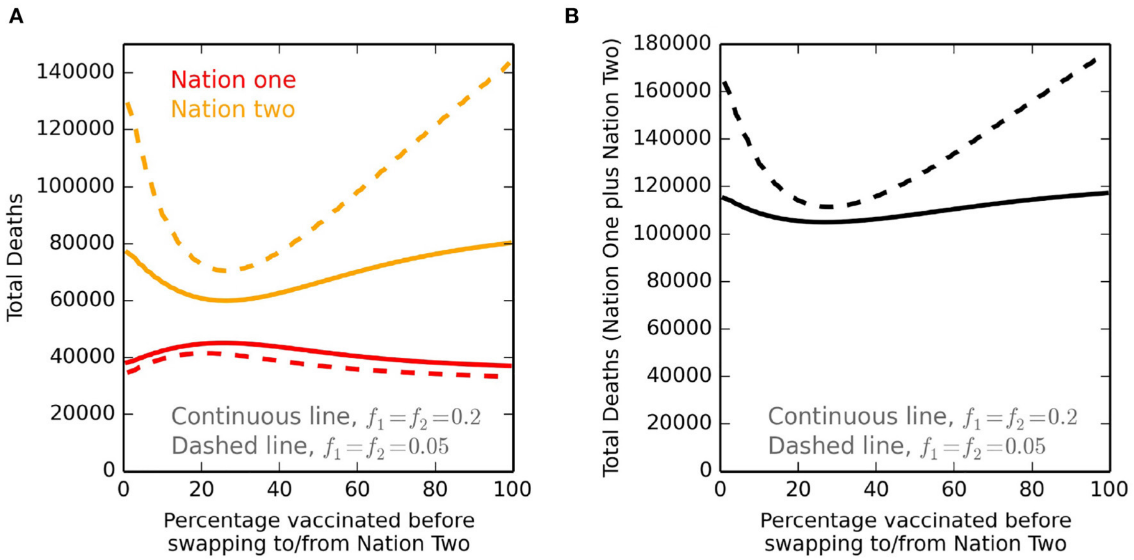

FIGURE 2 | Deaths for different X values defining vaccine sharing. **(A)** Total deaths for nation one (red) and nation two (orange), at the time of full vaccination of both nations. The vaccine sharing policy is the same as that presented in **Figure 1**, except that here the percentage of nation one vaccinated before sharing, X, is tested across all percentage values. Hence, for extensive travel exchange with $f_1 = f_2 = 0.2$ and with $X = 20\%$, the values shown are identical to the annotated total deaths in the second row of **Figure 1**. The continuous lines are for $f_1 = f_2 = 0.2$, and the dashed lines are for less travel exchange with $f_1 = f_2 = 0.05$. All other parameters are as given in **Table 1**. **(B)** Shows the total deaths, and so is the addition of the nation one and nation two deaths of **(A)**.

instance, tourists to key European countries in summer months, although these will be from multiple other nations.

We repeat the calculations in **Figure 1**, for all vaccine threshold X values, and calculate total deaths in nation one and nation two (**Figure 2**). COVID-19 related deaths, marked as annotations in the second row of **Figure 1**, are identical to those at $X = 20\%$ (**Figure 2**; continuous lines). Deaths for lower travel between countries, with $f_1 = f_2 = 0.05$, are also calculated (**Figure 2**; dashed lines). The curve minimums for nation two (**Figure 2A**) are a consequence of our sharing framework. For low X values, although nation two receives vaccines quickly after X% of nation one are inoculated, this only then vaccinates a small percentage X of nation two, before nation one continues its immunisation programme. High X values cause a substantial time to pass before nation two can start a vaccination programme. Both approaches cause higher deaths compared to the minimum for nation two. For nation one, there is relatively little variation in total deaths, irrespective of the choice of the X value. Total deaths in the donor country (nation one) are lowest when the country does not share vaccines ($X = 0\%$ and $X = 100\%$), and peak when the switch of vaccine from donor to recipient country occurs after ∼22% of the donor population is vaccinated. Lower travel exchanges (i.e., $f_1 = f_2 = 0.05$) have a protective influence on nation one, due to fewer imported infections as well as fewer infections by citizens of nation one when overseas. The effect is the opposite for nation two, as the lower amount of travel means a smaller exchange of more infected people from that nation are replaced with those from nation one who are less infected. In addition, lower exchanges from nation two to nation one, which has fewer infections, provides less protection as a smaller number of nation two susceptible people have travelled. Critically, for both sets of f values, is that the minimum deaths for nation one correspond to no initial sharing (i.e., at $X = 100\%$). Hence for our parameter values, gains by vaccinating people in nation two to lower imported infections are outweighed by no initial sharing, and thus vaccinating all of nation one as fast as possible. The sharing policy by nation one has a much larger impact on deaths in nation two, raising an important ethical issue. If nation one only shares vaccines after all its own citizens have first received it (i.e., $X \rightarrow 100\%$), then nation two has an especially high total number of deaths.

A particular interpretation of the minimum of nation two deaths (**Figure 2A**) is as follows. For the parameter values reported in **Table 1**, the basic reproduction number is $R_0 = \beta/\gamma = 1.25$. A very early assessment of the COVID-19 basic reproduction number (21) suggests it to have a much higher value, citing a range of 2.24–3.58, and so implicit in our transmission values is that they are for a later period with social distancing measures in place. Our value of 1.25 suggests that if more than 20% of the population of nation two are vaccinated (achieved in the first phase of vaccine policy if $X > 10\%$), then this would make the effective reproduction number, R (22), fall below unity. After this, besides the beneficial effects of vaccination, infection numbers would also fall by their own accord achieving what is sometimes referred to as "herd immunity." Although our sharing scenario is slightly contrived (e.g., top row of **Figure 1**), for the values presented in **Table 1**, the minimum for nation two deaths in **Figure 2** implies two key features. Giving away enough vaccines such that it allows a nation to have an effective reproduction number substantially below unity will save many lives. However, giving away many more vaccines, but waiting a longer period beforehand will result in more deaths for nation two. For both f values (0.2 and 0.05), we show the combined number of deaths for nation one and nation two together (**Figure 2B**). The minimum number of overall deaths is with an X sharing threshold of order 20–25%.

3.2. Additional Sensitivity Calculations

Reinfection remains a major uncertainty for the COVID-19 illness (23). Hence, as a factorial experiment, we consider potential non-zero values for immunity waning, σ, after illness. Seow et al. (24) report that acute immunity wanes as expected, but longer immunity from immunoglobulin antobodies can last beyond 94 days. Meanwhile, Dan et al. (25) find that the percentage of subjects seropositive for spike immunoglobulin, at 6–8 months post onset of symptoms, was 90%. For our period of 100 days of simulation, this may be a loss of around 5%, which can be approximated as $\sigma = 0.0005$. We repeat the calculations leading to **Figure 2**, but with this new non-zero value of σ (**Supplementary Figure 1**). As might be expected, with this relatively low reported loss of immunity, deaths (**Supplementary Figure 1**) are almost indistinguishable from those for complete immunity (**Figure 2**).

An additional extension of our analysis is to account for vaccines that do not have 100% efficacy. If $0 \leq e \leq 1$ is efficacy, with for instance a value of $e = 0.8$ corresponding to 80% effectiveness, then an easy amendment to our model is to replace every term Q in all equations with eQ. This very simplistic characterisation of efficacy would mean that V remains the number of vaccinated people, but it only now includes those with full protection. Hence for $e < 1$, the infected, susceptible and recovered groups would be larger compared to if $e = 1$. This alteration is valid where the aim of the model structure is to provide a basic estimate of the number of COVID-19 related deaths. However, in more complex model structures, for instance accounting for different less restricted behaviour by people who are vaccinated, then it may require an additional distinct group for those who have received a vaccine but remain susceptible. As a sensitivity study, we perform the simulations presented in **Figure 2** but with Q replaced by eQ and with $e = 0.8$ (**Supplementary Figure 2**). We find that the main features of **Supplementary Figure 2** are similar to those of **Figure 2**, but the number of deaths for nations one and two, for each X value, are much higher. Our elementary description of efficacy implies that a fraction e of those receiving a vaccine cannot be infected. However, reported vaccine efficacies may involve a more subtle definition. In particular a vaccine may be regarded as effective for a fraction e of those inoculated if many in that fraction still get infected but the implications are avoidance of serious illness or death. To model this requires a more complex framework with, for instance, an additional infected group of people who have been vaccinated I_v, but for whom the fatality rate α_v (day^{-1}) is much smaller than the non-vaccinated value α. Models are emerging that sub-compartmentalise the group infected by COVID19 [e.g., (26)]. An early assessment of the Oxford AstraZeneca vaccine suggests it to be 70% effective (27) and the Pfizer vaccine is reported as being 95% effective (28).

Waning of vaccine immunity can also be accounted for as a further extension of our analysis. In the analysis of vaccine efficacy, characterised by parameter e, this corresponds to a fraction, $(1 - e)$, of people for whom the vaccine does not work from the outset, but all others receiving it have permanent immunity. To instead model decreasing vaccine immunity, we introduce a daily fraction of those who have received a vaccine, but lose immunity, defined by parameter σ_V (day^{-1}). We modify the nation one vaccine group to account for the lowering of immunity, by adding an extra loss term of $-\sigma_V V_1$ to the right hand side of Equation (4). A balancing gain term of $+\sigma_V V_1$ is added to the susceptible group S_1, given by Equation (1). Similar changes can be made to the nation two equations for V_2 and S_2. We again repeat the format of the calculations leading to **Figure 2**, but now including this effect in both nations. Here we imagine the pessimistic scenario whereby new variants cause vaccine immunity loss over a period of 6 months, suggesting σ_V of order 1/180. Hence we set $\sigma_V = 0.005$ (but $e = 1$), and as expected, this results in more deaths (up to 20,000) based on our parameters (**Supplementary Figure 3**). Our vaccine rate Q and population sizes are such that by day 100, everyone will have received a vaccine. In the circumstances of complete vaccine efficacy ($e = 1$) and permanent immunity ($\sigma_V = 0$), then deaths after our modelled day 100 will be low. However, with low efficacy or loss of immunity, and in the absence of emerging and more effective vaccines, then death rates will remain high after day 100, adding to the totals shown in our diagrams. If the strength of waning immunity is similar for both vaccinated people, and for those in the recovered group after having been ill with COVID-19, then we simulate this with non-zero values for both σ and σ_v. Simulations in **Supplementary Figure 4** are identical to those of **Supplementary Figure 3**, except that now σ is also non-zero, and with $\sigma = \sigma_v = 0.005$. As expected, this creates a further rise in the number of projected deaths. However, this additional increase through both effects, compared to only σ_v set as non-zero (**Supplementary Figure 4** vs. **Supplementary Figure 3**), is less than that from introducing the waning vaccine immunity effect only (**Supplementary Figure 3** vs. **Supplementary Figure 2**).

We also consider the impact of initial conditions, and in particular if one nation has substantially more infections at the start of vaccine program. Different infection levels will relate to the previous history of lockdown and social distancing measures

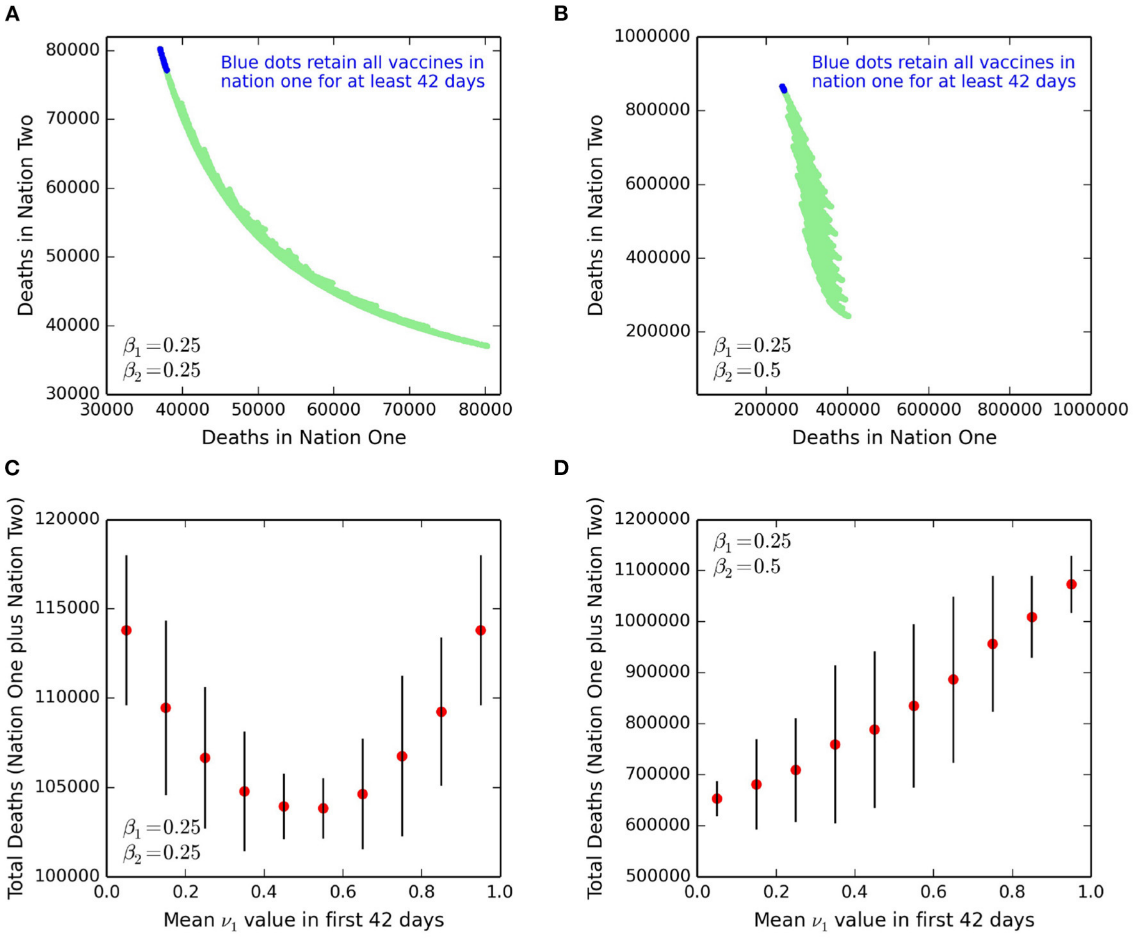

FIGURE 3 | Total deaths in both nation one and nation two at the time of complete vaccination of both nations. Each point in the top row corresponds to a single set of fortnightly policy decisions on vaccine sharing. **(A)** For parameter values and initial conditions presented in **Table 1**. **(B)** Asymmetric case where virus transmission is more prevalent in nation two, and so with $\beta_2 = 0.5$. In **(B)**, both axes are scaled identically to highlight the different death rates. The blue dots are where nation one retains all vaccines (i.e., $\nu_1 \equiv 1$) for at least the first three fortnightly periods. In **(C)**, we return to the same parameters and simulations shown in **(A)**, but now show the total deaths (those of nation one plus nation two), and disaggregated by the mean value of vaccine sharing, ν_1 in the first 42 days. The red dots are the mean values for each "bin" of size 0.1 for ν_1, and the vertical lines are ± two standard deviations. **(D)** Identical to **(C)**, except for the parameter values of **(B)** i.e., with high virus transmission in nation two.

within nations. The number of infections at any given time will also depend on the previous timecourse of the index cases, which are the initial people who introduce the virus to a nation (sometimes called "patients zero"). We instead first set nation one to have $I_1(0) = 0.5 \times 10^6$ initial infections, rather than the lower value of **Table 1**, and also lower $S_1(0)$ by 0.3×10^6 accordingly. We repeat the calculations leading to **Figure 2**, but with the new initial condition (**Supplementary Figure 5**). Again, the salient features of **Figure 2** are retained, but of note is that in particular for high exchanges $f_1 = f_2 = 0.2$, deaths in nation two are much higher, emphasising the effect of exported infections from nation one. We similarly adjust initial infections in nation two, by increasing it to $I_2(0) = 0.5 \times 10^6$ but keeping all other parameters as for **Table 1**. For high exchanges of people ($f_1 = f_2 = 0.2$), now deaths in nation one increase by a large amount due to imported infections through travel (**Supplementary Figure 6**).

The finding that to minimise overall deaths requires early vaccine sharing by nation one (minimum of curves in **Figure 2B**) remains valid in our sensitivity studies (**Supplementary Figures 1B–6B**).

3.3. A Broad Range of Vaccine Sharing Policy Options

In a next set of simulations (**Figure 3**), we scan a much larger range of possible approaches to vaccine sharing. We assume a policy decision is made each fortnight, and when nation one considers changing the value of ν_1. At days 1, 15, 29, 43, 57, 71, and 85, ν_1 can be set for the 14 days ahead as either 0.0, 0.2, 0.4, 0.6, 0.8, or 1.0. This policy approach yields 6^7 potential policy combinations for a given set of parameters. As previously, these sharing options are overridden if one country eventually becomes fully vaccinated, after which all vaccines are used in the other nation. For the set of parameters in **Table 1**, each policy choice is presented as a dot in **Figure 3A**. The values (**Figure 3A**) are the accumulated COVID-19 related deaths, shown for both nations, and up to the time of full vaccination in both nations. The slightly jagged appearance in the spread of solutions is a consequence of the numerical discretisation associated with the fortnightly policy decisions. In **Figure 3A**, any superimposed line of gradient minus one would correspond to a constant sum of deaths from combining those of both nation one and nation two. Hence the curvature in the plume of points again illustrates a potential issue of ethics. If nation one seeks to minimise its total number of deaths (low values on "x" axis, **Figure 3A**), then the gradient of points (top left of diagram) has a magnitude larger than unity. As such, every life saved in nation one corresponds to a number greater than unity of lives lost in nation two. Placing a constraint on selected policy options that for the first three fortnights, all vaccines are retained for nation one, corresponds to the blue dots. In similarities to the scenarios presented in **Figure 2**, such initial high retention levels of vaccines correspond to the lowest cumulative deaths for nation one. This finding suggests again that for the parameters and policy scenarios presented here, the hypothesis that sharing vaccines will lower imported infections and decrease total deaths in nation one cannot be supported when compared to simply vaccinating nation one as fast as possible.

We introduce an asymmetry to the parameters by raising the value of β_2 for nation two to 0.5 (**Figure 3B**). If the infectious stage of COVID-19 is 5 days [(15) and our **Table 1**], then with $\beta_2 = 0.5$, this corresponds to a R_0 value between two and three. This scenario, whereby transmission occurs twice as frequently in nation two, provides an outer bound worst case for our simulations. The new calculations of cumulative total deaths in both nations, at the time when everyone is inoculated and for $\beta_1 = 0.25$ and $\beta_2 = 0.5$, are shown in **Figure 3B**. The higher value of β_2, as expected, results in the total deaths in nation two to be vastly higher than those for when $\beta_2 = 0.25$. However, of note is that the deaths in nation one also rises by a large amount, confirming the effect of extensive travel (here $f_1 = f_2 = 0.2$) to and from nation two that has weaker controls on virus transmission. The blue dots in both panels again correspond to where, for the first three fortnights, nation one retains all vaccines ($\nu_1 \equiv 1$). To aid illustration, the axis range in **Figure 3B** for both nations is identical, showing the gradient of the plume of points is now even larger. This high gradient implies that any change in sharing policy that saves additional lives in nation one, will correspond to substantially more lives lost in nation two, again raising ethical issues.

To capture more simply the issue of equity, we present the total number of deaths as a function of initial levels of vaccine sharing (**Figures 3C,D**). The simulations and parameters of **Figure 3C** are identical to those of **Figure 3A**, and similarly **Figure 3D** uses the same projections as **Figure 3B**. In **Figure 3C**, a symmetry exists as expected with identical parameters for nation one and nation two, and so the minimum total deaths are achieved when a half of vaccines are given by nation one to nation two. **Figure 3D** illustrates that if we model nation two as having a higher transmission rate, then the minimum number of total deaths is when nation one gives away most or all of their vaccines following the start of their production.

4. DISCUSSION AND CONCLUSIONS

4.1. General Findings

We have investigated the role of different policies of vaccine sharing on managing COVID-19 infections. Our equation set is designed to model the extent of SARS-CoV-2 virus transmission, during the period when a vaccine is verified as safe and its mass production and distribution starts. Two nations are considered ("one" and "two"), the first of which has discovered and is making a vaccine, and where there is extensive travel between the two countries. We create a model framework to ask whether given travel, it is beneficial for nation one to share vaccines with nation two to lower imported infections? Equations (1)–(4) and (7)–(10), in tandem with the parameters and initial conditions of **Table 1**, are parameter-sparse, relatively simple, yet capture the main processes needed to address that question. Our headline finding is that for the parameters investigated, despite the risks of imported infection, in order to minimise deaths in nation one the best strategy is for that nation to vaccinate all citizens first before subsequently sharing it. This inference is achieved by iterating numerically over a range of possible sharing strategies. However as expected, lower levels of travel with nation two which has more infections, decreases the number of COVID-19-related deaths in nation one. We recognise the hardship that reduced travel causes, and especially for those with employment in the tourism and hospitality sector. The solutions presented reveal that although some vaccine sharing will likely mean more deaths in nation one, it can cause a disproportionately large saving of lives in nation two. This finding raises obvious ethical issues regarding vaccine distribution. As any particular nation becomes increasingly inoculated, vaccines may then save many more lives by being sent elsewhere.

As a nation starts to achieve a high number of inoculations, reaching herd immunity, then more lives will still be saved with further vaccination. However, at this point, the probability of a life saved per vaccine administered will be higher if it used elsewhere, in a location with little or no vaccine coverage. Vaccine sharing, as a positive externality to infection dynamics, may set up complex issues in control infections and elasticity. Such elasticity is where the prevalence of infection changes the levels of vaccination uptake (29, 30). High elasticity provides self-interested individuals with less incentive to be vaccinated as coverage increases, as they expect to gain from herd immunity. Hence it may become increasingly difficult to minimise the prevalence of infections, and therefore associated deaths, due to COVID-19 in the nation that developed the vaccine. In these circumstances, with a stalling of vaccine uptake, then extensive sharing is likely to achieve further benefits in the first nation by managing overall risks of mortality associated with the virus. Sharing will reduce risks of imported infections where there is substantive travel with other nations.

4.2. Caveats

The modelling framework used in this study is not exempt from caveats and limitations. For instance, we have not explored where two nations have markedly different populations and so $S_1(0)$ and $S_2(0)$ are dissimilar. The fractions of nations travelling, given by f_1 and f_2, may also not balance, for instance should one country be a popular tourist destination. Temporary self-quarantining of people after travel, possibly in tandem with raised testing regimes (e.g., at airports), will lower levels of imported infections, and these effects would require adjustment to our equations. In addition, some parameters may not be fixed in time. For instance, the number of vaccines that can be produced per day may grow substantially in time, making Q time-dependent. Arguably, any nation seeing the benefits of vaccination causing immunity may choose to simultaneously work to lower transmission rate further (i.e., make β a function of time), as part of a push to completely remove the virus as fast as possible. A further caveat is that our equations do not include any within-country compartmentalisation of populations, noting others conclude that vaccine priority should be for those at greater risk, such as the elderly and the immune-compromised (31, 32). The assumption of complete or high immunity for those who recover from COVID-19 remains an open scientific question. Investigating more extreme parameter ranges or policy options may yet find that the best solution, in terms of cumulative deaths of nation one, is some early vaccine sharing. Our flexible mathematical structure may be applicable at more local scales within countries, to understand different policies for major cities and between which substantial travel occurs. In the other direction, the simulation structure is available to extension to understand interactions between more than two countries.

A further caveat is that we do not account for any fraction of infected individuals who, upon realising they are unwell and suspect (correctly) they have COVID-19, decide to not travel. If a is the fraction of infected people who plan to travel, and still travel, then this would likely also include the sizeable number of people with COVID-19 who are asymptomatic. Inclusion of this effect would modify, for instance, Equation (1) for susceptible people in nation one, to instead be as given as **Supplementary Equation (1)**. In the instance where nation two has high infection levels, then the implication for those susceptible in nation one of less travel by unwell people (i.e., by a lower a value) in **Supplementary Equation (1)** is as follows. The first right-hand term of **Supplementary Equation (1)** will be affected mainly by the last component, with af_2I_2 replacing f_2I_2 in Equation (1). This change implies that fewer infected people will travel from nation two to nation one, lowering imported infections. However, such suppression of travel by this mechanism will have less effect on the second right-hand term of **Supplementary Equation (1)**, which describes the risk of infection by f_1S_1 susceptibles (i.e., non-infected people) in nation one travelling to nation two.

A major ongoing concern of the COVID-19 crisis is the emergence of virus variants (e.g. in Brazil, India, United Kingdom and South Africa), and that might be vaccine resistant, have higher transmission levels, or both. For instance, the Delta variant first found in India may have more vaccine resistance (33). If a new variant becomes the dominant strain, then our framework can accommodate this by different vaccine efficacy e, waning vaccine immunity σ_v, and transmission β parameter values. If reducing overall virus infection globally lowers the risk worldwide of new variants of concern emerging, then this relates to vaccine sharing should some policies lower overall infection levels more than others.

More complexity can be added to our simulation framework by configurations that consider variation in transmissibility and susceptibility within the populations of nations. Distinctions may be defined by age-dependent variation in social mixing (34) and mortality, clinically vulnerable vs. non-vulnerable, or variation in existing medical conditions that may partially depend on poverty levels. Specific vaccine rollout plans may also be modelled, such as prioritising vaccinations to frontline health workers who will have much higher levels of interactions with infected individuals. Such variations would require substantial additional parameters (mortality levels and inter-group infection transmission rates) and model compartments, all requiring quantification. More generally, whilst many countries have focussed on vaccinating the eldest first, as they are considered more vulnerable, the COVID-19 crisis raises other issues of inter-generational equity. For instance, younger people may be disproporitionately affected by unemployment, post-COVID-19 national debt burdens, and research is needed to see if they are particularly impacted by mental health issues caused by lockdowns (35). The order of within-country vaccination of groups may affect these factors, for instance, by inoculating some groups faster to enable return to full employment. The issue of elasticity in vaccine uptake is also not included in our equations.

