The Epidemiology of Respiratory Infections in Mobile Populations

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Abstract

Respiratory Tract Infections (RTIs) in mobile populations such as travellers are prevalent and can escalate into severe illnesses. Timely identification and treatment of these conditions are imperative to prevent disease progression. This thesis aims to to evaluate the epidemiology of RTIs in travellers and mobile populations using mobile applications.

Study I examined the ethical dimensions of mobile apps in travel medicine through a systematic literature review, encompassing seven papers. Privacy and data protection emerged as paramount ethical concerns, highlighting worries over sensitive data exposure and a lack of international standards.

Study II focused on RTIs among travellers, employing an in-depth review and meta-analysis of 429 studies, including 86,841 potential symptoms and 807,632 confirmed RTI cases. A significant proportion of RTIs were associated with large public gatherings, so called "mass gatherings", with coughing being the predominant symptom. The prevalence rates stood at 10% [8%; 14%] for respiratory symptoms and 37% [27%; 48%] for confirmed RTIs.

Study III evaluated a novel mobile app, Infection Tracking in Travellers (ITIT), which documents travel-related symptoms alongside geolocation and weather data. The pilot study affirmed the app's user-friendliness and efficacy, with all participants finding it user-friendly and 63% recommending it to others.

Study IV entailed the assessment of infection in travellers using an enhanced ITIT version, enrolling 609 participants from various regions including Europe, South Africa, Japan, and Malaysia. Symptoms were reported in 35% of the registered trips, with respiratory symptoms accounting for 17% of trips. Humidity and atmospheric pressure were found to have a significant impact on respiratory symptoms. Post-travel questionnaires revealed that 12% of participants encountered symptoms post-return, with several engaging in self-treatment.

Study V explored the extent and intensity of SARS-CoV-2 symptoms among previously healthy young adults, like those in the Swiss Armed Forces, using the ITITp (Illness Tracking in Tested Individuals) smartphone application. Out of 502 individuals recruited from May 2020 to October 2021, 68 (13.5%) tested

positive, exhibiting a higher prevalence of typical COVID-19 symptoms, with 6% requiring hospital care.

In conclusion, these studies underscore the importance of understanding and monitoring RTIs in mobile populations. Mobile applications are instrumental in this endeavor by facilitating symptom self-reporting and real-time data provision. However, ethical concerns surrounding privacy and data protection necessitate prudent consideration. Further research is needed to optimize these tools for the monitoring of RTIs in mobile populations.

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List of Abbreviations

ACC . . . . . . Accuracy
AIC . . . . . . Akaike Information Criterion
ARIs . . . . . . Acute Respiratory Infections
AUC . . . . . . Area Under the ROC Curve
BASEC . . . . Business Administration System for Ethics Committees
CANDALS . . Citizenship, Ability, Neurodiversity, Disability, Age, Literacy and Size
CART . . . . . Classification And Regression Tree
CCLS . . . . . Common Cold-like Syndrome
CDC . . . . . . Centers for Disease Control and Prevention
CENTRAL . . Central Register of Controlled Trials
DALYs . . . . Global Disability-Adjusted Life Years
DBSCAN . . . Density-Based Spatial Clustering of Applications with Noise
DONs . . . . . Disease Outbreak News bulletins
GBD . . . . . . Global Burden of Diseases, Injuries, and Risk Factors Study
GDPR . . . . . General Data Protection Regulation
GOSH . . . . . Graphic Display of Study Heterogeneity
GPS . . . . . . Global Positioning System
H1N1 . . . . . Influenza A virus subtype H1N1
ILI . . . . Influenza-like Illness
ITIT . . . . . . Infection Tracking in Travellers
ITITp . . . . . Infection Tracking in Tested Persons
JBI . . . . Joanna Briggs Institute
K-NN . . . . . K-Nearest Neighbours
LRT . . . . . . Lower Respiratory Tract

LRTIs . . . . . Lower Respiratory Tract Infections
MERS . . . . . Middle East Respiratory Syndrome
MERS-CoV . Middle East Respiratory Syndrome Coronavirus
MICE . . . . . Multivariate Imputation by Chained Equations
PCR . . . . . . Polymerase Chain Reaction
PRISMA . . . Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO . Prospective Register of Systematic Reviews
RCTs . . . . . Randomized Controlled Trial
R_0 . . . . Basic Reproductive Ratio or Basic Reproduction Number
RSV-A . . . . Respiratory Syncytial Virus Type A
RT-PCR . . . Reverse Transcription Polymerase Chain Reaction
RTIs . . . . . . Respiratory Tract Infections
SANRA . . . . Scale for the Assessment of Narrative Review Articles
SARS . . . . . Severe Acute Respiratory Syndrome
SIM . . . . . . Subscriber Identity Module
SNF . . . . . . Swiss National Science Foundation
STROBE . . . Strengthening the Reporting of Observational Studies in Epidemiology
TOURIST2 . Tracking Of Urgent Risks In Swiss Travellers
UN . . . . United Nations
URT . . . . . . Upper Respiratory Tract
URTIs . . . . . Upper Respiratory Tract Infections
VFRs . . . . . Visitors of Friends and Relatives
WHO . . . . . World Health Organization

1
Introduction

Contents

1.1 The Evolution of Travel and its Impact on Global Connectivity

The advent of technology has reshaped global mobility, making the world more interconnected than ever before. This transformation is illustrated by the evolution of transportation: from the 19th-century square riggers, which took 21 days to navigate the North Atlantic route from New York to Liverpool [1, 2], to contemporary aircraft that cover the same distance in under 10 hours [3]. This drastic reduction in travel time has revolutionized our capability to explore and connect with different regions of the globe.