The equations presented and their solution to find a vaccine sharing policy that minimises deaths is amenable to the application of optimal control theory. Such methods have been successful in informing public health strategies regarding the avian influenza pandemic (36), the Chikungunya epidemic (37), and influenza (38). Optimal control has also been used in terms of minimising the cost of vaccine programmes, for human papillomavirus (HPV) (39) and influenza (40), and sometimes in tandem with other disease prevention methods e.g., mosquito control for dengue (41). Optimal control methods are elegant, ultimately the most appropriate mathematically, and provide a level of verification unachieveable by scanning numerically for a solution. We plan to undertake such analyses, solving the governing equations and additionally the adjoint, as required by optimal methods, along with satisfying constraints to ensure physical realism. However, our more fast-track initial "forward-mode" computation approach does have some advantages. We restricted ourselves to discrete periods of time between policy changes, potentially reflecting how decisions are undertaken with regular reviews. The discrete changes could, though, be used to approximate any smooth time-evolving trajectories discovered for $\nu_1(t)$ by optimal techniques.

4.3. Overall Summary

Our analysis represents two countries of similar size and levels of visitation rates, and where we set transmission rates to values that might reflect the on-going implementation of NPIs such as the use of lockdowns, personal protection equipment, and social distancing. The mass production and use of vaccines is considered to start at the beginning of our simulations. We assume that using a general SIRV (Susceptible, Infected, Recovered, Vaccinated) model is valid to describe the spread of COVID-19 illness. For our selected parameters and range of policy options, we find that reducing travel and keeping all vaccines until full inoculation will minimise COVID-19 related deaths in a nation (nation one) that produces a vaccine. Our initial hypothesis was that when accounting for travel, it is beneficial for nation one to share vaccines with nation two, to lower either imported infections, or infection risk when visiting nation two. For our selected default parameters, this effect appears relatively small. However, the extent of travel affects nation two more, as for example with larger exchanges, people of nation two are more protected when visiting nation one. If either nation has a higher initial infection level at the start of a vaccine program, as expected, travel will cause more deaths in the other nation.

What our calculations do highlight is the strong influence that any vaccine sharing policy has on the total deaths of nation one and two combined. In particular, to minimise deaths overall, nation one needs to offer nation two a substantial number of vaccines, and early on. In some instances, extensive sharing may result in only small increases in deaths in nation one (the vaccine producer), yet save a much larger number of lives in nation two. This finding also remains valid for the sensitivity calculations we performed and report. Early and sizeable vaccine sharing raises an ethical dilemma. Should the government of a nation producing a vaccine make their primary role to inoculate as fast as possible all those who have elected it, or to take a more global perspective, and share earlier on vaccines to save more lives overall? The issue of vaccine sharing and related ethics is likely to require substantial thought in the months ahead. Indeed, as of the beginning of year 2021, there has already been tension between the European Union and the United Kingdom on this matter. Although a very obvious point to make, it is worth reiterating that with the emergence of vaccines, deaths will be minimised by achieving its largest possible mass production. High production levels will most quickly vaccinate the country of its origin, and enable more rapid and substantial sharing internationally. As vaccines are now receiving approval as safe, our model framework can be used in a more operational context, entraining known parameters specific to individual countries.

DATA AVAILABILITY STATEMENT

The computer model scripts supporting the conclusions of this article will be made available by the authors, without undue reservation. The python computer scripts are also provided, in full, in the **Supplementary Material**.

AUTHOR CONTRIBUTIONS

CH conceived the conceptual framework and designed the associated numerical experiment. CH and TR built the equation set, and their numerical solution. MB provided advice on current COVID-19 understanding. All authors reviewed and contributed to writing the manuscript.

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SUPPLEMENTARY MATERIAL

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Mitigating Impacts of the COVID-19 Pandemic on Gorilla Conservation: Lessons From Bwindi Impenetrable Forest, Uganda

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The COVID-19 pandemic, affecting all countries, with millions of cases and deaths, and economic disruptions due to lockdowns, also threatens the health and conservation of endangered mountain gorillas. For example, increased poaching due to absence of tourism income, led to the killing on 1st June 2020 of a gorilla by a hungry community member hunting duiker and bush pigs. Conservation Through Public Health (CTPH), a grassroots NGO and non-profit founded in 2003 promotes biodiversity conservation by enabling people to co-exist with wildlife through integrated programs that improve animal health, community health, and livelihoods in and around Africa's protected areas and wildlife rich habitats. Through these programs, we have helped to mitigate these impacts. CTPH worked with Uganda Wildlife Authority and other NGOs to improve great ape viewing guidelines and prevent transmission of COVID-19 between people and gorillas. Park staff, Gorilla Guardians herding gorillas from community land to the park and Village Health and Conservation Teams were trained to put on protective face masks, enforce hand hygiene and a 10-meter great ape viewing distance. To reduce the communities' need to poach, CTPH found a UK-based distributor, for its Gorilla Conservation Coffee social enterprise enabling coffee farmers to earn revenue in the absence of tourism and provided fast growing seedlings to reduce hunger in vulnerable community members. Lessons learned show the need to support non-tourism dependent community livelihoods, and more responsible tourism to the great apes, which CTPH is advocating to governments, donors and tour companies through an Africa CSO Biodiversity Alliance policy brief.

Keywords: COVID-19, gorillas, conservation, one health, livelihoods

INTRODUCTION

The One Health approach recognizes that the health of people is closely connected to the health of animals, plants, and their shared environment (https://www.onehealthcommission.org/en/why_one_health/what_is_one_health/).

In November 2019, a highly contagious novel coronavirus, SARS-COV-2 closely related to bat coronaviruses was identified in China and some of the index cases linked to a wet live animal market in Wuhan, Hubei Province (1). COVID-19 affects both the upper respiratory and lower respiratory tracts with a mortality rate of as much as 6.5% of confirmed cases (2). With an estimated 80% of infected people becoming asymptomatic, a combination of increased urbanization (3), land use change (4), high human population growth rates and air travel (5) resulted in the virus spreading from one continent to another and within most countries in the world in a period of four months. World Health Organization (WHO) declared the COVID-19 epidemic as a pandemic on 11th March 2020.

By December 2020, there were over 80 million confirmed cases and 1.8 million deaths (Worldometer.com/coronavirus), and more infectious mutated strains and variants of the SARS-COV-2 virus were discovered resulting in additional lockdowns and travel restrictions. Though the African continent and Uganda in particular have had relatively few cases (6), the health care systems have been overwhelmed during the waves caused by a sharp rise in infections and deaths, in the few and inadequately equipped hospitals. Several cases and deaths among people in marginalized rural areas have gone undetected because people have inadequate health seeking behavior and majority cannot afford to pay for testing. These include people living in biodiversity hotspots that are rich in wildlife and have high human population densities.

Communities bordering protected areas in Africa are among the most marginalized with limited access to basic health and other social services as well as livelihoods options. Improving the well-being of communities bordering protected areas has contributed to conservation outcomes (7). Improving community health has the potential to reduce the risk of zoonotic disease transmission between people and great apes (8) and improve their attitudes to conservation (9). Improving community livelihoods has the potential to reduce hunger and the need to poach. Great apes are found within 21 countries in Africa of which 13 have great ape tourism at 33 sites. Ecotourism has provided benefits to local communities who are employed by locally based organizations to protect the wildlife or set up enterprises that sell crafts, food items, accommodation, and experiences including community walks and traditional entertainment, as well as services as porters who carry bags of tourists visiting gorillas and chimpanzees. This form of alternative livelihood has reduced the communities' dependence on the forest for food and fuel wood, contributing to the protection of endangered wildlife. Global lockdowns caused by the COVID-19 pandemic disrupted this sustainable financing for conservation by preventing travelers who provide critical revenue for conservation and sustainable development from reaching these tourist sites.

IMPACT OF COVID-19 ON GORILLA CONSERVATION

Humans and non-human great apes in Africa share over 98% DNA genetic material and zoonotic diseases have been transmitted between them causing morbidity and mortality (10–12). Furthermore, studies indicate that gorillas, chimpanzees, and other old world primates are just as susceptible as humans to COVID-19 because they have the same Angiotensin Converting Enzyme (ACE2) protein receptors that the SARS-COV2 virus attaches to (13, 14), making them highly susceptible to SARS-COV2 from humans. Wild great apes are at risk of contracting human diseases from the people they interact with including park staff, conservation personnel, researchers, tourists, and local communities. The first natural transmission of COVID-19 to primates occurred within 1 year of the pandemic in January 2021 when eight gorillas at San Diego Zoo Safari Park contracted the disease from an asymptomatic zoo keeper with three of them testing positive through fecal sample testing. A 48-year-old adult male gorilla developed severe signs and the rest of the younger members of the troop developed mild signs of COVID-19 (15, 16). Thus, the COVID-19 pandemic has not only resulted in a breakdown of human health care systems due to an overwhelming number of cases and disruptions to economies due to global lockdowns, but also presented a new threat to the conservation of wildlife. For a species as endangered as the mountain gorillas, the balance between health and economics has become even more critical for their survival during this pandemic (17).

The loss of tourism income for local communities bordering protected areas in Africa, due to a reduction in the number of tourists whose presence also provides some protection for the wildlife contributed to an increase in poaching (18). This could reverse the trend and conservation gains brought about by tourism for endangered mountain gorillas whose IUCN status was downgraded from critically endangered in 2018 as the only gorilla sub species showing a positive growth trend (**Figure 1**) in their population (19). Within the first 3 months of the pandemic reaching Uganda in March 2020, there was at least a doubling of snares retrieved with the same level of patrol effort at protected areas in Uganda as stated by the Uganda Wildlife Authority (20) including Bwindi Impenetrable National Park (BINP), home to 43% of the world's estimated 1,063 mountain gorillas (21). The absence of tourism due to the COVID-19 pandemic contributed to the killing on 1st June 2020 of the lead silverback of the Nkuringo gorilla group in BINP by a hungry and vulnerable community member hunting duiker and bush pigs for food and sale at the local market. Gorillas are not eaten in Uganda, but become accidental victims of snares set for other species. When the poacher speared a bush pig, its scream prompted the silverback gorilla to charge him to protect his family. The poacher then speared and killed the gorilla, claiming that it was in self defense. This killing of an endangered gorilla, a direct result of COVID-19 generated a worldwide acknowledgment of the devastating impact of the pandemic on the conservation of wildlife. The poacher was sentenced to 11 years in jail, the longest

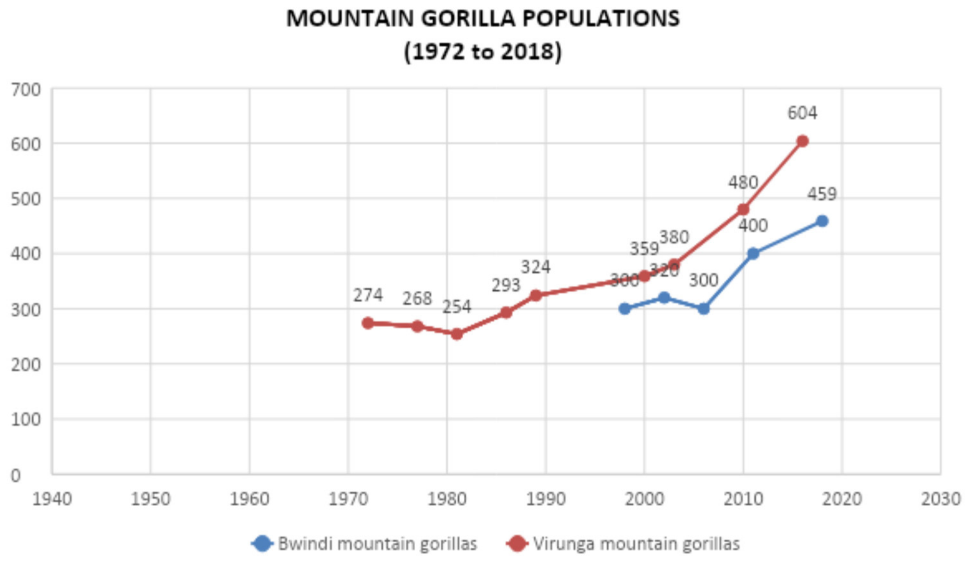

FIGURE 1 | Mountain gorilla population census results from 1970 to 2020 (Source compiled by Conservation Through Public Health).

that any person in Uganda has been sentenced for killing wild animals (22). Though this tough sentence was a deterrent to other community members, the increasing hunger due to the lack of tourism was likely to result in other similar incidents among desperate community members.

BUILDING A ONE HEALTH APPROACH TO CONSERVATION

Conservation Through Public Health (CTPH), a grassroots Ugandan NGO and US registered non-profit founded in 2003 promotes biodiversity conservation by enabling people to co-exist with gorillas and other wildlife through integrated programs that improve animal health, community health and livelihoods in and around Africa's protected areas and wildlife rich habitats. CTPH was established following fatal scabies skin disease outbreaks in Bwindi mountain gorillas that were traced to local communities with less than adequate hygiene and health services (23, 24). Through previously established grassroots programs founded on the principles of One Health, PHE (Population, Health and Environment) by adding community based family planning (25) and Planetary Health (26), CTPH has mitigated the health, and economic impacts of the COVID-19 pandemic on wildlife conservation.

Population, Health and Environment (PHE) is an integrated community-based approach to development that acknowledges and addresses the complex connections between humans, their health, and the environment (25). Planetary health recognizes the effects of human behavior on the environment, which in turn has an impact on human health (26). One Health has a strong emphasis on biosurveillance and biosecurity of farm animals and wildlife where, measures taken often involve the culling of animals in order to prevent the spread of diseases to humans. However, for better mitigation and prevention of epidemics, it is necessary to adopt a more than human approach, that also emphasizes the welfare of animals (27). Non-human primates, and gorillas in particular are emblematic species to show the value of a One Health approach that equally addresses the health of humans, animals, and their ecosystems.

MITIGATING THE IMPACT OF COVID-19 ON GREAT APE HEALTH AND COMMUNITY WELL-BEING

Reducing the Threat of Disease Transmission From People to Gorillas

There have been a number of incidences of human respiratory virus transmission from humans to wild great apes that originated from local communities or tourists (28–30). Owing to the potential for reverse zoonosis, guidelines to minimize disease transmission between people and gorillas were instituted by the government agency responsible for wildlife, Uganda Wildlife Authority (UWA) with support from International Gorilla Conservation Programme (IGCP) when tourism began in 1993 (www.igcp.org). These rules included not being allowed to visit the gorillas when showing signs of illness, maintaining a 5-m distance and turning away to cough or sneeze. Over the past two decades as the gorillas became more habituated to the presence of humans, the viewing distance between people and gorillas became closer than the new 7-m viewing distance, where research revealed that 60% of the time the tourists got closer than 3 m and 40% of the time, it was the gorillas that got closer than 3 m (31). Research studies also revealed that 51–73% of tourists were willing to wear masks (31, 32) to minimize the spread of respiratory diseases to gorillas.

To minimize the risk of COVID-19 and other respiratory diseases spreading from people to gorillas, CTPH worked with UWA and conservation and health NGOs including IGCP, Mountain Gorilla Veterinary Project/Gorilla Doctors, Max Planck Institute and Bwindi Community Hospital (BCH) to train 400 park staff to prevent transmission of diseases between people and from people to gorillas. Park staff who monitor the health of gorillas and protect them through law enforcement patrols in the forest, were trained to put on protective face masks, enforce hand hygiene, and a 7-m great ape viewing distance, which UWA increased to 10 m as an additional measure during the pandemic (33). The rangers were also provided with double layered cloth face masks and hand sanitizers. A new regulation was instituted to have mandatory temperature checks using a non-contact infrared thermometer, for every person entering the forest who also had to wash their hands and disinfect their boots before and during the trek to the gorillas.

The same training was given by CTPH, UWA, BCH, and Kanungu and Kisoro Districts Health Offices to 119 Gorilla Guardians who are community volunteers from the Human and Gorilla Conflict Resolution (HUGO) team, supported by UWA, IGCP, and CTPH to herd gorillas from community land to the park, which occurs a few days every month among habituated gorilla groups at Bwindi and to monitor their health when in community land (34). The Gorilla Guardians were also given double layered cloth face masks, hand sanitizers and liquid soap. CTPH, IGCP and The Gorilla Organization donated double layered cloth face masks and non-contact infrared thermometers to UWA and the Gorilla Guardians. Village Health and Conservation Teams (VHCTs) who are community health volunteers, trained by CTPH since facilitating their formation in 2007, to conduct behavior change communication at the household and village level on good hygiene and sanitation, infectious disease prevention and control, family planning, nutrition, sustainable agriculture, gorilla, and forest conservation as well as report homes visited by gorillas were also trained by CTPH, BCH, Kanungu and Kisoro District Health Office staff and UWA, to mitigate COVID-19, which resulted in an increase in hand washing facilities at their homes because of the fear of contracting the disease. Tuberculosis and other respiratory diseases were managed together with COVID-19 where people presenting with cough, flu, and difficulty in breathing were tested for both diseases. Since the pandemic began, the VHCTs have reached over 5,000 households with critical health and conservation information and services. The 270 VHCTs were also trained to identify suspects and carry out contact tracing as well as counsel confirmed cases and their contacts. Gorilla Guardians and VHCTs were also given posters on preventing COVID-19 between people and from people to gorillas to disseminate in their community, which were made for CTPH by Solidaridad, a donor of CTPH. Over 500 posters were put at the park offices and disseminated among the local communities.

Conservation Through Public Health is working with UWA, BCH, Kanungu and Kisoro District Health offices, Uganda Virus Research Institute, University of Madison-Wisconsin, and other partners to test gorillas, and people interfacing with gorillas both inside and outside the park for COVID-19. During the pandemic, CTPH got new donors to fund these activities as part of emergency funding for COVID-19, including Arcus Foundation, International Union for the Conservation of Nature (IUCN) Save the Species and European Union, the British High Commission and individual donors, which was complimented by funding for ongoing activities supported by Tusk Trust, Whitley Fund for Nature, Population Connection and Wildlife Conservation Network.

Conservation Through Public Health (CTPH) joined the Uganda Ministry of Health (MOH) national disease taskforce in 2010. Through this platform, CTPH increased awareness among taskforce members of the susceptibility of gorillas and chimpanzees to COVID-19 from humans, influencing the national response to the pandemic where primate tourism reopened later than other wildlife based tourism primarily to protect the closely genetically related gorillas and chimpanzees from human diseases as stated in the speech of the President of Uganda in May 2020 (www.ntv.co.ug).

Reducing the Threat of Poaching

The absence of tourism income also became a threat to the survival of the mountain gorillas because the economic incentive for communities to protect them by not entering their habitat to poach was removed. Additionally, there was a reduction in tourism revenue that sustains park operations including anti-poaching patrols. This prompted the government to reopen primate tourism at the end of September 2020 where the benefits of reducing illegal entries in the habitat of great apes outweighed the risk of introducing COVID-19 from tourists to the endangered gorillas and chimpanzees because the risk of reverse zoonotic disease transmission was perceived to be greatly reduced through instituting the new standard operating procedures including mandatory wearing of masks within 10 m of great apes and increasing the viewing distance from seven to 10 m. Vaccination of people who interact with great apes potentially reduce the risk of COVID-19 disease transmission between people and great apes even further (35). Though tourism is still at an estimated 10–20% of pre pandemic levels largely due to lockdowns preventing international travel, it has brought hope to the Bwindi local communities and contributed to a reduction in poaching, as well as, generated revenue to support law enforcement operations that protect the gorillas and other species in their habitats.

When the COVID-19 pandemic reached Uganda in March 2020, double layered cloth face masks were bought from a local enterprise, Ride for a Woman, and provided to park rangers and other conservation personnel and community members including HUGOs, VHCTs and reformed poachers. This provided an income for the women and contributed to a reduction in poaching in the gorillas' habitat during the pandemic that resulted in a reduction in tourism due to global lockdowns.

In May 2020, CTPH got a new UK-based distributor, Moneyrow Beans, for its Gorilla Conservation Coffee social enterprise that had started in 2015 to provide above market prices for premium and specialty coffee sold locally and internationally to Lifestyle of Health and Sustainability (LOHAS) consumers who want to support gorilla conservation where a donation from every bag of coffee sold goes toward sustaining community health, gorilla health, and conservation education programs of CTPH. This social enterprise also had reduced sales because it relied on international tourists who could no longer travel to Uganda for tourism to the gorillas and other wildlife and who were the main customers for the coffee. Finding a new export market not dependent on tourism enabled 150 coffee farmers to earn some revenue and reduced their need to poach. It also enabled conscious consumers to fulfill their desire of supporting gorilla conservation during the pandemic through purchase of coffee in the UK, USA, Kenya, New Zealand and Australia.

As a response to the killing of Rafiki, the lead silverback of Nkuringo gorilla group by a hungry poacher, that led to the group reducing in size, CTPH started a new emergency food relief "Ready to Grow" program to provide fast growing seedlings that take 1–4 months to produce food, to reduce hunger in vulnerable community members where 1,002 families were the first to be provided with 10 types of fast growing seedlings helping to reduce hunger, starting with Nteko parish where the family of the poacher who speared Rafiki the gorilla were also beneficiaries. Among the vulnerable people who received seedlings were porters whose livelihoods were most affected by the lack of tourism, which they had began to solely depend on to meet their family needs, reformed poachers who CTPH had started to provide with group livestock income generating projects, Batwa hunter gatherers who were resettled outside the park when it was gazetted in 1991, Gorilla Guardians, local council chairpersons, and VHCTs who were also tasked with monitoring the success of the Ready to Grow program among the households. CTPH is currently measuring how improving the well-being of Bwindi local communities is reducing poaching and other illegal forest resource use during the pandemic.

Advocating for Responsible Tourism to Great Apes Through a One Health Approach

In March 2020, a network of African based NGOs and CBOs was created to strengthen the African voice in the Convention of Biological Diversity (CBD) resulting in the creation of the Africa CSO Biodiversity Alliance (ACBA) of which CTPH became a member. Through the ACBA platform CTPH worked with IGCP to develop a policy brief targeting African governments, donors and tour companies, (36) based on IUCN best practice guidelines for great ape tourism and lessons learned from 27 years of implementing great ape tourism in Uganda, which prior to the COVID-19 pandemic, was contributing to 60% of tourism revenue for UWA (37). Through the policy brief and the MOH COVID-19 taskforce, CTPH has been advocating for priority testing and vaccination of park staff coming into close contact with gorillas and chimpanzees.

In response to the pandemic, the ACBA designed a social media campaign on the risks of zoonosis to human health (38) and reverse zoonosis to great apes, with links to COVID-19, highlighting the danger of consuming bats, primates, and other high risk species, that have historically been the source of disease outbreaks and epidemics of Ebola, Marburg, and other zoonotic diseases in Africa and the risks of spreading diseases from people to closely related great apes (39, 40).

DISCUSSION

A One Health approach that equally addresses the health of humans and gorillas together to promote species and habitat conservation enabled CTPH to mitigate the impact of COVID-19 on gorilla conservation. Lessons from the COVID-19 pandemic in Uganda that can be applied to other countries in Africa and the developing world even after the pandemic has been brought under control, include the great need to prevent COVID-19 and other diseases between people and non-human great apes through responsible tourism and promotion of community health where great apes and other wild animals range. Another lesson is the need to reduce poaching by addressing hunger among vulnerable community members and by supporting community livelihoods. Tourism is one of the most effective ways of providing sustainable financing for conservation, however it must be carried out carefully to minimize the risk of zoonotic disease transmission to great apes from tourists who could bring in fatal viruses like SARS-COV-2. In order for tourism to contribute to a reduction in poaching from local communities, it must support local livelihoods. The pandemic has also demonstrated the need to provide other sustainable financing mechanisms for conservation when tourism is not possible. This includes increasing access to international markets by encouraging responsible consumption through purchase of ethically sourced products that improve community livelihoods with a direct positive impact on conservation, such as Gorilla Conservation Coffee. The delicate balance between the increased risks to the health of great apes from tourists and increased poaching in their habitat due to the absence of tourism has to continually be assessed to determine whether to suspend or reopen great ape tourism during pandemics (17).

Thus, there is a critical need for One Health approaches that improve human, animal and ecosystem health together and support communities through tourism and livelihoods that are not dependent on tourism. Such approaches can be scaled globally to build resilience and minimize the health and economic impact of pandemics like COVID-19 on humanity and wildlife particularly in low to middle income countries (41, 42).

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: www.ctph.org.

AUTHOR CONTRIBUTIONS

GK-Z, SR, and LZ designed the programs. AN led the implementation of the field programs. GK-Z led advocacy initiatives and wrote the manuscript. GK-Z, SR, and LZ participated in implementation of the activities. All authors contributed to the article and approved the submitted version.

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Cross-Species Transmission of Coronaviruses in Humans and Domestic Mammals, What Are the Ecological Mechanisms Driving Transmission, Spillover, and Disease Emergence?

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Coronaviruses cause respiratory and digestive diseases in vertebrates. The recent pandemic, caused by the novel severe acute respiratory syndrome (SARS) coronavirus 2, is taking a heavy toll on society and planetary health, and illustrates the threat emerging coronaviruses can pose to the well-being of humans and other animals. Coronaviruses are constantly evolving, crossing host species barriers, and expanding their host range. In the last few decades, several novel coronaviruses have emerged in humans and domestic animals. Novel coronaviruses have also been discovered in captive wildlife or wild populations, raising conservation concerns. The evolution and emergence of novel viruses is enabled by frequent cross-species transmission. It is thus crucial to determine emerging coronaviruses' potential for infecting different host species, and to identify the circumstances under which cross-species transmission occurs in order to mitigate the rate of disease emergence. Here, I review (broadly across several mammalian host species) up-to-date knowledge of host range and circumstances concerning reported cross-species transmission events of emerging coronaviruses in humans and common domestic mammals. All of these coronaviruses had similar host ranges, were closely related (indicative of rapid diversification and spread), and their emergence was likely associated with high-host-density environments facilitating multi-species interactions (e.g., shelters, farms, and markets) and the health or well-being of animals as end- and/or intermediate spillover hosts. Further research is needed to identify mechanisms of the cross-species transmission events that have ultimately led to a surge of emerging coronaviruses in multiple species in a relatively short period of time in a world undergoing rapid environmental change.

Keywords: coronavirus, COVID-19, cross-species transmission, host range, MERS, One Health, SARS, spillover

INTRODUCTION

Coronaviruses (CoVs) cause respiratory and digestive diseases in humans and other animals, and are responsible for several emerging diseases. The severe acute respiratory syndrome (SARS) outbreak in 2002–2003 resulted in 8,422 human cases and 916 deaths in 33 countries (1). In 2012, Middle East respiratory syndrome (MERS) emerged, and over time has resulted in over 2,500 human cases and 866 deaths in 27 countries (2, 3). As of mid-2021, the novel coronavirus disease 2019 (COVID-19) pandemic has resulted in 4.2 million human deaths and 196.2 million cases in 221 countries and territories (4). Other animals have also been affected by these and other emerging coronaviruses, all of which resulted from cross-species transmission, and demonstrate the serious threat coronaviruses can pose to humans and other animals globally.

Named after their crown-shaped spike surface proteins, coronaviruses are enveloped, positive-sense single-stranded RNA viruses that belong to the family *Coronaviridae*, subfamily *Orthocoronavirinae* (5, 6). They split into four genera: *Alphacoronavirus*, *Betacoronavirus*, *Deltacoronavirus*, and *Gammacoronavirus* (5). The first two genera infect mammals primarily, whereas *Gammacoronaviruses* infect birds, and *Deltacoronaviruses* infect both mammals and birds (7). Coronaviruses further split into species; however, they exist as quasispecies due to the rapid evolution driven by their high mutation rates and homologous RNA recombination (8). Coronaviruses have the largest genomes (26.4–31.7 kb) of all known RNA viruses; thus, their genomes are especially prone to accumulation of mutations and recombined segments over time, which contributes to their diverse host range and potential for disease emergence (9).

Bats are considered reservoirs for most *Alpha-* and *Betacoronaviruses*, while wild birds are probable reservoirs for *Gamma-* and *Deltacoronaviruses* (10). Coronavirus spillover from reservoirs to other species, and subsequent cross-species transmission, is primarily mediated by recombination in the receptor-binding domain (RBD) of the spike protein (S) gene (11). The receptor-binding domain enables coronaviruses to infect hosts by binding to a host receptor, e.g., angiotensin-converting enzyme 2 (ACE2) in the case of SARS coronaviruses, for cell entry (7, 12, 13). Although research has revealed reservoirs and molecular mechanisms enabling cross-species transmission, and that viral evolution is facilitated by frequent cross-species transmission events (14), less is known about the environments favoring emerging coronavirus evolution in non-reservoir hosts.

Agriculture and industrialization expanded the global abundance of humans and domestic mammals (i.e., livestock and pets). Today, their combined biomass makes up 96% of all mammalian biomass on Earth (15). This may be the primary reason for disease emergence in humans and other animals (16). To help curb coronavirus disease emergence, it is important to identify current host ranges of existing coronaviruses in humans and domestic animals, and the circumstances associated with their cross-species transmission.

This review provides an updated succinct summary of known host ranges and cross-species transmissions of recently emerged coronaviruses in humans and domestic mammals. Moreover, I discuss commonalities among the ecological circumstances related to spillover and emergence of several coronaviruses in various mammalian hosts, and how these may inform One Health interventions for preventing disease emergence.

EMERGING HUMAN CORONAVIRUSES

There are seven known human coronaviruses: the *Betacoronaviruses* SARS-CoV-1, MERS-CoV, and SARS-CoV-2, which caused SARS, MERS, and COVID-19, respectively, and the *Alphacoronaviruses* NL63 and 229E and *Betacoronaviruses* OC43 and HKU1, which cause the common cold in humans (17). The latter four may not be labeled as recently emerging coronaviruses, although they have spilled over at some point in the past. Bats are considered reservoirs for NL63 and 229E, whereas rodents are putative reservoirs for OC43 and HKU1 (17–19). NL63 possibly emerged several hundred years ago from recombination between ancestors to 229E in hipposiderid bats and coronaviruses circulating in African trident bats (19, 20). Based on phylogenetic analyses, cattle and camelids have been identified as probable intermediate spillover hosts for OC43 and 229E emergence one and two centuries ago, respectively (17, 18, 20). The bovine-to-human spillover that led to OC43 emergence likely coincided with a pandemic in 1890 (17, 21, 22). Indeed, OC43 and bovine coronavirus share 96% global nucleotide identity (23). Finally, extant lineages of HKU1 trace their most recent common ancestor to the 1950s, when it possibly spilled over from rodents (20).

Next, this section covers plausible spillover events—from reservoirs to humans via potential intermediate host species—that generated the recent SARS-CoV-1, MERS-CoV, and SARS-CoV-2, and their cross-species transmission potential.

SARS-CoV-1

Severe acute respiratory syndrome emerged in Guangdong, China, and caused the devastating 2000–2003 outbreak in several countries (1). Successful efforts curbed the epidemic: only a few cases occurred in late 2003 and early 2004 (24). There have been no known SARS-CoV-1-related cases since.

Based on genetic and epidemiologic investigations, the first SARS-CoV-1-infected individuals likely contracted the virus from masked palm civets or other wildlife in wet markets (24–27). Civet isolates revealed ongoing adaptation, suggesting that they were not reservoir hosts, but intermediate spillover hosts that contracted the virus from horseshoe bats (26–30). Substantial evidence confirms bats as SARS reservoirs (26, 28, 29, 31, 32).

Wildlife samples from a market in Shenzhen revealed that SARS-CoV-1 shared 99.8% nucleotide identity with isolates from civets and a raccoon dog, and that a ferret badger had seroconverted against SARS-CoV-1 (24, 26). Initial human cases reported direct or indirect contact with these animals via handling, killing, meat serving, or residing near wet markets (33). Surveys showed that animal (especially civet) traders, although asymptomatic, had disproportionately high seroconversion against SARS-CoV-1, suggesting they have been exposed to SARS-CoV-related viruses for several years before the SARS epidemic (24, 26). Intermediate spillover hosts were not necessarily required for the evolution of SARS-CoV-1, since a bat SARS-like coronavirus is able to bind to ACE2 in humans and civets for cell entry (34). Nonetheless, civets may have amplified the virus and brought it closer to humans (35).

Additional mammals are susceptible to SARS-CoV-1 infection. Cats, ferrets, guinea pigs, golden hamsters, common marmosets, grivets, and cynomolgus and rhesus macaques can be infected under experimental inoculation, seroconvert, and display similar pathological signs as humans, and the monkeys and guinea pigs usually display mild clinical signs, while cats and golden hamsters show no clinical signs (36–44). In two studies, inoculated ferrets only exhibited signs of lethargy (36, 37). Furthermore, cats and ferrets can shed SARS-CoV-1 and transmit the virus within each species (36). Cats have also been naturally infected by SARS-CoV-1 in an apartment block where residents had SARS, suggesting possible human-to-cat transmission (36). Although swine are susceptible to SARS-CoV-1 both experimentally and naturally, viral replication in (and shedding from) swine is poor (45–47). Mice and poultry are not susceptible to SARS-CoV-1 infection (45, 48, 49). Thus, SARS-CoV-1 was not uniquely adapted to humans, yet likely restricted to mammals.

MERS-CoV

Middle East respiratory syndrome cases are still being reported since it became endemic in the Arabian peninsula. Middle East respiratory syndrome does sporadically spread to other parts of the world, although with limited human-to-human transmission (50, 51). Most outbreaks originate from independent spillover events.

Bats are putative reservoirs for MERS, while dromedary camels and other camelids are intermediate spillover hosts (52–54). Although rare, camel-to-human transmission does occur (51, 55). Infected camels shed MERS-CoV via bodily fluids, especially nasal secretions, and exhibit sneezing, coughing, fever, and loss of appetite (56, 57). Camel care-takers or consumers of camel products are at risk of contracting MERS-CoV (51). People in direct or indirect contact with camels have disproportionately high seroconversion against MERS-CoV (58). Surveys from 2010 to 2013 in Saudi Arabia show that 90% of 310 and 74% of 203 camels were MERS-CoV seropositive (59, 60). Historical seropositive samples and phylogenetic analyses suggest that MERS-like coronaviruses have been circulating in camels for at least a few decades before MERS recently emerged in humans (52, 60–63). Camel markets with both live and dead animals are believed to serve as hotspots for MERS-CoV transmission (64).

MERS-CoV may infect additional species. Rhesus macaques, common marmosets, swine, llamas, rabbits, and alpacas have been infected experimentally, and the monkeys developed mild-to-moderate and moderate-to-severe disease, respectively, swine and llamas displayed rhinorrhea, while rabbits and alpacas showed no clinical signs, although alpacas shed MERS-CoV and transmitted it within its species (65–68). A virological survey found MERS-CoV in sheep, goats, donkeys, and a cow, but not in buffaloes, mules, or horses (69). A serological study confirms that equids might not be susceptible to MERS-CoV infection, although *in vitro* inoculation suggests otherwise (70). However, in an experimental inoculation study, sheep and horses did not show evidence of viral replication or seroconversion (68). Mice, golden hamsters, ferrets, and poultry are not considered susceptible to MERS-CoV infection, mainly because of their low host receptor homology with that of the MERS-CoV-susceptible species (67, 71).

SARS-CoV-2

The current COVID-19 pandemic was initially reported in Wuhan, China in 2019 (72, 73), although the origin of its pathogen, SARS-CoV-2, is still unclear. Its ancestor probably originated in bats, since SARS-CoV-2 is most closely related to the 2013 and 2019 isolates from horseshoe bats in Yunnan, China at the genome level, although not at the RBD level, suggesting neither might bind to human ACE2, and are thus not immediate ancestors of SARS-CoV-2 (72, 74, 75).

Conversely, isolates (pangolin-CoVs) from smuggled and diseased pangolins in Guangdong (2018–2019) are closely related to SARS-CoV-2 in the RBD region (76–80). Molecular binding simulations show that S proteins of SARS-CoV-2 and pangolin-CoVs can potentially recognize ACE2 in both humans and pangolins, suggesting possible pangolin-to-human spillover (76, 77). However, because pangolin-CoVs (including strains from Guangxi) are not the closest relatives to SARS-CoV-2 at the genome level, they are likely not direct ancestors of SARS-CoV-2 (76, 78, 79). Nevertheless, a 2019 pangolin-CoV isolate from Guangdong displayed high genome-wide similarity with both SARS-CoV-2 and SARS-CoV-2's closest relative (from bats), suggesting SARS-CoV-2 may have originated from recombination among coronaviruses present in bats and other wildlife (76, 77, 79, 81).

Like SARS-CoV-1, SARS-CoV-2 infects species with high ACE2 homology. Cats, ferrets, golden hamsters, tree shrews, common marmosets, grivets, and cynomolgus and rhesus macaques have been infected with SARS-CoV-2 experimentally, shed the virus, and displayed similar or milder clinical and pathological signs as humans, although cats may not show signs of disease (82–91). Conversely, dogs have low susceptibility to SARS-CoV-2, and show lack of clinical signs or dog-to-dog transmission, possibly due to their low levels of ACE2 in the respiratory tract (82, 91–93). Yet, cat-to-cat, ferret-to-ferret, hamster-to-hamster, and bat-to-bat transmission of SARS-CoV-2 have been confirmed experimentally (82, 90, 91, 94). However, mice, swine, and poultry are not susceptible to SARS-CoV-2 infection (49, 71, 82).

Accumulating evidence supports naturally occurring human-to-cat SARS-CoV-2 transmission, such as multiple reports worldwide of SARS-CoV-2-positive cats from confirmed or suspected SARS-CoV-2-positive owners (95). Natural human-to-dog transmission may be possible, as was confirmed by seroconversion and SARS-CoV-2 presence in two out of 15 dogs in close contact with COVID-19 patients, where the viral sequences from each dog-and-owner pair were identical (92). Serological and virological surveys, conducted several months after the pandemic started, indicate that SARS-CoV-2 prevalence is much lower in pet and street cats and dogs than in humans, even if pet owners had suspected or confirmed SARS-CoV-2 infection (96–100). Thus, cats and dogs can get infected under natural conditions, but rarely. However, certain environments might amplify natural infections and cross-species transmission. Human-to-mink, mink-to-mink, and mink-to-human transmission of SARS-CoV-2 have occurred on fur farms in several countries (95, 101–104). SARS-CoV-2 has also been transmitted to tigers, lions, and gorillas in zoos, raising concern for wildlife conservation (105).

Apart from the mink farm outbreaks, evidence so far suggests limited SARS-CoV-2 maintenance in domestic mammals or risk for secondary zoonoses (104). However, the panzootic potential of SARS-CoV-2 necessitates expanding veterinary surveillance (104, 106), especially if domestic and/or wild animals were to maintain SARS-CoV-2 as the human population undergoes vaccination, making COVID-19 control more difficult.

EMERGING CORONAVIRUSES IN DOMESTIC MAMMALS

Since the advent of agriculture (∼8,000 BC), several spillover events have led to the emergence of novel pathogens in humans and domesticated animals (16). Genetic analyses place the common ancestor to all known coronaviruses at around 8,000 BC, and those of each genus at around 2,400–3,300 BC (10). Like humans, domestic mammals have been experiencing an increasing rate of novel coronavirus emergence, especially within the last century.

Bovine coronavirus (BCoV) likely emerged from rodent-CoVs around 1400 AD (17, 107). Bovine coronavirus is transmitted via the fecal–oral route, causing bloody diarrhea and respiratory infections in cattle (108–110). Bovine coronavirus-like viruses have also been detected in other domestic and wild ruminants (108). Bovine coronavirus can infect dogs experimentally, although subclinically (111). Turkeys show clinical signs of enteritis when infected with BCoV experimentally, but chickens are not susceptible (112). Equine-CoV, discovered in 1999, plausibly also descended from BCoV and causes enteritis in horses (113–115).

There are two dog coronaviruses: an *Alphacoronavirus* called canine enteric coronavirus (CCoV), transmitted fecal-orally, with serotypes CCoV-I and CCoV-II, and a *Betacoronavirus* called canine respiratory coronavirus (CRCoV), which causes kennel cough (116). Canine respiratory coronavirus was discovered in 2003 from a kennel outbreak (117). It was later also detected in samples from 1996 (118). It is closely related to BCoV and OC43, and genetic analyses suggest that CRCoV arose from a recent host-species shift of BCoV from bovine to canine hosts (117, 119).

Canine enteric coronavirus was first isolated from an outbreak in military dogs in 1971 (116). Initially, CCoV infections were believed to be restricted to the enteric tract causing mild diarrheal disease (120), but an increasing number of lethal pantropic infections suggests that CCoV is responsible for an emerging infectious disease in canines (116). There are three proposed subtypes of CCoV-II: original CCoV-IIa, recombinant CCoV-IIb, and CCoV-IIc (116). The two biotypes of CCoV-IIa have different tissue tropism and pathogenicity: "classical" CCoV-IIa is restricted to the small intestine causing enteritis, but the emerging "pantropic" CCoV-IIa causes leukopenia and is often fatal (116, 121). In 2019, an Asian pantropic CCoV-IIa strain was also isolated from a wolf in Italy (122), suggesting spillover to wildlife of imported strains (123). Cats and swine are also susceptible to CCoV (124–126).

There are six porcine coronaviruses: four *Alphacoronaviruses*, transmissible gastroenteritis virus (TGEV), porcine respiratory coronavirus (PRCoV), porcine epidemic diarrhea virus (PEDV), and swine acute diarrhea syndrome coronavirus (SADS-CoV), one *Betacoronavirus*, porcine haemagglutinating encephalomyelitis virus (PHEV), and one *Deltacoronavirus*, porcine deltacoronavirus (PDCoV) (127). Transmissible gastroenteritis virus, PEDV, SADS-CoV, and PDCoV cause severe enteritis that are fatal in piglets, PHEV causes digestive and/or neurological disease, and PRCoV causes mild respiratory disease (127).

Transmissible gastroenteritis virus, discovered in 1946 (128), likely emerged from CCoV-II (129), and its less virulent descendent PRCoV was identified in 1984 (130). Porcine haemagglutinating encephalomyelitis virus, first described in 1957, likely descended from BCoV (127). Porcine epidemic diarrhea virus emerged in the 1970s in Europe and Asia, likely from bat-CoVs, and was introduced in North America in 2013 after a new PEDV strain emerged in China in 2010 (131–134). A serological study indicates that PEDV subsequently spilled over from domestic to feral swine populations in the US (135). Porcine deltacoronavirus was first detected in swine samples from 2009 in Hong Kong (10, 132). In 2014, PDCoV caused the first-reported outbreaks in USA and South Korea (136, 137). It was proposed that the virus' ancestor originated from recombination between sparrow-CoV and bulbul-CoV (138). Porcine deltacoronavirus is most closely related to *Deltacoronaviruses* sampled from Asian leopard cats and ferret badgers in Guangdong and Guangxi markets (the first documented cases of *Deltacoronaviruses* in mammals) (139), suggesting that these species could have acted as intermediates for interspecies PDCoV spillover (140). In 2016, SADS outbreaks emerged in Guangdong with evidence strongly suggesting bat-to-swine spillover origin (141).

There is one coronavirus that primarily infects cats: feline coronavirus (FCoV). This *Alphacoronavirus* exists in two serotypes: FCoV-I and FCoV-II (142). Both cause digestive diseases and are transmitted fecal-orally. FCoV-I is the most common type, but less virulent than FCoV-II (143, 144). Comparative sequence studies indicate FCoV-I is genetically similar to CCoV-I, and FCoV-II emerged from recombination between FCoV-I and CCoV-II (121, 142, 145, 146). Conceivably, FCoV-I and CCoV-I evolved from a common ancestor, while CCoV-II and FCoV-II arose as more virulent recombinants (129). For each serotype, there are two biotypes with different pathogenicity: feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIPV). Feline enteric coronavirus usually causes mild diarrhea, whereas feline infectious peritonitis (FIP) is lethal. Feline infectious peritonitis virus evolves from FECV via within-host mutations in the S gene that alter cell tropism, and emerges during persistent infection of FECV (142, 147). However, a novel FIPV strain may have been transmitted horizontally (144). In 2004, a disease resembling FIP was also

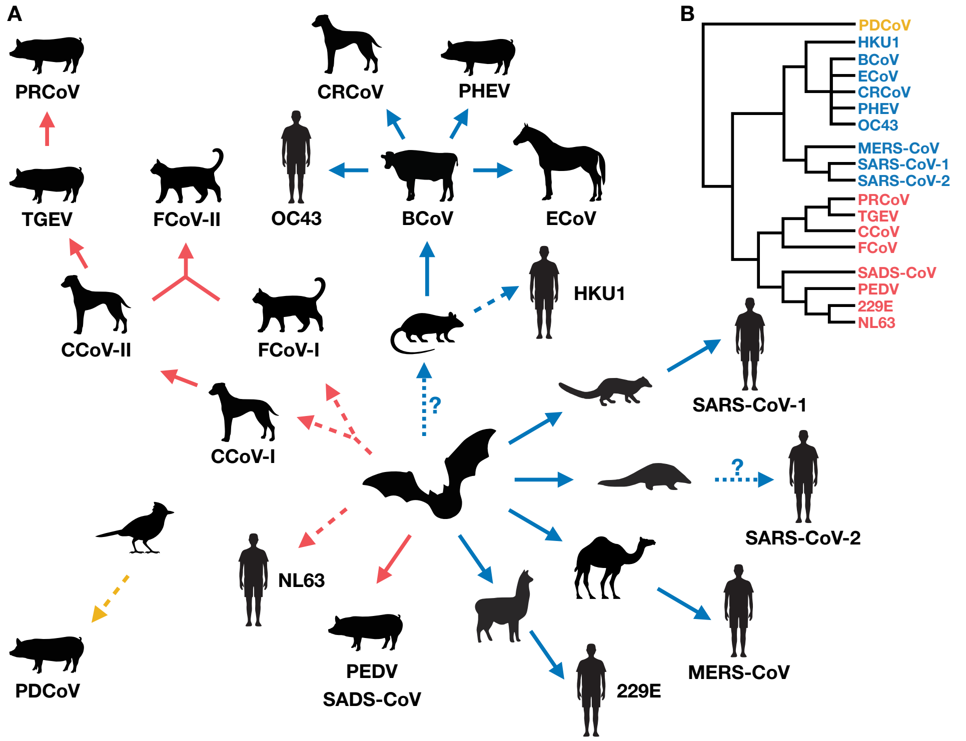

FIGURE 1 | (A) The evolution and radiation of coronaviruses in humans and domestic mammals (via potential wild intermediate spillover host species). The radiation suggests there could be a vicious cycle of coronavirus emergence, whereby newly emerged viruses in new hosts increase the likelihood of producing more new recombinants. Red, blue and yellow arrows indicate the direction of spillover of coronavirus emergence for *Alphacoronaviruses*, *Betacoronaviruses,* and *Deltacoronaviruses*, respectively. Solid arrows represent direct (confirmed or suspected) coronavirus transmission between host species (although indirect transmission via an unidentified intermediate host is not excluded), and dashed arrows represent suspected indirect transmission via an unidentified intermediate host (although direct transmission is not excluded) (10, 17, 104, 127, 139, 141, 156). Dotted arrows with a question mark indicate uncertain spillover events. **(B)** A simplified phylogeny of the coronaviruses covered in this review, drawn from published findings (5, 129, 157).

discovered in ferrets caused by an emerging ferret systemic coronavirus, a decade after the first and less virulent ferret coronavirus (enteric) was discovered (148). Feline infectious peritonitis likely emerged in the late 1950s, within a decade after the first TGE cases in swine in USA (128, 149). Thus, FCoV is closely related to TGEV and CCoV, and recombinants among all three have emerged (150–152), probably because all three can cross-infect cats, swine, and dogs (125, 151, 153–155).

DISCUSSION

Coronaviruses in humans and domestic animals are closely related (**Figure 1**), and have emerged recently and at an increasing rate. The circumstances associated with their emergence are high-animal-density environments that favor interspecies interactions, such as kennels, shelters, farms, and markets (**Table 1**), which increase disease prevalence and promote cross-species transmission. Indeed, studies show that seroprevalence of CCoV is higher in kennels compared to the rest of the dog population, and shelters co-housing dogs with cats harbor recombinant canine-feline coronaviruses (116, 151, 153, 159). Further, commercial agriculture has led to large numbers of domestic animals living in close proximity to humans, possibly driving the emergence of OC43 from cattle, and 229E and MERS from camelids.

Additionally, animals kept under poor conditions or exposed to stress (e.g., during transport) suffer from poor health and suppressed immune systems, rendering them more susceptible to infections (64, 160). For example, mink fur farms, where animals are usually kept in small, unhygienic enclosures, generated new strains of SARS-CoV-2 causing secondary zoonoses (95, 101–103). The wildlife trade and wet markets are conducive to disease emergence as well, since animals are transported and kept in small, unhygienic cages next to many different animal species (160). Indeed, a study showed that civets in markets were disproportionately positive for SARS-CoV-1 compared to civets on the supplying farms (30). Further, SARS-CoV-1 isolates from a civet and a racoon dog at the same market, but from different regions of China, had an identical S-gene sequence, which differed from that of the other civet isolates, indicating the occurrence of cross-species transmission at the market (26). Accordingly, the concept of One Health is important for suppressing coronavirus emergence.

Little is still known about host ranges and cross-species transmissions of coronaviruses. Most studies on this topic

TABLE 1 | First reported outbreaks and probable host species involved in the cross-species transmission events of recently emerging coronaviruses (or new virulent strains of re-emerging coronaviruses) in humans and domestic mammals covered in this review.

Primary host	Emerging coronavirus (*or new virulent strain*)	Year and location of first reported cases	Intermediate spillover host or host of viral predecessor	Potential reservoir host	Environment associated with emergence	References
Human	SARS-CoV-1	2002 Guangdong, China	Masked palm civet (*Paguma larvata*)	Bat (*Rhinolophus* spp.)	Wet market	(1, 24–30, 156)
	MERS-CoV	2012 Saudi Arabia	Dromedary camel (*Camelus dromedarius*)	Bat (*Taphozous perforatus*, *Rhinopoma hardwickii* and *Pipistrellus kuhlii*)	Camel farm and market	(2, 3, 52–54, 64, 156)
	SARS-CoV-2	2019 Wuhan, China	Malayan pangolin (*Manis javanica*)?	Bat (*Rhinolophus* spp.)	Wildlife trade and/or wet market?	(72, 73, 75, 79)
Pig	Porcine epidemic diarrhea virus (PEDV)	1978 Belgium	Unknown	Bat (*Scotophilus kuhlii*)	Swine farm	(156)
	New virulent PEDV strain	2010 Southern China	Unknown	Bat (*Scotophilus kuhlii*)	Swine farm	(132)
	Porcine deltacoronavirus (PDCoV)	2009 Hong Kong	Asian leopard cat (*Prionailurus bengalensis*)? Ferret badger (*Melogale moschata*)?	Avian, sparrow and bulbul	Illegal live-animal market?	(132, 138–140)
	Swine acute diarrhea syndrome coronavirus (SADS-CoV)	2016 Guangdong, China	Unknown	Bat (*Rhinolophus* spp.)	Swine farm	(141, 156)
Dog	Canine respiratory coronavirus (CRCoV)	2003 United Kingdom	Cattle (BCoV)	Rodents? Bats?	Kennel	(10, 17, 106, 115, 116, 118)
	Canine enteric coronavirus (CCoV)	1971 Germany	Unknown	Bat (*Rhinolophus* spp.?)	Military dog kennel	(10, 115, 126, 156, 158)
	Pantropic CCoV-IIa	2005 Italy	Unknown	Bat (*Rhinolophus* spp.?)	Pet shop	(10, 115, 120, 126)
Cat	Feline coronavirus (FCoV)	1963 United States	FCoV-I: Unknown FCoV-II: Cat and/or dog (FCoV-I × CCoV-II)	Bat (*Rhinolophus* spp.?)	Shelters and catteries	(10, 127, 149)
	Horizontally-transmitted FIP FCoV-II	2011 Taiwan	Cat and/or dog (FCoV-I × CCoV-II)	Bat (*Rhinolophus* spp.?)	Shelter	(10, 127, 144)

The entry "Unknown" may either suggest that an intermediate spillover host exists but it has not been identified, or that it may not exist. Question marks represent uncertainty. FCoV-I × CCoV-II denotes recombination between FCoV-I and CCoV-II.

have been motivated by finding appropriate animal models for vaccine development, or identifying potential host species enabling viral persistence. However, future studies should expand their surveys beyond domestic, captive, or common laboratory animals for a fuller comprehension of coronavirus emergence and the extent of its radiation (**Figure 1A**). Surveillance efforts of coronaviruses in the wild are underway (e.g., PREDICT, Global Virome Genome) (161, 162), which are important for identifying new coronaviruses with zoonotic potential [reviewed in (163)], tracking spillover pathways, and potentially filling in the host range gaps of known coronaviruses in humans and domestic mammals.

Concurrently with the global expansion of humans and domestic mammals, various coronaviruses have emerged as a result of cross-species transmission among humans, and domestic and wild animals. Conceivably, the human and domestic mammal population increase yielded a large enough susceptible population to maintain coronavirus circulation, provided more opportunities for novel coronavirus emergence via spillover among different species, and brought humans and domestic animals in closer contact with wild reservoirs (164–166). The mechanisms governing the surge and radiation of these recently emerged coronaviruses require further investigation. Actions reducing people's dependency on domestic animals and animal products, while improving the health of the animals remaining in captivity, may mitigate coronavirus emergence.

AUTHOR CONTRIBUTIONS

NN performed the literature review and wrote the manuscript.

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Heterogeneity in the Effectiveness of Non-pharmaceutical Interventions During the First SARS-CoV2 Wave in the United States

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Background: Attempts to quantify effect sizes of non-pharmaceutical interventions (NPI) to control COVID-19 in the US have not accounted for heterogeneity in social or environmental factors that may influence NPI effectiveness. This study quantifies national and sub-national effect sizes of NPIs during the early months of the pandemic in the US.

Methods: Daily county-level COVID-19 cases and deaths during the first wave (January 2020 through phased removal of interventions) were obtained. County-level cases, doubling times, and death rates were compared to four increasingly restrictive NPI levels. Socio-demographic, climate and mobility factors were analyzed to explain and evaluate NPI heterogeneity, with mobility used to approximate NPI compliance. Analyses were conducted separately for the US and for each Census regions (Pacific, Mountain, east/West North Central, East/West South Central, South Atlantic, Middle Atlantic and New England). A stepped-wedge cluster-randomized trial analysis was used, leveraging the phased implementation of policies.

Results: Aggressive (level 4) NPIs were associated with slower COVID-19 propagation, particularly in high compliance counties. Longer duration of level 4 NPIs was associated with lower case rates (log beta −0.028, 95% CI −0.04 to −0.02) and longer doubling times (log beta 0.02, 95% CI 0.01–0.03). Effects varied by Census region, for example, level 4 effects on doubling time in Pacific states were opposite to those in Middle Atlantic and New England states. NPI heterogeneity can be explained by differential timing of policy initiation and by variable socio-demographic county characteristics that predict compliance, particularly poverty and racial/ethnic population. Climate exhibits relatively consistent relationships across Census regions, for example, higher minimum temperature and specific humidity were associated with lower doubling times and higher death rates for this period of analysis in South Central, South Atlantic, Middle Atlantic, and New England states.

Conclusion and Relevance: Heterogeneity exists in both the effectiveness of NPIs across US Census regions and policy compliance. This county-level variability indicates that control strategies are best designed at community-levels where policies can be tuned based on knowledge of local disparities and compliance with public health ordinances.

Keywords: SARS-CoV-2, non-pharmaceutical intervention (NPI), doubling time, mortality rate, United States

INTRODUCTION

During the first COVID-19 wave (15th January to 31th May 2020), the disease spread rapidly across the globe, infecting over 3 million people with the SARS-CoV-2 virus. One-third of all reported cases and one-quarter of all deaths were in the United States. Public health interventions to reduce the spread of COVID-19 in the US varied in timing and level of aggressive measures undertaken. No official US policy existed to prevent COVID-19 transmission until January 31, 2020, when a presidential order blocked the entry of non-US citizens into the US traveling from China. The state of Washington declared the first State of Emergency (February 29), followed by California (March 4) and Maryland (March 5); however, many counties implemented restrictive policies prior to state action. For example, three counties in Washington (King, Pierce, Snohomish) and four in Arkansas (Grant, Jefferson, Pulaski, Saline) ordered school closings on March 12 vs. statewide closures on March 17; counties in Pennsylvania, California, and New Jersey closed non-essential businesses prior to the state; and counties in California and Idaho issued restrictions on mass gatherings before state policies.

Early action by counties was motivated by both the ability to legislate response and the multifaceted issues that impact disease risk at local levels. Such issues include racial disparities, with a disproportionate number of Black and Hispanic Americans reported to be infected or dying (1–3), urban vs. rural characteristics that influence transmission and policy implementation (4), and disease spillover from neighboring counties, which can be exacerbated by economic disparities and shared environmental risks (5). There is growing consensus that SARS-CoV-2 is an airborne pathogen, spread primarily through respiratory aerosols (6–8) that can be influenced by both micro- and macro-environments. Much work has focused on indoor micro-environments to help understand superspreading events, such as in restaurants, call centers, and large social gatherings (9–11). The relationship between COVID-19 transmission and macro-environmental factors is more difficult, with early work evaluating relative humidity (RH), temperature, and UV exposure; however, findings have varied with some studies finding no effect (12), inverse relationships (13), or mixed effects (14, 15). Elevated humidity has been associated with an increase in organic aerosols and higher levels of small particulate air pollutants (PM2.5, PM10, and O_3) (16, 17), which have been correlated with transmission (18, 19); however, the simultaneous use of RH and temperature in models of viral respiratory illness is not recommended due to their direct functional relationship (20).

Among other factors, the absence of vaccines during the COVID-19's first wave resulted in the application of non-pharmaceutical interventions (NPI, also known as community mitigation strategies) to control COVID-19. Unfortunately, without a randomized trial to quantify the effect size of NPIs or the potential causes of heterogeneity across different regions of the US, policymakers relied on modeling studies and early evidence from Asia to guide decisions. These included susceptible-exposed-infectious-recovered (SEIR) models attempting to quantify the effects of isolation and contact tracing (21) and how varying NPI effectiveness may influence demands on critical care resources (22); and studies in Wuhan and Hong Kong reporting how strict interventions (i.e., quarantine, social distancing, shelter in place and active case detection) reduced the COVID-19 reproductive number (R_0) (23, 24). Over the past year, several studies have attempted to quantify NPI effects, with a recent meta-analysis summarizing studies from around the world that quantified how various strategies helped contain COVID incidence (25). In the US, the majority of studies trying to quantify NPI effects have focused on the state-level (i.e., state-level policies impacting state-level cases and deaths) (26–29). For example, White and Hebert-Dufresne (27) analyzed five state-level policy effects, finding that only restaurant restrictions significantly correlated with higher doubling times; Chernozhukov et al. (26) study four state policies using a structural equation modeling approach, showing important effects of masking, business closures, and stay-at-home orders on both cases and deaths; and Auger (28) studied the effect of statewide school closures on COVID-19 cases and deaths using a negative binomial interrupted time series analysis, finding a 62% decline in cases and 58% decline in mortality following school closure. However, these studies ignore county-level heterogeneity and restrict their analyses to a specific set of policies without considering the joint effect of two policies implemented simultaneously. Aggregating county-level data ignores important social determinants as well as the reliance on county governments by states to make essential decisions regarding policy implementation and enforcement that explain variations in NPI effectiveness (29, 30). The most comprehensive county-level analysis to date in the US was conducted by Ebrahim et al. (30), who found both widespread county-level variation in policies and identified business closures as having the most important effect on COVID-19 cases; however, this study was limited to just one-third of US counties and relied on the estimation of R0 rather than using reported cases.

The goal of this study is to evaluate national and sub-national effects of the four levels of NPIs using county-level data on policies, cases and socio-environmental factors during the first wave in the US until implementation to Phase 1 reopening (lifting of policies), if specified, otherwise to May 29. We leverage the phased implementation of policies at the county level, using a stepped-wedge cluster-randomized trial (SW-CRT) framework (31). We quantify NPI effects on COVID-19 daily case incidence, doubling time, and reported deaths across nine US Census regions.

METHODS

Outcome Data

Multiple data sources were used to confirm county-level daily cases and deaths from SARS-CoV2 infection. Data from the Johns Hopkins University Center for System Science and Engineering Coronavirus Resource Center (JHU-CSSE, https://coronavirus.jhu.edu/) were compared to county data reported on state health department's websites, using the state data when discrepancies were noted (i.e., counties from 34 states using the JHU-CSSE data were discrepant with state-reported county data). In addition, any county whose cumulative cases or deaths declined over time was flagged and adjusted using state- or county data. The final data are counties from all 50 US states and the District of Columbia extending from January 22 through May 29, 2020. US territories (American Samoa, Guam, the Northern Mariana Islands, Puerto Rico, and the U.S. Virgin Islands) were excluded.

Policy Data

The effective date of each public health intervention and the phased reopening at the state and county levels was initially extracted from online policy databases (32–36). For discrepancies or missing county policies, we obtained policy dates in two steps: (1) searching the county's state government website for reported county policies; and (2) if state websites did not report county policies or if the county reported at least one COVID-19 case prior to the issuance of any state order, we conducted a systematic search of gray literature for each county's policies, focusing on county websites (if existent) and local news websites. We categorized 12 policies into 4 levels of disease control following the New Zealand alert system and Oxford classification (37, 38): Level 1 (low)—governor declaration of a State of Emergency; Level 2 (moderate)—school closures, restricting access (visits) to nursing homes, or closing restaurants and bars; Level 3 (high) – non-essential business closures, suspending non-violent arrests, suspending elective medical procedures, suspending evictions, or restricting mass gatherings of at least 10 people; and Level 4 (aggressive)—sheltering in place / stay-at-home, public mask requirements, or travel restrictions. These levels are mostly cumulative, meaning counties tended to implement policies sequentially and jointly, for example, 67% of counties implemented almost all level 3 policies at the same time, while 23% implemented them within 7 days of their initial level 3 policy. Note that our initial analysis found no effect of the two federal policies blocking entry to the US for non-US citizens (i.e., from China issued January 31 and from Schengen European countries issued March 11) on COVID-19 morbidity or mortality propagation; thus, we classified them as the "non-intervention" period. Finally, NPI effects were measured up to 5 days after county reopening, defined as opening non-essential businesses (with capacity restrictions), allowing public gatherings of more than 10 people, opening public spaces, or easing shelter in place orders. All but 12 states entered some phase of reopening by May 29 and six states allowed counties to open at their discretion (CA, IA, MD, NE, OR, WY).

Policy compliance was measured by comparing the number of trips recorded in each county from 2020 to 2019 based on data from the Maryland Transportation Institute and Center for Advanced Transportation Technology (https://data.bts.gov/Research-and-Statistics/Trips-by-Distance/w96p-f2qv). Several studies have demonstrated the utility of mobility data as proxy measures of policy compliance (30, 39–41). Using results from Nouvellet et al. (42), we defined gradients of mobility decline associated with reductions in R0. A four-level variable for compliance was created, where non-compliance (level 0) was defined as a mobility difference from 2019 to 2020 of $<15\%$, low compliance (level 1) as a decline in mobility of 15–30%, moderate compliance (level 2) as a decline of 30–50% and high compliance (level 3) as mobility declines $>50\%$. We then summed the time-lagged 10-day compliance and divided by maximum compliance (30) to create a scaled measure, from 0 to 10, representing the average level of policy compliance over the past 10 days. A value closer to 10 indicates high compliance (low mobility compared to 2019), while values closer to zero indicate lower compliance (more mobility). We expect to see values close to zero prior to the initiation of polices and as policies were removed.

Demographic and Environmental Data

Demographic data are from the US Census Bureau. This includes county-level age, sex and racial composition, migration, and educational data from the 2018 American Community Survey (43), land area to compute population density (1,000 people per square-km) (44), and poverty (45). Analyses were stratified by the nine US Census regions (Pacific, Mountain, West North Central, East North Central, West South Central, East South Central, South Atlantic, Middle Atlantic, New England) to evaluate differential policy effects.

We use the USDA Rural-Urban Continuum Code that categorizes counties into nine levels of rural-urban characteristics (46). Three levels indicate metropolitan areas of (1) 1 million or more people, (2) 250,000 to 1 million people, and (3) fewer than 250,000 people. Four urban levels classified by size and adjacency to a metropolitan area: (4) 20,000 or more people adjacent; (5) 20,000 or more, not adjacent; (6) 2,500 to 19,999, adjacent; and (7) 2,500 to 19,999, not adjacent. And two rural levels: (8) $<2,500$ population, adjacent to a metropolitan area; and (9) $<2,500$ population, not adjacent.

Environmental data are from the North American Land Data Assimilation System (NLDAS). The NLDAS provides several daily hydrometeorological measures, for which we define 10-day temporal lags of minimum air temperature (Celsius), specific humidity (g/kg) and bias-corrected shortwave radiation (W/m^2).

Statistical Methods

Outcomes were defined at the county level as the number of new daily cases, new deaths, and case doubling time. Doubling time is the number of days required to double the cumulative case count on a particular day. Policy levels were time-varying, coded as a 1 while a level was active and 0 otherwise, and as the number of days since an intervention level was initiated.

Descriptive differences in policy implementation were examined using Chi-square and *t*-tests. To evaluate intervention levels and socio-environmental factors, negative binomial mixed models were fit using an approach similar to a Hussey and Hughes SW-CRT analysis (47). The model is specified as follows:

$$\ln\left(y_{it}\right) = \ln\left(N_i\right) + x_0\beta_0 + x_1\beta_1 + \ldots x_p\beta_p + u_i$$

Where y_{it} is the outcome (cases, deaths, doubling time) for county i on study day t; $\ln(N_i)$ is the offset where N_i is the population density for county i; parameters $x_p\beta_p$ represent the fixed predictors (x_p) and their associated parameters; and u_i is the random county effect. For the new cases and death models, we use population density as the offest, but no offset is included for doubling time. In addition, for case and death models, period (study day) is included as a continuous variable while the doubling time model uses period as a categorical variable (similar to the SW-CRT modeling approach). When entered as a continuous variable, we evaluated inclusion of linear and quadratic period terms. Each outcome was fit for the country as a whole and separately for each US Census region, combining East and West North Central states, East and West South Central states, and Middle Atlantic and New England states. Finally, to test policy effects, we evaluate the time-varying policy variables, i.e., duration of intervention, which are entered into case and doubling time models simultaneously, but as individual time-varying policy effects in death rate models (i.e. comparing policy 2 vs. 1 or nothing, policy 3 vs. 0–2, etc.). Since there are four policies, we use the Holm-Bonferroni multiple comparisons correction to evaluate significance (48).

Case and doubling time models were identified using one randomly selected census region and then evaluating model fit using AIC (49). Variables considered include: rural-urban continuum code; minority (Black and Hispanic) and total population density; net county migration rate in 2018; percent of the 2018 county population Black (alone or mixed race), Hispanic (alone or mixed race), living in poverty, or with a college education or higher; and climate parameters (10-day lags for minimum temperature, specific humidity, and UV radiation). Once a final model was determined, it was used to fit to all regions combined (adding an indicator for census region) and for each individual census region. Final models are shown in the full regression tables (**Supplementary Table B0** for the country as a whole; **Supplementary Tables B1, C1, D1** for COVID-19 models of cases, doubling time, and deaths by Census region, respectively). Climate variables were evaluated only using doubling time and death outcomes. Final models were fit using SAS 9.4 with Gaussian adaptive quadrature.

Secondary to our evaluation of policy effects, we use the above models to describe social and environmental disparities observed across Census regions. In addition, we conduct an analysis on factors associated with policy compliance by comparing change in county compliance during the first 15 and 30 days of March to socioeconomic and environmental characteristics. Therefore, since we define compliance as a 10-day lagged sum of compliance, we fit two models to estimate factors associated with compliance change from March 1 to 15 (i.e., change compliance from April 21-March 1 to March 5–15) and change from March 1 to 30. The compliance model includes random county effects within states and estimates both standardized and non-standardized beta coefficients. Standardized Beta coefficients only standardize predictor variables, not the response; therefore, the interpretation of the standardized beta is a one standard deviation unit change in a covariate being associated with a change in compliance. We note that on March 1, 98.8% of counties did not have any COVID policies; by March 15, 50.9% had enacted at least policy level 2; and by March 30, 98.9% of counties established policy level 3 or 4.

RESULTS

We obtained complete data from 3,142 counties. 339 counties (10.8%) from 26 states created policies prior to their state government, the majority (211 or 62%) were located in Texas, Nebraska, Missouri, and Pennsylvania. Counties initiating policies prior to the state were more likely to be located in metropolitan areas (17.5% metro counties vs. 6.8% non-metro countries adopted early policies, $p < 0.001$), have populations with higher educational levels, higher percentages of Hispanic population, and fewer people living in poverty (respectively, counties with early policy adoption had 26.3, 15.9, and 13.8% of their populations with a college degree, Hispanic descent [mixed or alone], and living in poverty, vs. 21.0, 8.5, and 15.3% for countries that did not adopt early policies, $p < 0.001$).

Speed of policy adoption varied, with fewer days spanning initial case detection and initiation of NPIs in counties located in North and South Central states, while counties in New England, Middle Atlantic, and Pacific states had more days between initial case detection and policy initiation (**Figure 1**). However, in these later three regions, the first COVID-19 case was detected an average of 10 days prior to North and South Central states. Counties in these three regions (Pacific, Middle Atlantic and New England) had the longest duration of level 1 policies, but the shortest duration of time from initial case detection to the most strict (level 4) policies (**Table 1**). County and state governments in New England and Mountain states were more likely to initiate policies before the first reported COVID-19 death compared to other regions (data not shown). Once initiated, policy duration averaged 5.7, 3.6, 11.9, and 44.3 days for levels 1–4, respectively, with significant variation by state and some states having zero days for any particular level (**Supplementary Table A1**, **Table 1**).

Compliance with policies was highly variable. As expected, prior to the initiation of most policies (January and February 2020), compliance measures were low (i.e., no policies to follow). Most states and counties initiated strict policies in March 2020, which is reflected by the sharp increase in compliance in most regions during this month (**Figure 2**).

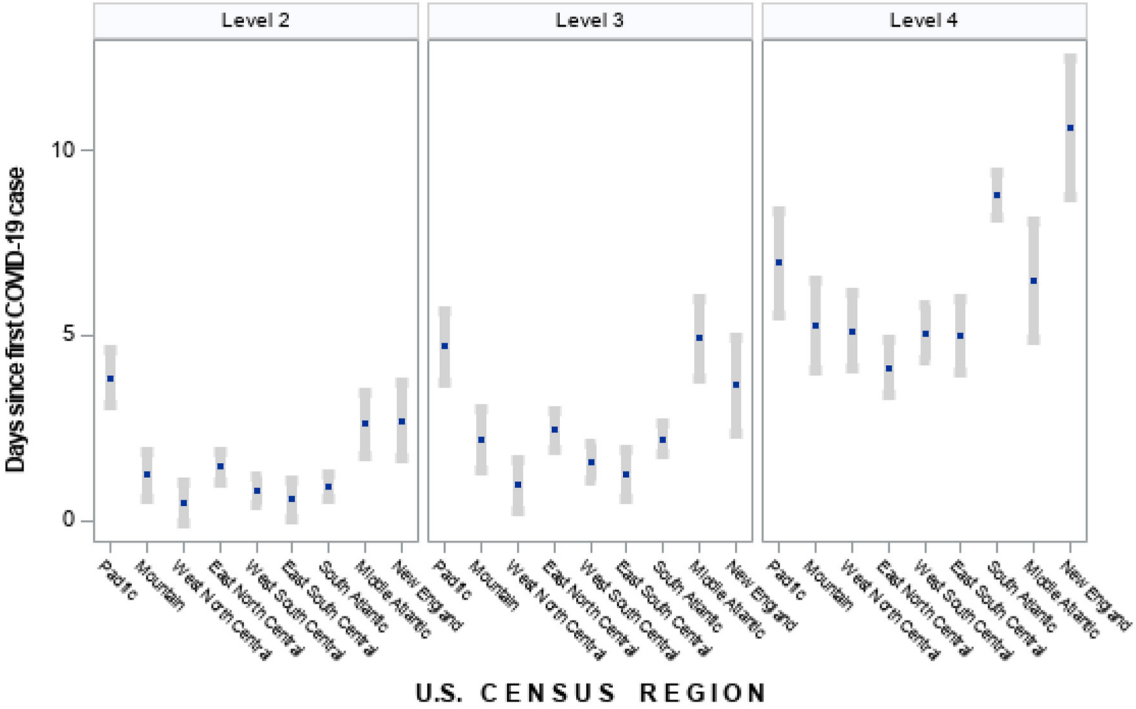

FIGURE 1 | Time between first COVID-19 case to policy initiation by US census region (mean days and 95% confidence interval). Policies classified under each level of intervention: Level 2—school closures, restricting access to nursing homes, closing restaurants and bars; Level 3—non-essential business closures, suspending non-violent arrests, suspending elective medical procedures, suspending evictions, restricting mass gatherings of at least 10 people; Level 4—sheltering in place/stay-at-home, mask requirements in public, travel restrictions. States classified for each region are as follows: Pacific—CA, WA, OR, HI, AK; Mountain—MT, WY, ID, NV, UT, CO, AZ, NM; West North Central—ND, SD, NE, KS, MN, IA, MO; East North Central—WI, IL, MI, IN, OH; West South Central—TX, OK, AR, LA; East South Central—KY, TN, MS, AL; South Atlantic—FL, GA, SC, NC, VA, WV, DC, MD, DE; Middle Atlantic—NY, PA, NJ; New England—ME, CT, NH, MA, CT, RI.

TABLE 1 | Median policy duration by US census region.

Census region	Level 1 Median (IQR)	Level 2 Median (IQR)	Level 3 Median (IQR)	Level 4 Median (IQR)
Pacific	11 (8–13)	2 (1–3)	3 (0–6)	33 (14–52)
Mountain	4 (4–5)	4 (1–4)	6 (0–8)	30 (11–48)
North Central	6 (5–7)	4 (2–4)	8 (4–14)	23 (0–45)
South Central	6 (4–6)	2 (1–5)	9 (5–13)	31 (14–47)
South Atlantic	5 (4–6)	4 (1–8)	10 (6–15)	27 (10–44)
Middle Atlantic & New England	9 (5–10)	3 (1–4)	2 (0–5)	34 (15–52)

In Middle Atlantic and New England States, there was high, homogenous compliance with few counties reporting moderate changes to mobility; however, counties in Mountain, West North Central, East South Central and South Atlantic exhibited high heterogeneity in compliance. Even within states, considerable heterogeneity was observed; for example, four states did not have any counties implement level 4 policies: Iowa, Nebraska, North Dakota and South Dakota. Among these four, policy compliance increased rapidly, but only counties in Iowa maintained high and relatively homogenous policy compliance across the state (**Supplementary Table A1**, **Supplementary Figure A1**). Similarly, four states had over 70 days with a level 4 policy (California, Hawaii, Illinois, New Jersey) with three experiencing high, homogenous compliance across the state and one (Illinois) having increasing heterogeneity in compliance over time (**Supplementary Figure A1**).

Policy Effects on COVID-19 Propagation and Mortality

Case Rates

Model results for the country as a whole indicate that, under conditions of high policy compliance (scaled value of 8), intervention level 4 achieved a 50% reduction in COVID-19

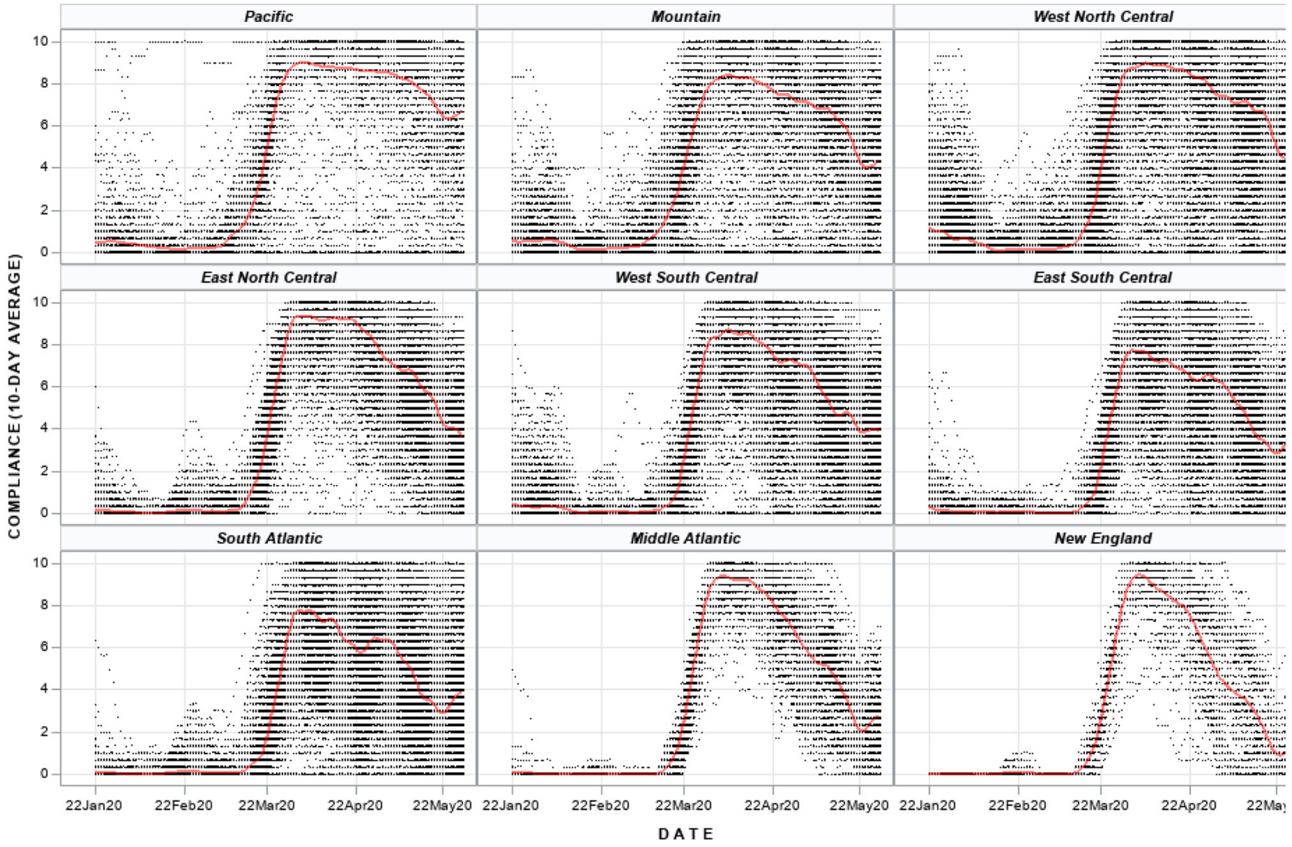

FIGURE 2 | Compliance with policy interventions for US counties by census region. Each dot represents a county in the US and each county has a daily time series of compliance. The red line is a fitted penalized b-spline. US Census Regions: Pacific—CA, WA, OR, HI, AK; Mountain—MT, WY, ID, NV, UT, CO, AZ, NM; West North Central—ND, SD, NE, KS, MN, IA, MO; East North Central—WI, IL, MI, IN, OH; West South Central—TX, OK, AR, LA; East South Central—KY, TN, MS, AL; South Atlantic—FL, GA, SC, NC, VA, WV, DC, MD, DE; Middle Atlantic—NY, PA, NJ; New England—ME, CT, NH, MA, CT, RI.

case rates in 16 days (95% CI for 16-day case reduction: 40.2–61.8%), compared to 22 days for intervention level 3 (95% CI: 35.1–71.5%, **Figure 3**, **Table 2**). Intervention levels 1 and 2 never achieve significant reductions in case rates; in fact, longer duration of level 1 policies was positively associated with cases. Under conditions of low compliance (scaled value of zero), only duration of level 4 policies achieved a significant decline, while level 1 policies were inversely associated with COVID-19 cases. The time needed for level 4 policies to achieve a 50% decline increased to 20 days under these conditions.

Policy effects were variable across US Census regions (**Table 3**). For an average level of policy compliance (scaled value of 6), intervention level 4 was significantly associated with declines in COVID-19 case rates in Pacific and Mountain regions, yet did not achieve significance in other regions (**Table 3**, **Supplementary Figure B1**, **Supplementary Table B1**). Further, intervention level 3 was associated with a reduction in cases in the Pacific region, but an increase in cases in North Central States. Intervention level 1 was the only intervention not associated with any changes to COVID-19 rates across all US Census regions.

As noted, policy compliance impacted policy effectiveness at national and Census region levels. Each unit increase in compliance was associated with a log beta decline in case rates of 0.002 and 0.001 for policy level 3 and 4, respectively (95% CI, −0.0024 to −0.0016; −0.0012 to −0.0008 respectively) at the national level. Compliance during level 4 policies was significantly associated with reduced case rates across all US Census regions (**Supplementary Table B1**).

Doubling Time

For the country as a whole, only duration of policy level 4 achieved statistical significance to increase doubling time (**Table 2**). Levels 2 and 3 had p-values under 0.05, but after adjusting for multiple comparisons, we cannot reject the null hypothesis of no effect; however, it is noteworthy their effect sizes were positive, indicating that the level 2 and 3 policies trended toward reduction of overall COVID-19 propagation. Each day on intervention level 4 was associated with an increase in log beta doubling time of 0.02 (95% CI: 0.01–0.03, $p < 0.0001$). When calculating the predicted doubling time from the data, level 4 policies achieve a peak 40 days after initiation with an estimated doubling time of 24 days (95% CI, 19.1–29.5) compared to 23 days after initiation of level 3 policies for an estimated doubling

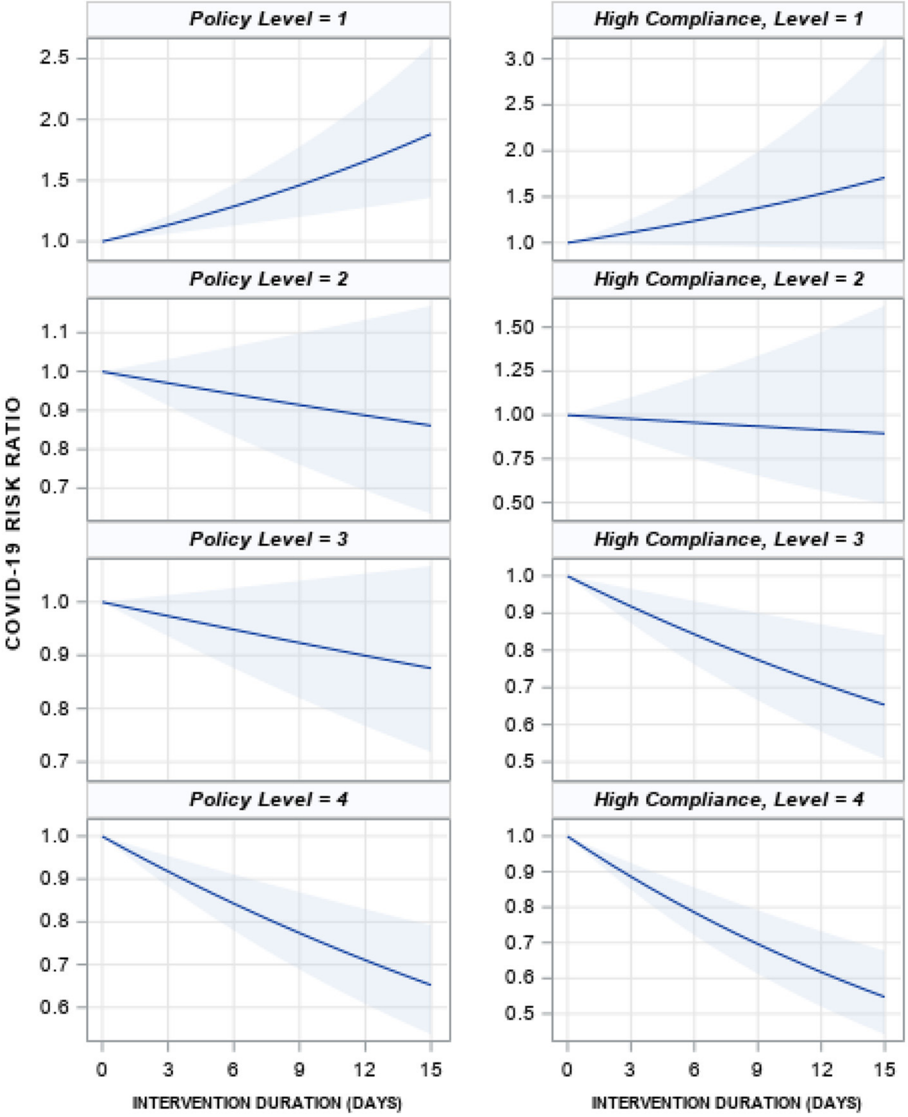

FIGURE 3 | Mean effect of each policy level on the COVID-19 case rate if the policy was implemented for 15 days, low and high compliance. The solid blue line is the mean effect size for each intervention with 95% confidence intervals (shaded blue). A value of 1 represents no change, 1.5 is a 50% increase in cases and 0.5 is a 50% decrease. The left column is for low compliance (no change in behavior in 2020 compared to 2019, scaled value 0) and the right is for high compliance (scaled value 8). Effect sizes are from negative binomial models reported in **Supplementary Table B0**.

time of 17.6 days (95% CI, 14.5–22.3) (**Figure 4**). Levels 1 and 2 never achieve increased doubling times.

By US Census region, duration of level 4 policies in Pacific, Mountain and North Central states have a positive effect on doubling time, but in other regions, duration of level 4 policies reduced doubling time (**Table 3**, **Supplementary Table C2**). In addition, level 3 policy duration was significantly related to longer doubling times in Pacific and Mountain states, but shorter doubling times in Middle Atlantic and New England states. Level 1 policy duration was significantly associated with shorter doubling times in South Central, South Atlantic, Middle Atlantic and New England states, and longer doubling times in Pacific and North Central states.

Policy compliance was an important factor to explain doubling time. At the national level, higher policy compliance increased doubling time (log beta 0.036, 95% CI 0.03–0.04), yet higher compliance during policies 1 through 3 reduced doubling time. In other words, both policy level 3 and compliance increase doubling times; however, as compliance increases, the effect of policy level 3 declines. By Census region, the effect of compliance varied, increasing doubling time in North Central and South Atlantic states, but reducing doubling times in others.

Deaths

This analysis includes data from 73,676 COVID-19 deaths, the majority in Middle Atlantic (36%), East North Central (19%),

TABLE 2 | Model predicted policy effects on case rates, doubling time, and death rates for all US counties.

	Case rates		Doubling time		Death rates	
	Log beta	**(95% CI)**	**Log beta**	**(95% CI)**	**Log beta**	**(95% CI)**
Fixed intervention effect						
Level 1	0.768	(0.56–0.97)†††	0.059	(−0.03–0.15)	2.371	(1.18–3.57)††
Level 2	1.373	(1.14–1.6)†††	0.082	(−0.03–0.19)	2.999	(1.8–4.2)†††
Level 3	1.516	(1.28–1.75)†††	0.072	(−0.04–0.19)	3.187	(2–4.38)†††
Level 4	1.707	(1.47–1.94)†††	0.143	(0.03–0.26)†	3.539	(2.35–4.72)†††
Duration of intervention effect						
Level 1	0.03	(0.01–0.05)††	0.004	(−0.01–0.01)	−0.018	(−0.05–0.01)
Level 2	−0.018	(−0.04–0)	0.012	(0–0.02)†	0.028	(0–0.05)†
Level 3	−0.012	(−0.02–0)	0.011	(0–0.02)†	0.062	(0.04–0.08)†††
Level 4	−0.032	(−0.04–0.02)†††	0.020	(0.01–0.03)†††	0.056	(0.04–0.07)†††

$^{\dagger\dagger\dagger}p < 0.0001$, $^{\dagger\dagger}p < 0.01$, $^{\dagger}p < 0.05$.

*The log beta values represent the log change in the outcome when an intervention policy is in place or the change for the number of days the policy is in effect. Results are from three negative binomial models using all counties from the US (**Supplementary Table B0**). Case and Doubling Time Models included the same covariates, except for the addition of population density in the Doubling Time Model. The model for Death Rates was reduced to ease model fit.*

New England (15%), South Atlantic (11%), and Pacific (7%) states. For the country as a whole, duration of policy levels 3 and 4 were both significantly associated with higher death rates (**Table 2**); however, the distribution of deaths indicate potential heterogeneity. Indeed, model results by Census region indicate duration of levels 1 and 2 had no effect on death rates for any Census region (**Supplementary Table D1**); level 3 policy duration was significantly related to lower COVID-19 death rates in North Central states, yet higher death rates in South Central, South Atlantic, Middle Atlantic, and New England states; and duration of level 4 was only related to lower death rates in Pacific states (other regions with *p*-values under 0.05 were not significant after the Holm-Bonferroni adjustment). We note that models for death rates had to be simplified with fewer covariates to allow for model convergence.

The effect of policy duration on death rates is sensitive to measures of compliance. This is particularly true for level 3 policies as seen in **Figure 5**, where high levels of compliance resulted in significantly lower death rates that low levels of compliance in North Central, South Central, and South Atlantic states. Policy compliance did not influence the effectiveness of other policies.

Social and Environmental Disparities

As noted in Methods, we conducted a secondary evaluation of social and environmental factors associated with COVID-19 cases and deaths, as well as factors related to policy compliance. These variables include county-level measures of: poverty, unemployment and income; average level of educational attainment; socio-demographic characteristics (population density, minority population, %Black, %Hispanic); and hydro-meteorological characteristics. Model results related to policy compliance are reported in **Table 4**.

Poverty

Poverty and income data used in this study are from the US Census Bureau's Small Area Income and Poverty Estimate (SAIPE). At the national level, as expected, higher levels of poverty are associated with shorter doubling times and higher death rates, yet, counterintuitively, lower case rates. When evaluating poverty effects by Census region, poverty was not associated with doubling times in any region, but was positively associated with case rates in Mountain states and inversely related to cases in all other regions. In contrast, elevated poverty was consistently associated with elevated COVID-19 death rates in all regions. Although poverty was not associated with 15-day change in compliance, a county's poverty level was the most important factor explaining low compliance with any policy after 30 days.

Education

Education data are 5-year averages estimated by the American Community Survey. At the national level, the percent of the county with at least a Bachelor's degree was not associated with case rates, but was associated with increased doubling times. By Census region, higher education was consistently associated with increased doubling time, yet variability existed when analyzing case rates with education associated with higher case rates in Mountain, Middle Atlantic, and New England states, but lower cases in South Central states. Higher education was also consistently associated with increased policy compliance, for both the 15 and 30 day changes in compliance.

Socio-Demographic

Social and demographic data are county racial, ethnic and total population characteristics: %Black, %Hispanic, population density, and the USDA Urban-Rural Classification. None of these factors were identified as related to death rates and population density was not evaluated in case rate models as population size is used as an offset in the model. At the national level, %Black and %Hispanic populations were associated with elevated case

TABLE 3 | Multivariate model results* for case incidence and doubling time by US census region.

		Pacific states.		Mountain states		North central states		South central states		South Atlantic states		Middle Atlantic & New England	
		Log beta	**(95% CI)**	**Log beta**	**(95% CI)**	**Log beta**	**(95% CI)**	**Log beta**	**(95% CI)**	**Log beta**	**(95% CI)**	**Log beta**	**(95% CI)**
Case incidence model results	10-Day compliance	0.328	(0.24–0.42)†††	0.222	(0.15–0.29) †††	−0.039	(−0.09–0.01)	0.08	(0.02–0.14)†	0.25	(0.19–0.31)†††	0.332	(0.23–0.43)†††
	Duration of intervention (days)												
	Level 1	0.016	(−0.03–0.06)	0.1	(0.02–0.18)†	0.013	(−0.04–0.07)	0.033	(−0.03–0.1)	0.047	(−0.01–0.1)	0.076	(0.03–0.12)††
	Level 2	−0.095	(−0.2–0.01)	−0.2	(−0.27–0.13)†††	−0.021	(−0.07–0.02)	−0.077	(−0.13–0.02)††	0.061	(0.02–0.1)††	0.16	(0.09–0.23)†††
	Level 3	−0.103	(−0.21–0.005)	−0.037	(−0.09–0.0143)	0.049	(0.03–0.07)†††	0.015	(−0.02–0.05)	0.034	(−0.01–0.08)	0.035	(−0.03–0.1)
	Level 4	−0.147	(−0.18–0.11)†††	−0.047	(−0.1–0.004)	0.028	(0.01–0.05)†	0.01	(−0.02–0.04)	0.001	(−0.04–0.04)	0.037	(−0.02–0.09)
	10-day compliance* duration of intervention												
	Level 1	−0.002	(−0.01–0.004)	−0.008	(−0.02–0.002)	0.009	(0.002–0.016)††	−0.007	(−0.01–0.001)	−0.015	(−0.02–0.008)††	−0.01	(−0.02–0.001)†
	Level 2	−0.013	(−0.03–0.003)	0.007	(0–0.014)	0.013	(0.01–0.018)†††	0.012	(0.01–0.019)††	−0.014	(−0.02–0.008)†††	−0.016	(−0.03–0.007)††
	Level 3	−0.013	(−0.02–0.001)†	−0.004	(−0.01–0.002)†††	−0.002	(−0.003–0.001)†††	0.001	(−0.001–0.003)	−0.006	(−0.008–0.004)†††	−0.012	(−0.02–0.005)††
	Level 4	−0.002	(−0.003–0.001)†††	−0.003	(−0.004–0.002)†††	−0.001	(−0.001–0.001)†††	−0.002	(−0.002–0.002)†††	−0.001	(−0.001–0.001)††	−0.004	(−0.004–0.004)†††
Doubling time model results	10–day compliance	−0.072	(−0.119–0.024)††	−0.043	(−0.07–0.014)††	0.126	(0.105–0.147)†††	−0.012	(−0.034–0.009)	0.043	(0.025–0.062)†††	−0.101	(−0.142–0.06)†††
	Duration of intervention (days)												
	Level 1	0.077	(0.041–0.112)†††	0.001	(−0.045–0.048)	0.144	(0.112–0.177)†††	−0.083	(−0.116–0.049)†††	−0.058	(−0.085–0.032)†††	−0.029	(−0.057–0)†
	Level 2	0.265	(0.197–0.333)†††	−0.029	(−0.11–0.052)	0.022	(−0.007–0.052)	−0.105	(−0.133–0.077)†††	−0.021	(−0.042–0.001)	−0.085	(−0.172–0.003)
	Level 3	0.361	(0.279–0.444)†††	0.116	(0.035–0.197)††	−0.002	(−0.022–0.019)	−0.008	(−0.027–0.011)	0.013	(−0.008–0.034)	−0.208	(−0.297–0.119)†††
	Level 4	0.376	(0.305–0.447)†††	0.129	(0.048–0.21)††	0.014	(−0.006–0.035)	−0.027	(−0.044–0.009)††	−0.024	(−0.045–0.003)†	−0.128	(−0.216–0.04)††
	10-day compliance* duration of intervention												
	Level 1	0.003	(0.001–0.005)††	−0.004	(−0.008–0.001)†	−0.022	(−0.024–0.02)†††	0.002	(0–0.004)	0.004	(0.002–0.006)†††	−0.001	(−0.003–0.002)
	Level 2	0.008	(0.002–0.014)†	0.011	(0.007–0.02)†††	−0.005	(−0.007–0.003)†††	0.01	(0.008–0.012)†††	−0.004	(−0.005–0.002)†††	0	(−0.003–0.003)
	Level 3	0.011	(0.006–0.016)†††	0	(0–0.001)	0	(0–0)	−0.003	(−0.003–0.002)†††	−0.003	(−0.004–0.003)†††	0.008	(0.006–0.011)†††
	Level 4	0.002	(0.002–0.003)†††	0.001	(0.001–0.001)†††	0	(0–0)	0.001	(0.001–0.001)†††	0.0002	(0–0)†††	0.003	(0.003–0.003)†††

$^{\dagger\dagger\dagger}p < 0.0001$, $^{\dagger\dagger}p < 0.01$, $^{\dagger}p < 0.05$.

Results are from 2 separate sets of negative binomial models, six per set for each Census region. Estimates are log beta incidence rates where negative values indicate reductions in the outcome (i.e., lower case rates or lower doubling time) and positive values indicate increases in the outcome. The full multivariate models are shown in **Supplementary Table B1 for case incidence and **Supplementary Table C1** for doubling time.*

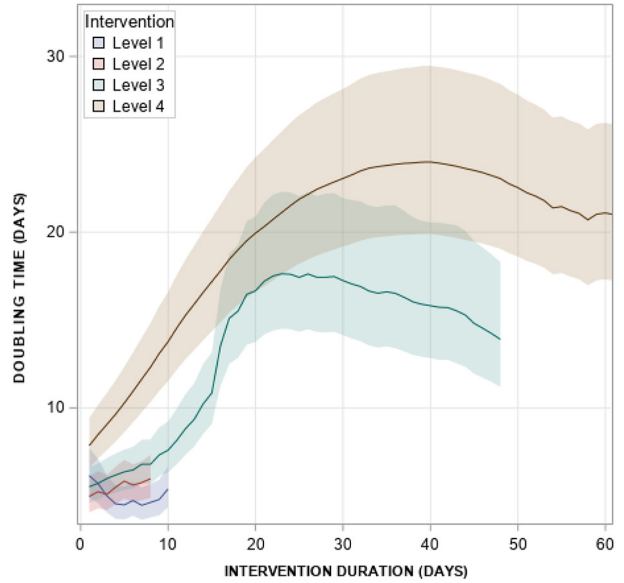

FIGURE 4 | Model-predicted doubling time by policy intervention level. Model predictions are from the final Doubling Time model shown in **Supplementary Table B0**.

rates, which was consistent across Census regions. Case rates were also consistently higher in metropolitan areas as well as non-metropolitan areas with more than 20,000 people compared to smaller counties (i.e., non-metro areas under 20,000 people and rural counties). By Census region, %Black and %Hispanic were both associated with elevated cases in North Central, South Atlantic, Middle Atlantic, and New England states. %Black was also associated with elevated cases in South Central states while %Hispanic was associated with elevated cases in Pacific states. Case rates by urban-rural classification varied considerably by Census region: Pacific and South Atlantic states had similar patterns with smaller counties having higher rates that larger counties; Middle Atlantic and New England states had the opposite patterns (large counties had higher rates compared to smaller counties); and the other Census regions had mixed patterns. Counties with the highest policy compliance levels tended to have larger %Hispanic, lower %Black populations, and be in counties with larger population sizes (i.e., non-metropolitan counties with >20 K people and larger).

Climate

Hydrometeorological data were used to define 10-day temporal lags of minimum air temperature, humidity, and shortwave radiation. The relationship between climate parameters and COVID-19 was variable, and these relationships often differed between case doubling time and deaths (**Supplementary Figures D1, D2**). Solar radiation, for example, which is frequently invoked as a negative forcing on COVID-19 transmission on account of its relationship with UV radiation intensity (50, 51), is associated with increased case doubling time (i.e., decreased transmission) in coastal regions but with decreased doubling time in the North Central and South Atlantic regions. For deaths, most northern census regions (Middle Atlantic, New England, North Central, Mountain) had tend toward decreased deaths with increased solar radiation, but southern regions had mixed relationships.

Increases in specific humidity and minimum temperature were associated with decreased doubling time and increased deaths for the county as a whole (specific humidity: log beta −0.006, 95% CI −0.009 to −0.003 for doubling time, 0.015, 95% CI 0.003–0.027 for deaths; minimum temperature: log beta −0.005, 95% CI −0.006 to −0.003 for doubling time, log beta 0.015, 95% CI 0.0075-0.0225 for deaths). In the South Central, South Atlantic and Middle Atlantic/New England Census regions, minimum temperature and specific humidity exhibited the same inverse relationship with doubling time (i.e., higher values, shorter doubling times) and positive relationship with death rates (higher values, higher death rates). Other regions had contrasting relationships. For example, specific humidity was significantly associated with lower doubling times in Pacific states, but higher doubling times in North Central; however, specific humidity had a (non-significant) downward trend with death rates in those two regions.

Regarding policy compliance, after 30 days, no climate factors were associated with compliance.

DISCUSSION

This study evaluates the effectiveness of four non-pharmaceutical intervention categories on COVID-19 case rates, doubling time, and deaths at the county level in the US, and the heterogeneity that exists across Census regions. We find that during the first wave of COVID-19, the most restrictive NPI policies (level 4) were the most effective at reducing case rates and increasing doubling time of COVID-19 compared to any other policy level. In addition, we observed that higher levels of policy compliance, as measured by changes in county-level mobility from 2019 to 2020, resulted in larger reductions in cases but lower increases in doubling time for these restrictive NPI. Analysis of NPI effectiveness across Census regions revealed strong variation across regions and within states. Level 4 policies were associated with reduced case incidence only in Pacific states and increased doubling time only in Mountain states, yet associated with higher case rates in North Central States and lower doubling times in multiple regions, noting in particular that the effect sizes for doubling time in Mountain vs. Middle Atlantic/New England states were exactly the same value but in opposite directions.

Surprisingly, duration of level 4 policies was associated with higher rates of death at the national level, but when analyzed separately by Census region, associated with lower rates of death in Pacific, North Central, and South Atlantic states (also trended to lower rates in Mountain and South Central regions, but was not statistically significant). Given than Middle Atlantic and New England states comprised 51% of all deaths reported during the first wave, the relationship in these two regions likely dominated the national trend. The initiation of level 4 policies was slowest in these regions, allowing for both case and mortality momentum

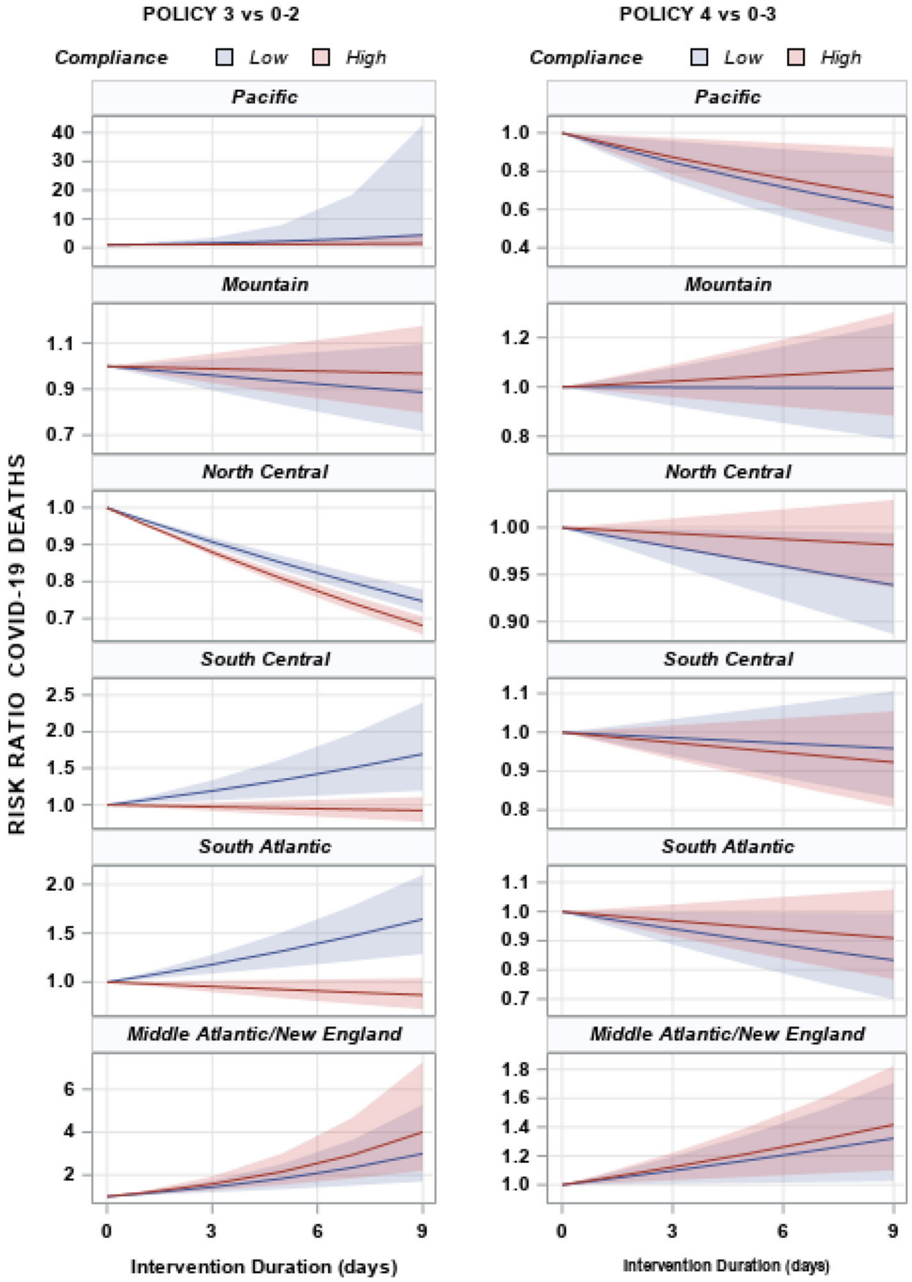

FIGURE 5 | Risk ratio and 95% confidence intervals of COVID-19 deaths by duration of policy for each US census region. Shaded areas represent the 95% confidence interval for each region. US Census Regions: Pacific—CA, WA, OR, HI, AK; Mountain—MT, WY, ID, NV, UT, CO, AZ, NM; North Central—ND, SD, NE, KS, MN, IA, MO, WI, IL, MI, IN, OH; South Central—TX, OK, AR, LA, KY, TN, MS, AL; South Atlantic—FL, GA, SC, NC, VA, WV, DC, MD, DE; Middle Atlantic—NY, PA, NJ; New England—ME, CT, NH, MA, CT, RI.

that resulted in the positive association observed. It is clear from **Supplementary Table D1** that level 4 policies not only reduced death rates in other regions, but higher compliance may complement policy effectiveness.

Why do NPIs exhibit such variation in effects? As alluded to above, policy compliance likely plays a key role, which we measured as the change in mobility over a 10-day period in 2019 vs. 2020. It is not surprising that we find compliance to be associated with enhanced policy effectiveness and reduced COVID-19 burden, i.e., higher compliance was significantly related to lower case rates and higher doubling times for each day on level 4 policies in all Census regions, as well as lower death rates in most regions during both level 3 and level 4 policies. However, we found considerable variation

TABLE 4 | Socioeconomic characteristics associated with policy compliance (changes in mobility) during the first 15 and 30 days of March 2020.

		Compliance change March 1 to March 15		**Compliance change March 1 to March 30**	
		Beta (SE)	**Standardized beta (SE)**	**Beta (SE)**	**Standardized beta (SE)**
Intercept		0.225 (0.547)	2.32 (0.253)†††	19.614 (0.982)†††	25.17 (0.338)†††
% Of county population:	With Bachelor degree	0.056 (0.008)†††	28.68 (3.899)†††	0.097 (0.015)†††	49.44 (7.557)†††
	Hispanic	0.009 (0.006)	6.66 (4.344)	0.028 (0.011)††	21.50 (8.278)††
	Black	−0.012 (0.006)†	−9.97 (4.916)†	−0.015 (0.012)	−11.99 (9.473)
	Living in Poverty	0.024 (0.013)	7.94 (4.462)	−0.114 (0.026)†††	−38.35 (8.656)†††
Net migration rate		−0.006 (0.006)	−3.54 (3.505)	0.057 (0.011)†††	35.98 (6.788)†††
2018 County population density, 1,000 people/km^2		−0.112 (0.098)	−3.44 (3.021)	0.12 (0.191)	3.69 (5.877)
Rural-urban continuum code (Ref = 9-Rural <2,500 people, not adjacent to metro)	1—Metro >1 million people	1.025 (0.251)††	19.35 (4.74)††	5.431 (0.488)†††	102.48 (9.198)†††
	2—Metro, 250 K-−1 million people	1.869 (0.233)†††	33.83 (4.226)†††	6.13 (0.454)†††	110.96 (8.214)†††
	3—Metro, <250 K people	2.122 (0.226)†††	37.32 (3.97)†††	5.769 (0.439)†††	101.47 (7.721)†††
	4—Non-metro, >20 K people, adjacent to metro area	2.47 (0.258)†††	34.77 (3.635)†††	6.548 (0.502)†††	92.19 (7.065)†††
	5—Non-metro, >20 K people, not adjacent to metro area	2.429 (0.338)†††	22.58 (3.145)†††	6.771 (0.659)†††	62.95 (6.128)†††
	6—Non-metro, 2,500–19,999 people, adjacent to metro area	1.542 (0.197)†††	33.63 (4.298)†††	5.425 (0.383)†††	118.29 (8.357)†††
	7—Non-metro, 2,500–19,999, not adjacent to metro area	1.573 (0.203)†††	30.01 (3.878)†††	5.248 (0.396)†††	100.14 (7.55)†††
	8—Rural, <2,500 people, adjacent to metro	0.889 (0.244)††	12.68 (3.485)††	2.058 (0.476)†††	29.36 (6.789)†††
Minimum temperature		−0.08 (0.017)†††	−37.14 (8.103)†††	0.012 (0.031)	5.68 (14.249)
Solar radiation		−0.003 (0.002)	−6.84 (4.315)	0.002 (0.004)	3.56 (8.194)

$^{\dagger\dagger\dagger}p < 0.0001$, $^{\dagger\dagger}p < 0.01$, $^{\dagger}p < 0.05$.

Results are from two separate models of compliance change over time, adjusting for within state county correlation. The interpretation of the standardized beta is a one standard deviation unit change in a covariate being associated with a change in compliance.

in compliance both within Census regions and within states (**Figure 2**, **Supplementary Figure A1**) indicating that adherence to policies has strong community and census-level mediating factors. This is consistent with our findings that that compliance varies by levels of poverty, educational level, racial/ethnic composition, and rurality. Recent studies corroborate these findings and also highlight the importance of perceived risk, occupation, and local social pressures (52–55). Importantly, we find poverty levels to be the most important factor in explaining compliance, which was also found in other studies (52, 56). This relationship between poverty, policy compliance, and COVID-19 risk is tied to the overall literature of population vulnerability and the burdens of low-income households to maintain food security and financial stability during a time when businesses and employment opportunities were closing (57).

Overall, the results of this study are consistent with findings from Wuhan (23) and Europe (58) that reported significant declines in the effective reproductive number following implementation of NPIs that included quarantine, travel restriction, shelter-in-place, school and business closures, and social distancing. Results are also consistent with studies in the US highlighting the effect of shelter-in-place (5, 59) and closure of schools, restaurants and businesses (26–28). However, in contrast to these studies, we combine multiple NPIs into an ordered grouping of policies that tended to be implemented simultaneously, thereby avoiding the potential biases in assigning attributable risk reduction to individual policies when their roll-out occurs concurrently with others. For example, 51% of counties had school and restaurant closures occur <2 days apart (level 2 NPI), and 55% initiated restrictions on mass gatherings and non-essential business closures within 2 days (level 3 NPI). It is very difficult, statistically, to measure independent policy effects in an observational study when those policies are implemented in such close temporal proximity. The stepped-wedge approach, although not designed for observational data, is a novel attempt to control for these overlapping periods.

The stepped wedge approach was only applied to the doubling time models, primary due to difficulties in achieving model convergence for case and death rate models. For doubling time, we produced predicted estimates for each NPI adjusting for all covariates entered into the model (**Figure 4**, **Supplementary Figure C1**). These predicted doubling times adjust for all the observed heterogeneity across counties, demonstrating that policy impact is likely not continuous in reality, but achieves a peak after a certain amount of time. Overall, we report level 4 achieving peak doubling time after 40 days and 23 days for level 3. This peaking is likely associated with reduced perceptions of local risk and reduced compliance even when policies are still in effect. For Census regions, they all appear to reach a peak doubling time for level 4 policies with the exception of Middle Atlantic and East North Central, which tended to have less heterogeneity in policy compliance compared to other regions as indicated in **Figure 2**. This plateauing of intervention effects remains an important area of research, which is tied to issues related to adherence, transportation, and racial and economic disparities. The timing of policy implementation may also have introduced heterogeneity across regions. We observed that states experiencing early cases (Pacific, New England, and Mid-Atlantic) had significantly longer gap times between case detection and NPI initiation than states experiencing their first COVID-19 case later. This difference in policy initiation time is likely due to non-coastal US Regions learning from experience of coastal regions to implement NPIs more quickly. Unfortunately, early response during the first wave, which proved effective, may have given policy-makers false confidence as 12 states reported case spikes on June 23 and 7 states reported highs for hospitalization (https://covidtracking.com/)—all but one of these states began removing social distancing protections by May 11 and all but four are located in Mountain, North and South Central regions.

In addition to evaluating policy effects, this study reported the effects of temperature, specific humidity, and solar radiation related to COVID-19. These mixed results highlight a number of important points on climate predictors of COVID-19: (1) the regional heterogeneity of the relationship between climate parameters and SARS-CoV-2 is consistent with the variability observed in studies of MERS-CoV infection and climate (60–63); (2) climate analyses are sensitive to choice of response variable and analysis period, and may not provide stable results at the stage of epidemic data collection considered in this study—for example, our results tend to run in the opposite direction of those reported by Ma et al. (64), but the studies use different response variables (R_t vs. doubling rate), as well as different periods of analysis, ranges of climate variability, and statistical methods; (3) there is substantial inter-regional variability in climate sensitivities, such that large scale analyses are not necessarily representative of regional climate influence; and (4) it is difficult to isolate climate effects from those of other predictors, and analyses that examine climate variables without adequate control for policy and other factors are prone to spurious climate associations. We recommend further research be conducted at different spatial scales (community, census tract, etc.) to better characterize the climate-COVID-19 relationship.

Limitations

There are several limitations to note in our study. First, the analysis does not have an accurate representation of the availability of testing (or the number of tests administered) at the county level for the time series. As this availability changed over time for all counties in the US, we cannot accurately characterize the population at risk for COVID-19 case detection. However, we are more confident in COVID-related deaths reported. Second, our measure of compliance is based on reduced mobility in countries, but not a direct measure of adherence. In some states, policy levels 3 and 4 were viewed as an affront to civil liberties. While the use of mobility data has been shown to be an appropriate proxy for compliance, studies focusing on smaller geographic units may be able to obtain more accurate data on compliance to measure NPI "dose." Third, we do not look at individual interventions. However, this was a choice as the sets of NPIs are considered a more appropriate response than single interventions, which have never been employed historically without others. Finally, we would ideally be applying these methods to a randomized design, which is impossible for

COVID-19. Thus, our inferences are drawn from observational data regardless of our SW-CRT analytical framework.

CONCLUSION

The most aggressive NPIs (shelter-in-place, public mask requirements, and travel restrictions) were the only policies that are consistently associated with a reduction in COVID-19 cases and doubling times in the US between January 2020 and the phased re-opening of states. However, when analyzing by Census region, considerable variation of NPI effectiveness is observed, likely due to variations in policy adherence. Socio-environmental factors, including poverty, racial/ethnic status and educational levels, contribute to heterogeneity of COVID-19 propagation, NPI adherence and NPI effectiveness. These results may inform public health policy as states continue to manage the ongoing pandemic.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

WP and ST conceived the study. WP, ST, BZ, PL, and CW contributed to the design of the study. WP, RD, and BZ organized the data. WP, DF, and G-VI contributed to analysis. WP wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.754696/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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POLICY BRIEF
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SARS-CoV-2: International Investigation Under the WHO or BWC

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In late 2019, the novel and highly infectious coronavirus SARS-CoV-2 caused a worldwide outbreak of a severe respiratory infectious disease, known as COVID-19. The disease has started in China and turned into one of the worst pandemics in human history. Due to the very fast global spread of the pathogen, COVID-19 is a great challenge for the Public Health Systems. It had led to a variety of severe limitations in private and public life worldwide. There is a lively public debate about possible sources of SARS-CoV-2. This article aims at providing a better understanding of controversial biological and political issues regarding COVID-19. Recommendations are made for possible actions under the umbrella of the World Health Organization and in respect to the Biological Weapons Convention.

Keywords: SARS-CoV-2, COVID-19, BWC, forensic investigation, transparency measures, WHO, UNSGM, UN

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INTRODUCTION

In December 2019, an outbreak of an unknown viral pneumonia was reported in the city of Wuhan, capital of China's central Hubei province (1). The virus was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which belongs to the virus family of *Coronaviridae* (2) and causes the disease commonly known as *Coronavirus Disease* 2019 (COVID-19). Since its official reporting in December 2019 globally, more than 273 Mio cases and more than 5.35 Mio COVID-19 related deaths (as of December 20, 2021) are registered (3). Therefore, COVID-19 has the potential to become one of the most severe and fatal pandemic disease to date (4). The World Health Organization (WHO) declared COVID-19 in February 2020 as a Public Health Emergency of International Concern. Additionally, due to its numerous negative effects on physical and mental health, social well-being, on economies and societies leading to the exacerbation of inequalities within and between countries the Seventy-third World Health Assembly expressed its concerns about the global pandemic (5).

In general, the COVID-19 pandemic is responsible for a variety of severe limitations and changes in private and public life worldwide. Shrinking economies were an immediate result from induced lockdowns, which led to a rise in unemployment and therefore decreasing demands of consumer goods. For example, the world trade had a steep decline in the first half of the year 2020 because the merchandise trade indicating a year-on-year drop of around 18.5%. According to the World Trade Organization this was caused by the coronavirus pandemic and the associated lockdown measures in many countries (6). Fortunately, after recovering in the second half of 2020 the decrease of the international merchandise trade volume was only 5.3% in 2020 (7). In the second semester of 2021 the world merchandise trade underwent a rebound, though varying among regions, exceeding the experts' predictions (8).

The drastic restrictions of public life, education and business activities in combination with a deliberately spread of misleading information about COVID-19. All this together led to concerned citizens and civil unrest in many countries. Some people might even dive into conspiracy theories believing the deliberate release of the virus as one possibility (9). Adding to that, unsubstituted claims were made that the virus might be engineered and part of a clandestine Chinese Bioweapons Program. At the center of these speculations is the Wuhan Institute for Virology (WIV), which is located close to the wet-market where COVID-19 might have its origin. Undoubtedly, the WIV is a well-known research institute with a strong focus in coronavirus research. However, there is reason to believe that the WIV could have been involved in secret Chinese military projects due to its relations to Chinese military researchers. Of note, there are no proofs available in the open literature that such a program does exist (10, 11). In part, these speculations were fueled by the fact that initial reports of an unusual pneumonia in Wuhan were obviously suppressed by local Chinese authorities (12–14). On September 12, 2019, the WIV database containing information on collected virus strains and genome sequences was removed from the internet/open-access (15).

Consequently, there were calls for an international investigation to identify the source of the COVID-19 outbreak (16, 17). However, it is not yet clear under which organizational umbrella such an investigation could take place and which institution could perform an internationally acceptable unbiased investigation regarding the causes of this pandemic. The intensive debate about acceptable conditions for a WHO-China joint investigation (finally performed early in 2021, see below) highlight these shortcomings of neutral investigation conditions even more.

In this policy brief, we discuss the role of the WHO as a first point of contact for an investigation of the source of the COVID-19 pandemic and possible roles of the Biological and Toxin Weapons Convention (BWC). Scientific publications, media reports, and official governmental statements were analyzed to investigate possible solutions for strengthening public health responses to the COVID-19 pandemic. A special focus was put on instruments discussed within the BWC regime and the academic biosecurity community. Possible investigation scenarios based on current international accepted mechanisms and initial steps how to investigate the source of a pandemic like COVID-19 were also elaborated.

Critical Questions About the Origins of the SARS-CoV-2 Outbreak

Several publications conclude that SARS-CoV-2 originated from nature and was not man-made or released accidently from a research laboratory (18–22). Nevertheless, the SARS-CoV-2 outbreak raised questions if:

i. the outbreak was a consequence of a laboratory accident?
   Scientific reports have documented a few accidental coronavirus releases from Chinese laboratories in the past (23–25). In 2004, a local outbreak of SARS-CoV-1 was reported in China due to laboratory-acquired infections (LAI). Chinese governmental authorities quickly contained these outbreaks (26). In a WHO report from May 2004, it states that "WHO and Chinese authorities view with concern the occurrence of laboratory-associated SARS cases." (27). Publications that are more recent express their worries about inadequate biosafety management systems, insufficient resources for efficient laboratory operation, deficiency of professional capacity and a missing open culture in connection with this biosafety level (BSL) 4 laboratory (28, 29). LAI-infected personnel or staff performing environmental sampling of potentially infected bats, all being part of research activities conducted by the WIV, could cause the spread of the virus.
ii. SARS-CoV-2 is a genetically engineered virus?
   One of the most urgent questions related to the COVID-19 pandemic was, if this infectious disease outbreak was caused by a genetically modified coronavirus. Scientists at WIV indeed conducted extensive research projects on coronaviruses including virus strains closely related to SARS-CoV-2. They used standard methods in virus cell culture as well as genetic engineering. Several manuscripts were published including so-called gain-of-function (GOF) experiments (30–33). Currently, the Congress of the United States is investigating the National Institute of Allergy and Infectious Diseases (NIAID) grant project number R01AI110964. This grant was awarded to Eco Health a US non-profit organization which funded Coronavirus-research at the WIV as a sub-grantee (34). Within this research project, additional GOF experiments were carried out (32). Both, the NIAID and the Eco Health risk assessments of the proposed GOF experiments did not seem to reflect the required balance between risks and benefit (35). Detailed investigations of SARS-CoV-2 genomes have revealed two notable regions of interest within the spike protein-coding gene:

   1) The ACE2 receptor-binding domain of the spike protein: This protein is exposed to the viroid surface and acts as a ligand for the host cell angiotensin-converting enzyme 2 (ACE2) receptor. Binding of the viral spike protein to the ACE2 receptor is a key step for virus entry into the host cell (36, 37).
   2) The second notable region is a furin cleavage site, which is located at the junction of S1 and S2 subunit of the spike unit. This peptide insertion is involved in the proteolytic cleavage of the spike protein. Enveloped viruses like the coronaviruses require proteolytic cleavage of the spike unit to be able to infect the host cell (38, 39). SARS-CoV-2 has a unique polybasic cleavage site (RRAR) which could influence transmissibility and host range (40). Only a few other coronaviruses are known for having different amino acid sequence motifs of the proteolytic cleavage site (41, 42).

iii. SARS-CoV-2 was already circulating for longer, but infections were not made public.
   There are also reports pointing to a much earlier occurrence of SARS-CoV-2 than December 2019, as has been communicated by the Chinese health authorities. There was one case reported

from a 55-year-old resident from Hubei province published in the South China Morning Post on 17 November 2019 (43, 44). Further laboratory-confirmed COVID-19 cases in humans which did not have had direct contact to the Wuhan city wet market, were reported starting from December 1, 2019 (45). In France, the first patient known to be infected with the pandemic coronavirus ("index patient") was hospitalized in December 2019 (46). Therefore, the virus might have circulated for much longer. In October 2019, some athletes who attended the Military World Games went sick with symptoms similar to COVID-19 (47, 48). Chinese authorities dated the earliest known COVID-19 case back to the beginning of November 2019.

Interestingly, a possible precursor virus related to SARS-CoV-2 could be the causative agent for the infection of six mineworkers in Mojiang, Yunnan province, in April 2012 (49, 50). These workers got severely ill showing symptoms attributed to a SARS-CoV-1 infection. Subsequently a coronavirus infection was later confirmed by the WIV (51). From 2012 to 2015, WIV scientist has collected annual samples of bats in the same cave in which the six mineworkers got infected (51, 52) This theory proposes the possibility that the origin of the SARS-CoV-2 virus could be from in the WIV stored samples taken from theses infected Mojiang Miners.

In sum, there is scientific evidence pointing to a natural spillover of SARS-CoV-2, but there is also other evidence supporting manmade sources of the COVID-19 pandemic. Therefore, it is important to investigate thoroughly the COVID-19 outbreak on a sound scientific basis [see for example the critics of Graner et al. (53) of the publication from Holmes et al. (22)]. In the following section, we first analyze possible ways for an international investigation of the COVID-19 outbreak under the umbrella of the WHO, before we examine potential contributions of procedures linked to the BWC regime.

POLICY OPTIONS AND IMPLICATIONS

Investigation Under the Responsibility of WHO, the First Step

Which international organization could be taken responsible for the unambiguous investigation of a pandemic outbreak? Independently obtained results of an investigation would ideally be recognized by the international community as a whole. The United Nations (UN) as the largest and most powerful international organization represents 193 countries in the world. In general, the UN could initiate such an investigation (**Figure 1**) (54). As a specialized agency of the UN, the WHO's primary function is to promote human health globally. Several times in the past, the WHO has played a leading role in eradication of infectious diseases especially by supporting vaccination campaigns.

End of January and mid of February 2020, two WHO-China Joint Missions were carried out. During the first mission, visits of different facilities in Hubei province were conducted. Furthermore, ongoing epidemiological surveillance processes were analyzed. Infection prevention and control measures as well as the deployment of a RT-qPCR test kit for the detection of the new coronavirus were discussed with Chinese officials (55). Epidemiological aspects, response and preparedness measures, containment and collaborative programs were investigated during the second mission (56). The goal of the second mission was to inform about the national and international planning of the WHO regarding the following steps to improve readiness and preparedness for non-affected COVID-19 areas. Nevertheless, there was no bioforensic investigation of the COVID-19 outbreak carried out by an independent research team. In May 2020, the WHO Emergency Committee recommended a joint investigation to be conducted by experts for human and animal health. This joint investigation should also aim the rapid identification of the zoonotic source of SARS-CoV-2 (57). This could trigger a third WHO-China Joint Mission making use of modern bioforensic methods. As there are currently no international guidelines for forensic investigations of a pandemic, lessons learned from this field mission could be used by the WHO experts to prepare a draft guideline for future investigations. The International Health Regulations (IHR) are designed to prevent or control the spread of diseases and they providing guidance for adequate public health response (58). At the seventy-third World Health Assembly (WHA), first steps were decided to improve countermeasures required for the containment of COVID-19 (published in resolution WHA73.1, pages 6 and 7 (5). In July 2020, the inauguration of an independent Panel for Pandemic Preparedness and Response (IPPR) was announced by the WHO Director-General, which will evaluate the response to the COVID-19 pandemic, globally (59). Further efforts have been made in August 2020 to examine the effectiveness of the IHR and to prepare the ground for necessary amendments (60). In reaction to increasing public pressure, the Chinese government agreed to host a Joint WHO-China Study from 14 January to 10 February 2021. Aim of this mission was the analysis of potential zoonotic sources of SARS-CoV-2 and the search for intermediate hosts of this virus. The multidisciplinary team of Chinese and international experts performed several investigations on the ground in Wuhan and presented key findings in a final report (61) The report received critics due to the lack of firm data supporting the conclusions presented, for example ruling out a lab accident as "extremely unlikely" (62). In a press statement, the WHO Director-General later made clear that investigations of the origins of SARS-CoV-2 must go on (63).

The COVID-19 pandemic could act as a model for efficient international assistance and future cooperation in the public health sector and beyond. What emerged evident during the first months of this pandemic is the need for improvements in communication and better-synchronized containment measures by all countries worldwide. In this respect, the delayed reporting of human-to-human spreading of the disease did cost valuable time (several weeks) before appropriate health protection measures such as social distancing, masks, and isolation of clusters of infected people were put into action. It should be noted that the time required for efficient disease containment measures mandatory for an efficient infectious

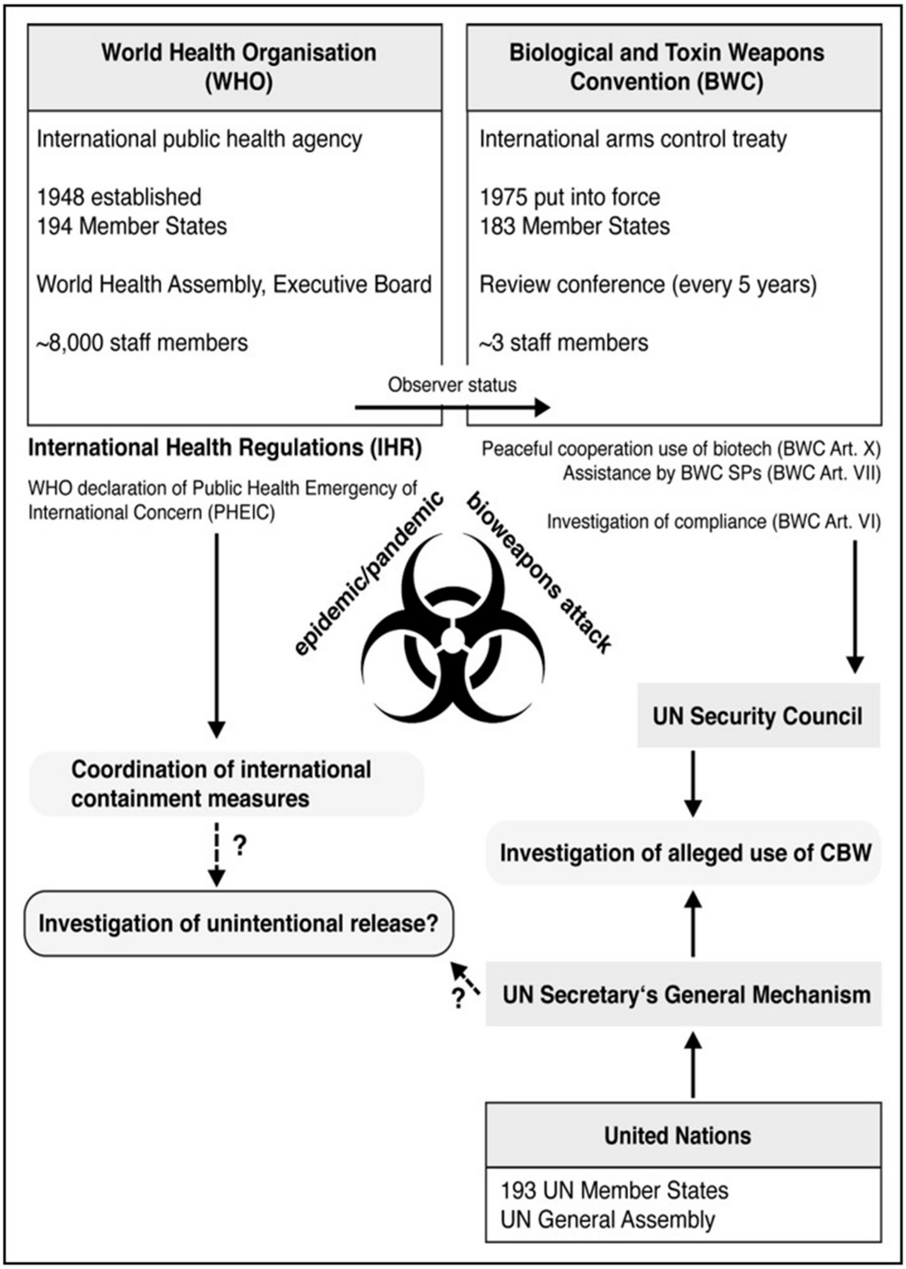

FIGURE 1 | Possible interplay between WHO and BWC investigative mechanisms. Shown are key features of both, the WHO and the BWC regime including status of membership and decision-making bodies. Although acting in different areas (WHO, human health; BWC, biological arms control), there might be an interplay between internationally agreed investigative mechanisms usable for the analysis of the COVID-19 outbreak.

disease containment might be quite reasonable. This holds even truer in cases where asymptomatic disease carriers already shed sufficient amounts of the virus to initiate new chains of infection. Here, an improved epidemiological – and less political – driven reporting system would allow to keep pace with such dynamic disease outbreaks. In the following section, we contemplate investigative procedures linked to the BWC regime.

Investigation of the COVID-19 Pandemic in Respect to Procedures of the BWC

The Biological and Toxins Weapons Convention (BWC) of 1972 is a multilateral arms control treaty banning the development, production, stockpiling and - in addition to the Geneva Protocol of 1925 - use of biological weapons (BW) (**Figure 1**). Currently, 183 UN countries are Member States of the BWC. Although there are no indications for a deliberate release of SARS-CoV-2, the BWC regime offers a framework for a coordinated reaction by BWC Member States on the question of the origin of the COVID-19 pandemic.

In particular, Article VII of the Convention[1] calls upon States Parties for mutual assistance in the case of a biological weapons (BW) attack. Required resources and capacities for detection and diagnosis of natural occurring pathogens and toxins, which could be provided by at least some BWC Member States, are also well suitable for analyzing unexpected disease outbreaks. Furthermore, measures for counteracting against the use of BW could also be applicable for containing an epidemic and could help to prevent a possible international public health crisis. Suitable measures include large-scale quarantine, transport and hospitalization of severe cases across national borders or the deployment of medical emergency teams in affected countries. Mass vaccination programs, the *ad hoc* establishment of large-scale medical infrastructure like field hospitals, and the installation of field laboratories could be used to improve public health systems responses to severe epidemics/pandemics. But most importantly, BWC Member States offering assistance to a country challenged by a disastrous biological event or incident is meant to enhance confidence among States Parties.

In 2020, United Nations Secretary-General António Guterres highlighted the danger of a deliberate use of diseases as weapons at a Security Council video conference. Especially, diseases that were deliberately altered to be more virulent or intentional released are of concern, as we are not yet prepared to deal with such viruses on a global scale. The Secretary-General also commented on the requirement of a verification mechanism to implement confidence-building measures within the framework of the convention. The BWC regime should be better prepared to cope with upcoming biological threats by improved preventative measures, enhanced response capacities and effective countermeasures (64).

In case of an alleged use of biological warfare agents, the UN Security Council (UNSC) should have the obligation to take action and to initiate an investigation. However, in the current political situation the UNSC often has difficulties to find consensus on urgent questions related to human safety and security. For example, there is no common understanding within the UNSC on procedures to investigate alleged chemical weapons attacks, e.g., during the Syrian civil war.

Due to the absence of any legally binding verification mechanism within the BWC regime there are no procedures implemented *en detail* on how BWC States Parties should act in the event of an abusive spread of pathogens. In the case of alleged use of biological weapons States Parties could approach the UN Security Council (UNSC) and asks for investigation of the complaints, but this procedure has never been evoked and given the political tensions frequently seen in the UNSC it appears difficult to predict the outcome of such an appeal. Negotiations of BWC verification protocol failed in 2001 and currently there are no clear indications for a restart of this process. It would be more than desirable to see an impulse set by the COVID-19 pandemic for BWC Member States to again engage in strengthening of the BWC. At the 2021 BWC Meeting of Experts, the US Under Secretary of State for Arms Control and International Security provided ideas for such a move forward in her statement[2]. The Ninth Review Conference of the BWC in August 2022 offers the opportunity for Member States to actively address the above-mentioned challenges in a cooperative manner.

The amendment of the BWC by an additional protocol would be another possibility to provide States Parties to react fast and efficient on incidents related to possible uses of BW. Such an addendum could regulate standardized investigative measures and, if necessary, sanctions or obligations of the international community in such an event.

Another approach is the UN Secretary-General's Mechanism (UNSGM) mechanism, which was established as a verification instrument of the Geneva Protocol for investigating an alleged use of chemical and biological weapons. UN General Assembly established this mechanism with resolution A/RES/42/37 C (1987). The UN Secretary-General can react on appeals also by single UN Member States in the case of alleged use of chemical and biological weapons. Several Member States of the BWC consider the UNSGM also as a valuable tool for an investigation of unusual outbreaks of infectious diseases in case of a potential alleged use as a bioweapon. Although the UNSGM is currently the key instrument in the international toolbox of the investigation of unusual biological incidents, it is limited to the investigation of the alleged use of bioweapons. In comparison to the strict quality standards within the investigations of chemical weapons, no quality standards are existing for biological weapons. In case of an investigation of the alleged use of a potential bioweapon laboratory results might be therefore easily questioned or even rejected.

The idea of activating the UNSGM is not accepted by all BWC States Parties, therefore its final authority to investigate biological incidents would be highly controversial. In 2020 and 2021, for example, Member States of the BWC have attempted to weaken the UNSGM and the power of the UN Secretary-General by submitting working papers and voting on their contents in the First Committee of the UN General Assembly. If a biological event was caused deliberately must therefore be assessed with high confidence before the UNSGM is applied to prevent political damage to this investigative instrument. However, the public debate about the origin of SARS-CoV-2 shows how difficult this might be to achieve. In order to further investigate the possibility of an incidential release of SARS-CoV-2 a transparent investigation would be required. Research at the WIV was partly

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[1] BWC Article VII: "Each State Party to this Convention undertakes to provide or support assistance, in accordance with the United Nations Charter, to any Party to the Convention which so requests, if the Security Council decides that such Party has been exposed to danger as a result of violation of the Convention".

[2] Ambassador Bonnie D. Jenkins stated that "[The Ninth BWC Review Conference] should establish a new expert working group to examine possible measures to strengthen implementation of the Convention, increase transparency, and enhance assurance of compliance. [...] It could be useful to build on some approaches suggested in past discussions, but our efforts should not be defined by them." Available at: https://geneva.usmission.gov/2021/11/22/remarks-to-the-2021-biological-weapons-convention-meeting-of-states-parties/ (Accessed: November 27, 2021).

funded in by the US money and conducted in collaboration with US scientists.

In the light of this complex situation, free international scientific exchange of scientists is essential, which is also supported by Article X of the BWC calling upon States Parties to cooperate for the peaceful use of biotechnology. In order to strengthen and cultivate scientific friendships in the areas of relevance to the BWC, a framework should be established. Within this framework scientists could meet and interact more closely – inspired by political questions related to the BWC, but not dominated by political tensions.

Cooperation of States under the WHO umbrella to further investigate the origins of SARS-CoV-2 appears to be the most intriguing way forward. Elements of the BWC regime might be give orientation on how to further proceed. In the following, we provide recommendations for an internationally agreeable investigation of the COVID-19 outbreak.

ACTIONABLE RECOMMENDATIONS

Investigation Under the Responsibility of WHO

Desirably, in agreement with all WHO Member States, a multidisciplinary international task force could be established within a new mandate to take medical, environmental, and biomedical samples in states parties of interest, e.g. China. This task force would be required to obtain and study available information relating to these allegations including interviews. It could further perform or delegate (with the support of the UNSGM laboratory network) the analysis of the beforehand acquired samples. Unfortunately, during the WHO-China joint investigation in 2021, limited capacity to investigate thoroughly resulted in unattainable objectives. In the future, the demand to agree on an mutual accepted mandate will also include a specific framework in which to operate successfully. Moreover, it must be clarified to what extend a country, by the time of an outbreak, would have the obligation to fully support such an investigation. The implementation of an internationally agreed procedure for a WHO investigative mechanism is for sure a most difficult endeavor. Strengthening public health and swift support as well as transparent investigation of severe infectious disease outbreaks should be investigated while considering the responsibility of all states regarding a sustainable global health. However, it would also be important that investigations into a pandemic origin would include a joint effort between WHO member states and experts from the country of interest. These measures could ensure a basis of trust. In addition, the support of the investigation team might assist affected countries with disease surveillance measures. The discussion of an investigated outcome will be held on a neutral and professional level and it must always be assumed that the presumption of innocence applies. If need for action is identified e.g. the improvement of essential laboratory infrastructure and the implementation of an appropriate biosafety and biosecurity management, it should be promoted within the international community (65).

Approaches for Forensic Investigations Under the BWC

In the BWC regime, there is still an ongoing political debate about the requirement for a verification mechanism. Nevertheless, BWC Member States should take every necessary step to further extend the agreed confidence-building measures by novel approaches including technical means. Another relevant aspect could be fostering international scientific cooperation under the umbrella of the Convention. In this respect, the COVID-19 pandemic could be a trigger for such activities. Clearly, a naturally occurring infectious disease outbreak is not a matter for the BWC. But treaty members frequently confirmed that capabilities for the detection of biological weapons attacks must be in place before such an incident might take place[3]. Adequate methods of microbial forensics useable to investigate the alleged use of biological weapons could also be applied for the analysis of the source of the COVID-19 pandemic (66, 67). This could be done either by agreement of BWC Member States to use these approaches in a combined effort, by the activation of the UNSGM triggered upon request by UN Member States or by decision of the UNSC to mandate such investigation. The latter two might be politically difficult to achieve depending on the political circumstance. However, the first option is based on experiences taken from the reaction of a couple of BWC Member States during the Ebola virus outbreak 2014–2016 in West Africa (68).

In the hypothetical case of the unintended release of a pathogen from a laboratory or biotechnological installation subsequently leading to an epidemic/pandemic, it is of utmost importance to quickly identify the corresponding facility. A network of governmental laboratories working at BSL-3 or even BSL-4 level would be of help. A database of research capabilities of these labs could be established. Database entries should focus on biosafety and biosecurity assessments of the work but would give no exact details about sensitive information in order to respect intellectual property and national security concerns. Network members could provide guidance how to monitor research activities of the listed labs, for example, in the context of a still-to-come Scientific Advisory Board of the BWC. Moreover, such mechanism could improve international standards in biosafety and biosecurity and ultimately support an open scientific exchange within the international community (69). Building trust among BWC Member States is an essential step, especially in the light of ongoing debate, about the (im-)possibility of the verification of the BWC. This is even more true, since some treaty Member States fear violations of intellectual property as well as negative impacts on national security by an intrusive verification mechanism. Industrial laboratories could also be included at a later stage, as confidence building has progressed. In addition, this might even be an appropriate way to implement a verification system within the BWC.

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[3] "States Parties noted the importance of ensuring that efforts undertaken are effective irrespective of whether a disease outbreak is naturally occurring or deliberately caused [...]. States Parties also recognized that capabilities to detect, quickly and effectively respond to, and recover from the alleged use of a biological or toxin weapon need to be in place before they are required." Report of the BWC Meeting of States Parties in 2010.

This process could be started by organizing scientific conferences organized by a UN organization (e.g., UNODA), which would be focused on various fora for a rather informal personal exchange between scientific and technical experts, politicians and diplomats. The idea is that there are no diplomatic constraints within the discussions of scientists. The annual BWC Meeting of Experts could be used as template for such conference, which would be held readily in advance to the next BWC Review Conference. At the scientific conference and in support by a newly founded science advisory board of the BWC working groups could be set up. Tasks of relevance to the BWC would include assessing the impact of new (bio-)technologies, requirements for internationally agreed safety and security standards in biological laboratories. Furthermore, internationally agreed standard procedures for the epidemiological and bioforensic investigation of outbreaks caused by the potential misuse of pathogens.

The mechanisms outlined above would allow for an improved open exchange on developments in science and technology between the three BWC regional groups (Western Group, East European Group and Non-Aligned Movement). Precondition for the proposed measures is, of course, the political will to further develop the BWC regime in a cooperative manner. Nevertheless, an enhanced scientific exchange along with better opportunities for less well-equipped BWC States Parties to participate and benefit from this process might increase the political commitment to the BWC regime including the required financial support.

CONCLUSIONS

The COVID-19 pandemic exposes frictions in the international system to counteract biological threats. Loss of confidence in internationally agreed mechanisms for reporting, monitoring and management of epidemics/pandemics is of great concern, especially for the WHO. Lack in transparency and delayed reporting of key epidemiological and biological data by some states in the course of the emerging COVID-19 pandemic clearly showed the need for improving international mechanisms counteracting biological threats. In the view of the current tense political situation, which is marked by mutual allegations of inappropriate COVID-19 countermeasures and negligent inadequate monitoring measures in biosafety and biosecurity between leading countries, the return to cooperative action for an unbiased SARS-CoV-2 outbreak analysis following scientific standards is highly desirable. In this respect, re-strengthening of the role of the WHO and its investigative mechanisms would be of utmost importance. The BWC, being primarily an arms control treaty, offers rather an outline than detailed practical steps to be taken for the analysis of unusual infectious disease outbreaks. Instruments such as the UNSGM could provide valuable tools for performing required scientific and technical analyses without necessarily triggering the mechanism. Nevertheless, there is still no internationally accepted running workflow how to perform the bioforensic investigation of pandemic outbreaks. The international community should take the responsibility for improving and protection global public health by activating relevant political instruments, which are designed for that very purpose.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Perceived Effectiveness and Sustainability of Face Masks Among German Citizens During the 2nd Wave of the COVID-19 Pandemic—A Cross-Sectional Study

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Background: The COVID-19 pandemic, which began at the end of 2019, has led to a significant increase in the demand for face masks in Germany and around the globe. Since non-reusable masks are often not correctly disposed of and are not biodegradable, their increasing use harms the environment. Both the ongoing pandemic and the rising environmental pollution eventually pose a threat to human health. Yet, it is unclear whether mask users are conscious of this, and which factors influence their choice of face masks. This study investigates the user preferences, perceived effectiveness, and the sustainability of different mouth/nose protection (MNP) to lay the foundation for developing more sustainable and effective alternatives.

Methods: A national (Germany-wide) cross-sectional study with a sample of 1,036 participants was conducted. Descriptive data analysis was deployed to describe trends and socio-demographic differences among the respondents. Different socio-demographic groups among the respondents were compared regarding their infection risk perception, compliance toward the use of personal protective measures, their choice of MNP, and knowledge level of sustainability and effectiveness of various MNP using inferential statistics (Chi^2 test/Whitney–Mann-*U*-test/Kruskal–Wallis-test).

Results: The results suggest that, in addition to protective effectiveness, the reusability of MNP is important to not just most respondents but especially to older participants. In contrast, the price, shape, and design were not as important. The knowledge level of the effectiveness and sustainability of MNP was high among the participants and was not associated with socioeconomic characteristics. However, the knowledge level directly influenced the choice of MNP.

Conclusion: There seems to be an inclination to use sustainable MNP, provided their level of protection is similar to medical masks or FFP2/FFP3 masks. The willingness to wear a sustainable option increases with age.

Keywords: masks, COVID-19, Germany, sustainability, effectiveness

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INTRODUCTION

The COVID-19 pandemic has led to an increased global demand for face masks for use by healthcare professionals and the general population as a measure to reduce the viral transmission of SARS-CoV-2. Due to the lack of effective therapeutics and vaccines during the early stage of the pandemic, behavioral measures were, and remain to be, crucial for reducing the risk of infection, such as hand hygiene, coughing/sneezing etiquette, and social distancing. In April 2020, the World Health Organization (WHO) recommended health care professionals and those experiencing symptoms or taking care of sick individuals to use MNP (1).

However, the effectiveness of this measure became the subject of controversial debate worldwide and in Germany, amplified by abrupt changes in mask guidelines and the limited availability of medical masks, which led to confusion and doubt regarding the efficiency of MNPs by the general public (2). Initially, the evidence available was not perceived sufficient by many international and German experts due to the lack and conflicting results of existing clinical trials (3–5). Against this background, experts expressed their concern that the masks could be misused and lead to a false sense of security (6). However, several international observational studies had already pointed to a protective effect of masks (7). During the 2003 SARS outbreak, the frequent use of surgical masks decreased the transmission risk by more than 60% (8). The community-wide use of disposable face masks in Hong Kong, which had the highest risk of COVID-19 importation from China, led to a significantly slower increase in COVID-19 cases at the beginning of the pandemic than in other countries (9). Furthermore, mask use contributed to a decline in influenza cases during the winter, leading to the shortest transmission period in the past 5 years (10). In this context, Cochrane and the World Health Organization (WHO) recommended that the evidence for public health interventions does not necessarily need to be derived from clinical trials (11, 12).

Although the WHO recommendation was shared by several national and international institutions such as the World Medical Association and the Robert Koch Institute (RKI) in Germany, many countries, including Germany, have made masks mandatory for everyone in selected public areas since May 2020 (2, 13). However, to avoid exhausting the supply of professional masks, German citizens were asked to cover their mouth and nose with cotton masks or MNPs instead of disposable masks (14). In June 2020, the WHO officially recommended healthy individuals to wear non-medical masks to secure the supply of medical masks for health care personnel while still controlling the spread of COVID-19 in places where physical distancing was not possible (15).

During the first year of the pandemic, complementary experimental studies showed that cotton, surgical, and N95 (FFP2) masks had a protective effect concerning the transmission of infective droplets (16). In line with these results, the community-wide use of mostly non-medical masks has proven to be effective, as it led to a quantifiable reduction in SARS-CoV-2 transmission in Germany and other countries (7, 9, 17, 18). Besides other infection prevention and control measures, this effect was mainly achieved by the high compliance of the population to wearing MNPs in public (19). Reports from Germany showed that 3% of the population was wearing masks at the beginning of March 2020, increasing to 38% in April and 62% in May. In July 2020, compliance went up to 66% and peaked at 75% at the end of January 2021 (20). A recent systematic review reaffirmed the significant link between the use of face masks and the reduction in transmission of COVID-19 via respiratory droplets (21). Moreover, a recent randomized controlled trail suggests that cloth masks can have a similar protective effect compared to medical masks (22).

While primarily non-medical masks were used in the first half of 2020 (cf. **Table 1**), the use of non-reusable masks such as medical masks and tightly fitted respirators (filtering face piece, FFP) with filtration efficiencies—characterized as FFP1 (80%), FFP2 (94%), and FFP3 (99%)—increased worldwide with the growing availability. In Germany, disposable masks (mainly medical and FFP2 masks) became increasingly available in 2020, with more than 300 million masks ordered and distributed by the Federal Ministry of Health (29). Toward the end of the second wave, on the 19th of January 2021, medical masks were made compulsory in shopping facilities and public transport, which led to increased compliance and demand (20, 30).

Even though disposable masks are usually more effective than reusable alternatives (cf. **Table 1**), their potentially harmful environmental impacts were neglected during the debate related to the pandemic.

Disposable face masks are recommended for single use only and consist of several polymers and fibers (31). Once they are disposed of (littering in public areas, landfills), they start leaking microplastics into the environment as the material polymers break down into smaller pieces (<5 mm) over time (32). Unfortunately, many people are disposing masks incorrectly, contributing to the increasing land and water pollution. According to estimations, approximately 75% of disposable masks and other pandemic-related waste will end up in landfills or the ocean (33). More specifically, about 1.5 million masks or 0.15–0.39 million tons of plastic debris enter global oceans within a year (34). Since disposable face masks take about 450 years to degrade under natural conditions, the adverse effects on the environment are expected to be long-lasting (35).

Given the lasting impacts of plastic debris, it is critical to understand the preferred mask types during the second wave of the COVID-19 pandemic and the factors that influence the choice of a mask while laying the foundation for the development of more sustainable and effective alternatives. Since the influential factors on the selection of masks, such as effectiveness and sustainability, may depend on the individual level of knowledge, another objective was to investigate how well German citizens were informed about the effectiveness and sustainability of different masks. Consequently, it was aimed to analyze how this knowledge was distributed among the German sample and whether it influenced the choice of MNP. The following questions were formulated:

TABLE 1 | Effectiveness level, reusability, global use of different masks (before September 2020).

Mask type	Community masks	Medical masks	FFP1	FFP2	FFP3
Filtration efficiency (23)	5–80%	95% (24)	80%	94–95%	99%
Total inwards leakage (25)	60% (26)	35% (26)	22% (27)	8% (27)	2% (27)
Reusability (15)	Recommended	Not recommended	Not recommended	Not recommended	Not recommended
Frequency of use worldwide	72.7%	27.8%		8.4%	0.4% (28)

1. Which type of MNP was used the most during the second wave of the pandemic? Which factors influence the choice of MNP among the German sample?
2. How conscious are the participants about the sustainability and effectiveness of different MNP? Is there an association between the level of awareness and the choice of MNP?
3. How are social characteristics (age, education level, perceived risk) related to each of the questions above?

MATERIALS AND METHODS

A cross-sectional study design employing an online survey was used to answer the formulated questions. The survey included a total of 20 questions. Before starting the survey, respondents were asked to give their consent (one question). The subsequent 19 questions were divided into four topics: (1) socio-demographic information including country of residence, age group, and educational level (three questions), (2) the perceived risk of getting infected with SARS-CoV-2 and user preferences of MNP in the context of the current COVID-19 pandemic (seven questions), (3) the level of knowledge about the effectiveness, the utility and sustainability of different MNP (eight questions), and (4) the users' attitude toward reusable face masks (one question), which closed the survey. The survey design included single-choice and multiple-choice items, Likert-scale items, and open-ended questions. The questionnaire was available in English and German (**Supplementary Material**).

The questionnaire's final design was pre-tested using a practice run and feedback interviews with members of the Research and Transfer Centre "Sustainable Development and Climate Change Management", Hamburg University of Applied Sciences (HAW Hamburg) in Germany and was adjusted for conciseness and clarity. The English and German questionnaires were distributed online via e-mail distribution lists, which were aimed directly at researchers, students of the HAW Hamburg, and partners of the Horizon 2020 project BIO-PLASTICS EUROPE. In addition, the survey was shared via the private and project-related (bioplasticseurope.eu) social media platforms LinkedIn, Facebook, and Instagram for a maximum possible outreach among multiple respondents. Responses were collected for around 4 months (115 days) from October 22, 2020, to February 15, 2021. The survey was repeatedly promoted during this period, primarily at the beginning of November, mid-December 2020, and mid-January 2021. Of the 1,631 international total respondents, 1,050 were living in Germany. Twelve respondents of the German subset were excluded since they did not agree to the consent form. At this stage, 1,038 respondents remained in the sample.

The data was analyzed using descriptive statistics, with frequency description, measures of central tendency, and dispersion. Different socio-demographic sub-groups among the respondents were compared regarding their perceived infection risk, compliance with wearing MNP as a personal protective measure, and their choice of a particular MNP type and aspects of sustainability (cf. **Table 2**). The group aged 60+, to which only two people were assigned, was not further considered in the analysis due to its small sample size. Consequently, the remaining sample size decreased to 1,036 respondents. For comparison of groups, the Chi^2 test was used for nominal variables. For 2 × 2 crosstabs and crosstabs containing five or more cells with fewer than five cases, the Fisher's Exact test was applied. In cases of insufficient computing capacity to apply the Fisher's Exact test, the Monte Carlo Simulation was employed. The Mann–Whitney-U-test and Kruskal–Wallis test were used for ordinal variables (5-point Likert scale). For Kruskal–Wallis test results indicating a significant difference between groups, pairwise analyses employing the Mann–Whitney-U-test with Bonferroni correction were performed. Differences of groups concerning the metric index of knowledge were investigated with the t-test and one-way ANOVA after confirming the assumption of a normal distribution. Statistical inference was performed for a significance level of 5%.

The online survey was created using the tool Lime Survey. The software RStudio (version 1.4.1103), R (version 4.0.3), SPSS (version 25), and Microsoft Excel (version 2008) were used for data analysis and visualization. The study results were then discussed in the context of the current scientific evidence on MNP effectiveness and aspects of sustainability.

RESULTS

Description of the Study Population

A total of 1,036 participants were included in further analysis. The most represented age groups were 18–25 years (58.8%) and 26–35 years (35.3%), whereas the older age groups 36–45 and 46–59 years were less represented, accounting for 4.5 and 1.4%, respectively. Most of the participants had a lower education level, with 47.8% holding a high school degree and 3.6 % holding less than a high school degree. More than one-third of the sample reported having a bachelor's degree (24.6%) or a degree from trade school (16.8%), and they were assigned to the middle education level. The minority belonged to the high education level, with 6.9% of the participants holding a master's degree

TABLE 2 | Overview of variable characteristics and statistical tests (binomial, †categorial, ‡ordinal).

Outcome	Groups	Tests applied
Perceived infection risk	Education level‡	Chi^2 test
	Age group‡	Fisher's Exact test
Compliance with MNP guidelines‡	Perceived infection risk	Mann-Whitney-*U*-test
	Education level‡	Kruskal-Wallis-test
	Age group‡	Kruskal-Wallis-test
Importance of reusability‡	Perceived infection risk	Mann-Whitney-*U*-test
	Education level‡	Kruskal-Wallis-test
	Age group‡	Kruskal-Wallis-test
Most frequent usage of MNP†	Perceived infection risk	Chi^2 test
	Education level‡	Fisher's Exact test
	Age group‡	Fisher's Exact test
True/false question on modes of protection of MNP†	Perceived infection risk	Chi^2 test
	Education level‡	Chi^2 test
	Age group‡	Exact test
	Most frequent usage of MNP†	Fisher's Exact test with Monte Carlo Simulation
Perceived self-protection potential of MNP†	Perceived infection risk	Chi^2 test
	Education level‡	Fisher's Exact test
	Age group‡	Fisher's Exact test
	Most frequent usage of MNP†	Fisher's Exact test with Monte Carlo Simulation
Perceived third-party protection potential of MNP†	Perceived infection risk	Chi^2 test
	Education level‡	Chi^2 test
	Age group‡	Fisher's Exact test
	Most frequent usage of MNP†	Fisher's Exact test with Monte Carlo Simulation
Correct usage cotton mask†	Perceived infection risk	Chi^2 test*
	Education level‡	Fisher's Exact test
	Age group‡	Fisher's Exact test
	Most frequent usage of MNP†	Fisher's Exact test with Monte Carlo Simulation
Correct usage medical mask†	Perceived infection risk	Chi^2 test
	Education level‡	Fisher's Exact test
	Age group‡	Fisher's Exact test
	Most frequent usage of MNP†	Fisher's Exact test with Monte Carlo Simulation
Perceived sustainability of medical masks†	Perceived infection risk	Chi^2 test
	Education level‡	Fisher's Exact test
	Age group‡	Fisher's Exact test
	Most frequent usage of MNP†	Fisher's Exact test with Monte Carlo Simulation
Perceived sustainability of FFP2 mask†	Perceived infection risk	Chi^2 test
	Education level‡	Fisher's Exact test
	Age group‡	Fisher's Exact test
	Most frequent usage of MNP†	Fisher's Exact test with Monte Carlo Simulation
Willingness to choose a biodegradable MNP	Perceived infection risk	Fisher's Exact test
	Education level‡	Chi^2 test
	Age group‡	Chi^2 test
	Most frequent usage of MNP†	Chi^2 test
	Importance of reusability‡	Chi^2 test
Knowledge index on MNP (metric index)	Perceived infection risk	T-test
	Education level‡	One-way ANOVA
	Age group‡	One-way ANOVA

and 0.3% a PhD or higher. For data analyses, the five education levels were grouped into three categories: "low education level" (51.4%), "middle education level" (41.4%), and "high education level" (7.2%).

The perceived risk of acquiring SARS-CoV-2 infection was assumed to be a factor influencing the choice of MNP (36). At the time of the survey's conduction, most respondents indicated not feeling at an increased risk of getting infected with SARS-CoV-2 (84.1%), whereas 15.9% of the respondents did. The perceived infection risk seemed to increase with age (cf. **Figure 1**), with the five age groups significantly differing from each other (Chi: 16.624, $p = 0.01$, ϕ:0.127). Besides age, the perceived risk was also associated with the education level, showing a minimal but significant difference between the groups (Chi^2: 6.772, df:2, $p = 0.034$, φ:0.081).

Comparison of Groups

Aspects of Awareness, Attitude, and Compliance Toward MNP

More than three-quarters of the respondents (81.1%) indicated that they "always" followed the protective guidelines imposed during the pandemic. Almost a third of all participants were "mostly" following the guidelines (16.6%), whereas some (0.9%) were "neutral". A few were "mostly not" or "never" following the guidelines, with 1.2 and 0.3%, respectively. Further analysis showed that the respondents' compliance significantly differed by age group (H(4): 10.816, $p = 0.013$, $\eta^2 = 0.007$), indicating that the youngest age group (18–25 years) was the most compliant. Pairwise analysis revealed a minimal but significant difference (U:103040.000, $p = 0.049$, $r = 0.085$) between the age groups of 18–25 years ($\bar{x}$: 4.82) and 26–35 years ($\bar{x}$: 4.71).

Reusability of MNP was rated "important" by more than half of the participants (43.4%). Approximately one third stated that the reusability of MNP is "rather important" (34.1%), while 8% were "neutral" about the reusability of MNP. A small proportion considered reusability in a MNP "less important" (9.5%) or "not important" (5.1%). Descriptive statistics indicated differences in the distribution between the education groups, especially concerning the answer option of "important" (cf. **Figure 2**).

Data analysis revealed that the perceived importance of reusability is slightly associated with the education level [H(2): 13.162, df: 2, $p = 0.001$, $\eta^2 = 0.01$]. The pairwise analysis identified a significant difference between the high education level and the middle education level (U:12271, $p = 0.004$, $r = 0.141$) as well as the low education level (U:14675.500, $p < 0.001$, $r = 0.151$), indicating a higher relevance of MNP reusability for the high education group ($\bar{x}$: 4.42) in comparison to the middle ($\bar{x}$: 3.97) and low education group ($\bar{x}$: 3.99).

Descriptive statistics further indicated an association between the perceived importance of reusability and age group with regards to the options "rather important" and "important" (cf. **Figure 3**), which was confirmed by the Kruskal-Wallis-test (H(4):20.092, df: 3, $p < 0.001$, $\eta^2 = 0.016$). Pairwise analysis revealed significant differences between the age group of 36–45 ($\bar{x}$: 4.52), the age group 18–25 ($\bar{x}$: 3.94) as well as the age group 26–35 ($\bar{x}$: 4.06), which supports the previous descriptive statistics.

MNP Preferences of the Respondents

More than half of the respondents (66.0%) reported wearing cotton masks most of the time, followed by 21.2% using medical masks. The more effective FFP2 and FFP3 masks were rarely used, reported by 7.1 and 0.2%, respectively. A scarf was used by 0.8% of the participants, and 4.7% used other options that have not been specified. Further analysis revealed that the choic of MNP was significantly associated with the age group (Chi: 25.270, $p = 0.042$, φ:0.099) and the perceived individual infection risk (Chi^2: 20.275, df:5, $p = 0.001$, φ:0.141), showing that those who perceive themselves vulnerable wore medical masks and FFP2 masks more often (cf. **Figure 4**).

When choosing an MNP for daily use, several factors appeared to play a role. The factor "comfort" was considered important by 78.9% of participants, followed by the "protection of others", which was important to 63.7% when choosing an MNP for daily use. The level of "self-protection" was important to 54.9%, and more than a third of the participants cared about the MNP's "sustainability level" (46.0%). The "price", "design", and "shape" were important to 31.1, 16.3, and 13.2%, respectively. As for which MNP was considered to be the most comfortable, most participants (52.0%) indicated the "cotton mask", followed by the "medical mask" (34.7%). The other MNPs were rarely indicated as comfortable with FFP2 (4.4%), other (4.3%), scarf (3.8%), and FFP3 (0.6%).

Knowledge Level of Different Types of MNP

The knowledge level of the effectiveness level and correct use of different MNP were operationalized by a summed-up metric index of Q1-Q5 during the survey's conduction (cf. **Table 3**). No differences could be identified between the age groups, education levels and the participants' perceived risk of infection, assuming that all respondents were similarly well-informed about different MNP's protective potential and correct use.

The participants' overall knowledge of the effectiveness of different MNP appeared to be high when consulting the descriptive statistics (cf. **Table 3**). The majority (53.6 %) of the participants described the protective function of different face masks correctly (Q1) by agreeing that all types of face masks provide third-party protection. The Fisher's Exact test revealed a significant association between the outcomes of Q1 and the "Most frequent usage of MNP" (Chi:28.461, $p = 0.010$ φ:0.102).

As for the effectiveness of different MNPs for self-protection (Q2), more than half of the participants (65.6%) chose the correct answer "FFP3", followed by the "FFP2" (26.6%).

Concerning the MNP's potential to prevent the user from spreading the virus to others (third-party protection), nearly half of the participants (42.3%) chose the "FFP3 mask" correctly to be the most effective MNP (Q4). About a third of the participants chose the wrong option, i.e., "FFP2 mask" (24.8%) or the "cotton mask" (3.0%). Further analysis suggests that knowledge of the third-party protection of different MNP may be associated with the choice of MNP, indicating that the knowledge of the effectiveness of different MNPs influences the preference toward a more effective MNP (Chi:64.919, $p < 0.001$, φ:0.110).

About half (47.1%) of the participants knew about the correct use of a cotton mask (Q4), being aware that this mask type

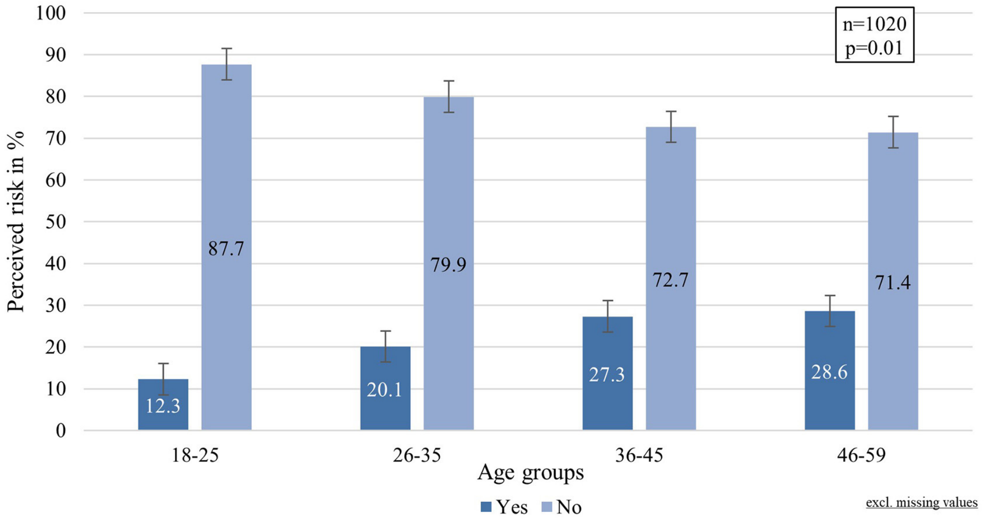

FIGURE 1 | Perceived risk of acquiring SARS-CoV-2 infection by age groups.

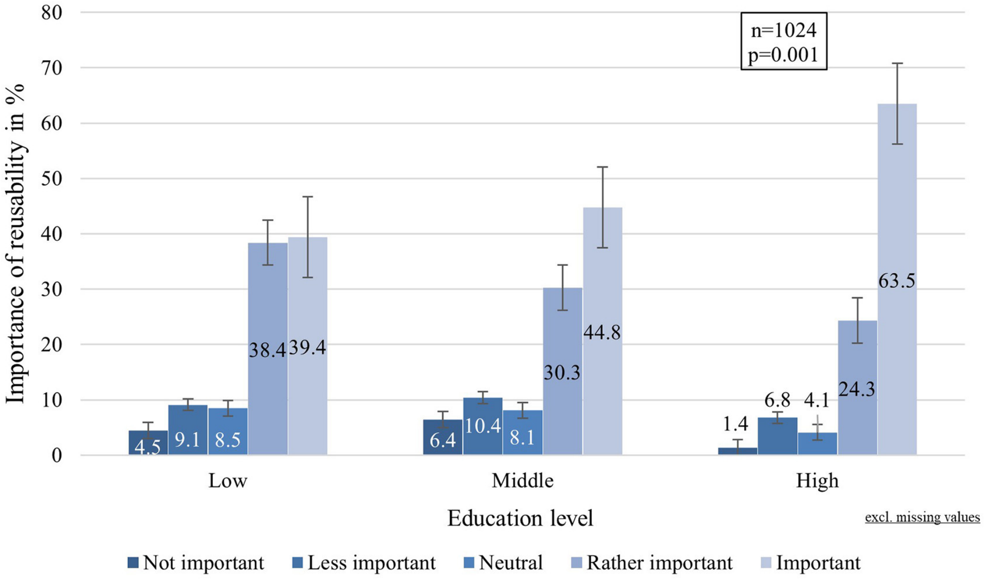

FIGURE 2 | Importance of reusability by education level.

should be exchanged and/or washed after a few hours of wearing to secure its effectiveness. This was significantly related to the choice of MNP (Chi:42.658, $p < 0.001$, φ:0.107) and the perceived infection risk (Chi:9.406, $p = 0.047$, φ:0.098). As for the correct use of a medical mask, 69.9% of the participants knew the right answer (cf. **Table 3**). With regards to the output of this question (Q5), a significant association toward the choice of MNP could be identified (Chi:59.754, $p < 0.001$, φ:0.123).

Knowledge of the sustainability of different MNPs was sufficient (Q6 and Q7), with 44.0% of the participants choosing the correct material of a medical mask ("synthetic polymers") and 49.1% answering the same question correctly about FFP2/FFP3 masks ("synthetic polymers"). However, almost half of the participants chose a "mix of cotton and synthetic polymers", which is wrong for both medical and FFP2/FFP3 masks (50.9 and 43.5%, respectively). Most of the participants knew about the low biodegradability potential of medical masks, FFP2 and FFP3 masks.

A total of 387 participants (41.7%) would choose a biodegradable mask if it provided the same level of protection as a medical mask, even if it were to cost more and looked less fashionable. The majority (58.3%), however, would not choose this sort of mask. The descriptive statistics indicated a

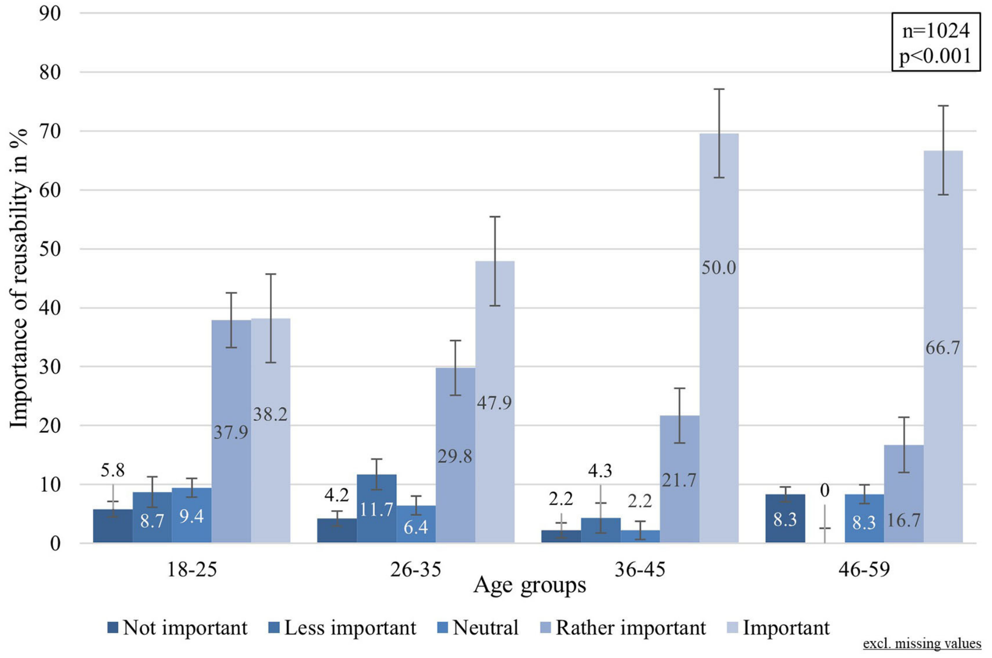

FIGURE 3 | Importance of reusability by age group.

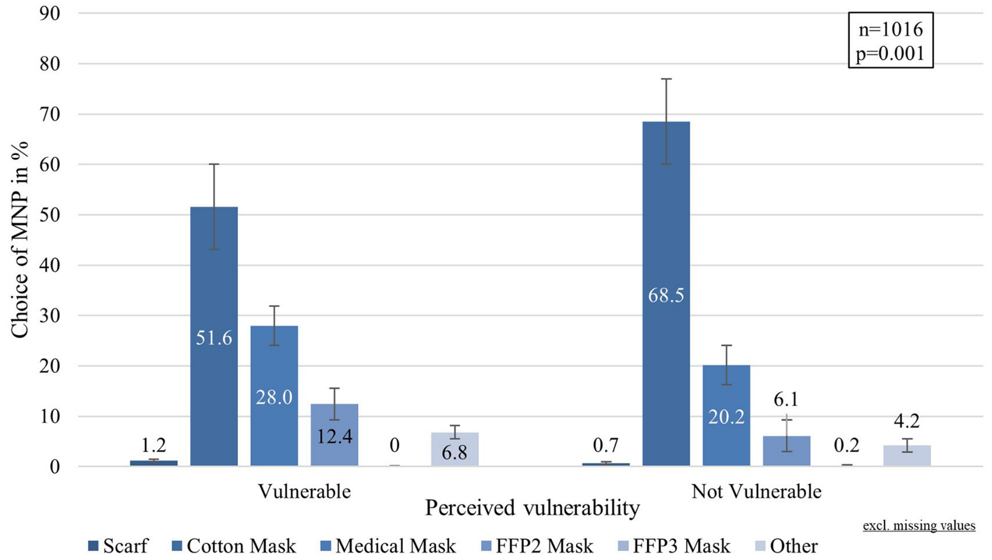

FIGURE 4 | Choice of MNP by perceived risk of infection.

relationship between the "willingness to choose a sustainable mask" and the "perceived importance of reusability" (cf. **Figure 5**), which was confirmed by further analysis, implying a highly significant association and a large effect (Chi^2:48.016, $p < 0.001$, φ:0.228). The age group (Chi^2:8.544, df:3, $p = 0.036$, φ:0.096) and the MNP choice (Chi:27.143, $p < 0.001$, φ:0.170) were also significantly related to the "willingness to choose a sustainable mask".

DISCUSSION

This cross-sectional study investigated the perceptions and knowledge of 1,036 German participants regarding the effectiveness and sustainability of different MNP associated with their socio-demographic characteristics and perceived SARS-CoV-2 infection risk. The study thereby provides insight into the second wave of the COVID-19 pandemic in Germany,

TABLE 3 | Questions operationalizing the knowledge level on different types of MNP.

Q1: Which statement about MNP in everyday application do you think is true?							**Total *n***
Single choice	Self-protection is given	Third-party protection is given*	Both answers are right	Both answers are wrong			
n (%)	41 (4.1)	541 (53.6)	231 (22.9)	196 (19.4)			1,009
Q2: Which type of MNP do you think protects yourself most effectively against SARS-CoV-2 infection in daily life?							
Single choice	Scarf	FFP2	Cotton Mask	FFP3*	Medical mask		
n (%)	1 (0.1)	256 (26.6)	18 (1.9)	632 (65.6)	56 (5.8)		963
Q3: Which type of mouth/nose protection do you think protects others most effectively against Sars-CoV-2 infection in daily life?							
Single choice	Scarf	FFP2	Cotton Mask	FFP3*	Medical mask	All above	
n (%)	2 (0.2)	243 (24.8)	29 (3.0)	414 (42.3)	153 (15.6)	137 (14.0)	978
Q4: How long do you think are you allowed to wear a cotton mask on average to secure its protective function?							
Single choice	Until it is totally wet	Several weeks (drying in between)	Several days (drying in between)	Only a few hours*	<1 h		
n (%)	182 (17.9)	17 (1.7)	231 (22.7)	480 (47.1)	109 (10.7)		1,019
Q5: When do you think a medical mask should be replaced by a new one?							
Single choice	After one time of wearing*	After several times	After several days of wearing	After several weeks of wearing	You never need to exchange it		
n (%)	702 (69.7)	247 (24.5)	48 (4.8)	5 (0.5)	5 (0.5)		1,007
Q6: What is a medical mask made of?							
Single choice	Cotton	Synthetic polymers (plastics)*	Mix of cotton and synthetic polymers	Viscose	Other textiles		
n (%)	7 (0.8)	375 (44.0)	434 (50.9)	33 (3.9)	3 (0.4)		852
Q7: What is a FFP2/FFP3 mask made of?							
Single choice	Cotton	Synthetic polymers (plastics)*	Mix of cotton and synthetic polymers	Viscose	Other textiles		
n (%)	1 (0.1)	369 (49.1)	327 (43.5)	43 (5.7)	12 (1.6)		752
Q8: Which MNP is most likely to be biodegradable? (Multiple Choice)							
Multiple choice	Cotton mask*	Medical mask	Scarf	FFP2 mask	FFP3 mask		
n (%)	965 (93.1)	37 (3.6)	124 (12.0)	8 (0.8)	6 (0.6)		1,036

*Correct answer option.

during which the German government had already imposed the use of MNP.

According to the results, the majority of the respondents wore cotton masks daily, followed by medical masks. In contrast, more effective masks, such as FFP2 and FFP3, were rarely used. Furthermore, associations were identified between the MNP used and age group as well as the perceived risk, indicating that older individuals who perceive themselves at increased risk were more likely to use the more effective mask types. Those trends in the usage of different MNPs are confirmed by a similar survey conducted in Germany at the start of the pandemic (37). This national survey showed MNP preference differences between age groups and supports our result that older people use professional instead of homemade masks (37). In the international context, similar usage frequencies were reported in the UK (38), whereas in Asian countries such as China, medical masks and N95 masks were the preferred choice over the same period (39, 40). This difference could stem from higher production capacities in China, which produced half of the number of professional masks needed for the world (41). Other studies indicate that the preferences concerning MNP differed between countries (40, 42), referring to the regulations and communication strategies in place that varied between countries and changed over time (43). In Germany, for example, during the first 3 months of the data collection, it was recommended to wear non-professional MNP, whilst at the end of data collection, medical masks were compulsory in shopping facilities and public transport (44), which has had an impact on the compliance of wearing a mask (20).

The overall compliance toward protective guidelines was high among most study participants, with differences between the age groups. Interestingly, the results show that the youngest age group (18–25 years) was the most compliant with wearing face masks. However, this age group was and continues to be criticized for not following the non-pharmaceutical rules to limit the spread of SARS-CoV-2 (45). While several national publications supported the results of the present study (46, 47), some studies found no association between compliance of wearing masks and age groups (44, 48), and others detected a positive association between increasing age and the likelihood of wearing a mask in public areas (39, 49). The mixed results suggest that the strength of the association varies according to the age group assignment and sample size per age group, which should be considered for the study at hand. In general, some studies indicated the compliance of German citizens toward this measure

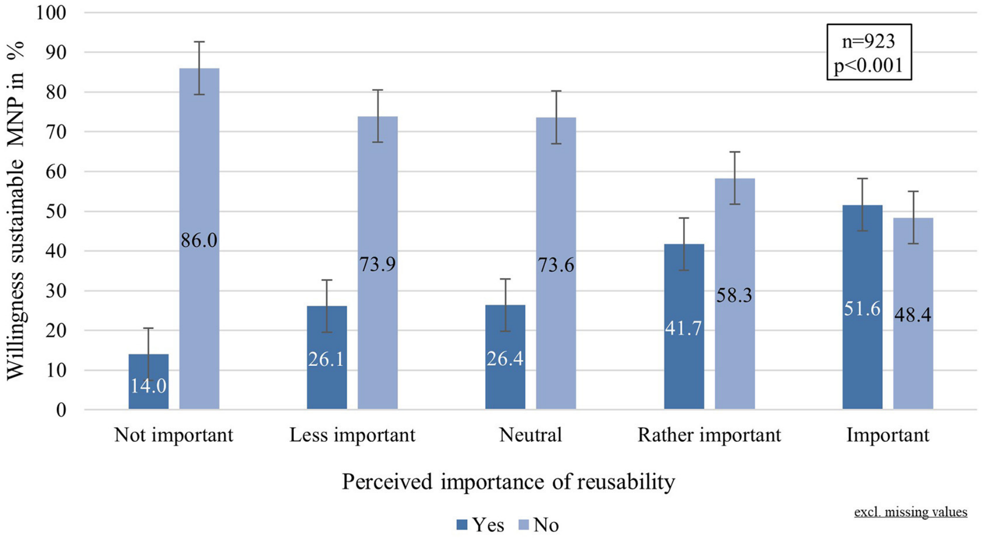

FIGURE 5 | Willingness to choose a sustainable mask by perceived importance of reusability.

to be high (49). However, when compared to other European and predominantly Asian countries, the compliance of the German population was relatively low during the second wave (20, 50).

The knowledge about the effectiveness of different masks, on the other hand, seemed high among all participants. Thanks to ongoing research and health education programs, the level of knowledge has increased throughout the pandemic. The majority considered themselves to be well-informed (51), whereas at the beginning of the pandemic young people were insufficiently informed about the effectiveness of masks (46). Most participants knew about different mask types' protective characteristics, without showing any differences between socioeconomic groups. However, an association was found several times between knowledge-related questions (Q1, Q3, Q4, Q5) and the choice of MNP (cf. **Table 2**), suggesting that knowledge of the effectiveness and sustainability of the MNP could influence their choice of protection.

According to the findings of this study, the users' choice of MNP was primarily influenced by the factors "comfort", "protection of third parties", "self-protection", and "sustainability level". Similar factors could be identified by other studies, with the most important being "comfort" (42, 52), followed by "efficiency", "access", "inconvenience", and "appearance" (52, 53). In the UK, however, "reusability" was perceived important by most of the people, followed by the "safety" and "comfort", whilst "price" and "accessibility" were considered less important (38).

Research on the awareness of product sustainability could confirm the positive association of higher education levels and the perceived high importance of reusability in the present study (54–56). For example, one study reported that highly educated people are more likely to behave in an environment-friendly way and reduce, reuse and recycle waste products (56). A similar trend could be observed in the older population when compared to younger age groups (57), supporting our results that older age groups perceive sustainability as more important than younger age groups. Overall, a large proportion of the participants knew about the sustainability level of different types of MNP. Nearly half were open to the use of biodegradable MNP when effective in protection, which differed, however, by age. As previously highlighted, older age groups were more willing to choose a biodegradable and effective but less fashionable mask.

As COVID-19 is known to pose an exceptionally high health risk toward the elderly (58), the imbalanced age distribution in the study population should be considered when interpreting the findings of this study. For example, the overall perceived risk of acquiring SARS-CoV-2 infection was relatively low in the whole study group, which might be due to the increasingly perceived risk of infection that was identified in the older age groups. Similar age-related associations have also been described in other studies (39). The distribution of different age groups among the population of this study may have biased the results, as participants aged 36–45 years accounted for only 4.5% and 46–59 years for only 1.5% of the total sample. The same applies to the education groups (low, medium, high), with the high education group accounting for only 7.2% of the sample. The survey was mainly shared with young students in the middle and lower education groups, given the selected distribution channels such as social media platforms and the HAW Hamburg mailing list. Moreover, the survey was only available online, which may have led to limited outreach to older populations. Finally, the results may not reflect the German population as a whole. Most of the young participants lived in Hamburg and were compliant toward the respective mask-related regulations, which differed from those in other federal states, such as Bavaria, concerning the date of enactment and strictness (59).

It can be concluded that although the knowledge and compliance levels were high among the German participants, the cotton mask was the preferred option during the second wave of the COVID-19 pandemic. The choice of MNP was mainly influenced by the comfort, effectiveness, and sustainability of the mask itself, which implies that in accordance with other outcomes, German citizens—especially older age groups—would be open to a reusable and comfortable solution, which protects themselves and others effectively against SARS-CoV-2.

The results obtained help in determining epidemiological risks identified in the study population and form a basis for further research on more sustainable and effective alternatives of MNP. The current COVID-19 pandemic has already resulted in a large amount of plastic waste that will impact the environment for many years. With these long term consequences in mind, greater emphasis should be placed on the production of more sustainable and environmentally friendly MNPs in epidemic management, especially in view of the growing threat of future epidemics (60).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MTCF: conceptualization, project administration, investigation, methodology, data curation, formal analysis, visualization, writing—original draft, and review and editing—original draft. WL: conceptualization, funding acquisition, supervision, and review and editing—original draft. JBa: conceptualization, methodology, supervision, and review and editing—original draft. JBo: conceptualization, methodology, project administration, supervision, validation, and original draft—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.768454/full#supplementary-material

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