Furthermore, travel, once a luxury exclusive to the upper echelons of society or to a small group of adventure seekers, has become accessible to a wider demographic. This democratization of travel, propelled by technological advancements and the increased availability of fast transportation modes like airplanes, has led to a sharp rise in international tourist arrivals–from 25.2 million in 1950 to 1.404 billion in 2018 (Figure 1.1) [4]. Despite the temporary setback caused by the COVID-19 pandemic, travel is projected to continue its upward trend with an estimated annual increase of 5%.

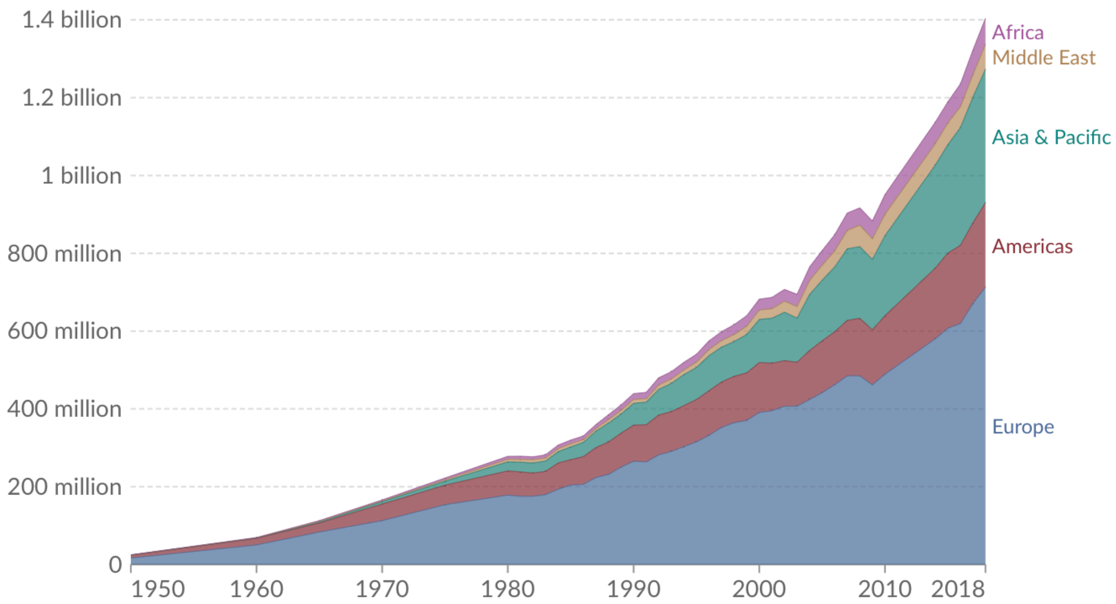

Figure 1.1: International tourist arrivals by region. Notes: International tourists are those who stay overnight and whose main purpose for visiting is not commercial. Sources: United Nations World Tourism Organization - World Tourism Barometer (2019)

However, this increased global mobility presents significant public health challenges, particularly in terms of disease transmission. The COVID-19 pandemic serves as a stark reminder of our global interconnectedness and vulnerability to RTIs. Originating in Wuhan, China, in November 2019, the SARS-CoV-2 virus breached international borders, reaching Japan and Thailand by early January 2020. By mid-January, it had spread to Europe and North America, and by late January, it had reached Australia. Africa and South America reported their first cases in February. In total, it took approximately 94 days for this respiratory virus to reach all continents [5].

1.2 Respiratory Tract Infections: Causes, Symptoms, and Diagnosis

Respiratory Tract Infections (RTIs) are a major determinant of global health outcomes. In 2019, Lower Respiratory Infections (LRIs) were responsible for 2.49 million deaths, ranking fourth among the 25 leading causes of global Disability-Adjusted Life Years (DALYs) and accounting for 3.8 percent of total DALYs (Figure 1.2) [6].

RTIs, which affect the respiratory tract extending from the nostrils to the alveoli in the lungs, can be categorised into Upper Respiratory Tract (URT) and Lower Respiratory Tract (LRT) infections. The URT encompasses the nostrils, nasal cavity, mouth, pharynx, and larynx, while the LRT comprises the trachea, bronchi and bronchioles, and alveoli. Thus RTI infections can be categorized as either URT or LRT, or span both [7].

Leading causes 1990	Percentage of DALYs 1990	Leading causes 2019	Percentage of DALYs 2019	Percentage change in number of DALYs, 1990–2019	Percentage change in age-standardised DALY rate, 1990–2019
1 Neonatal disorders	10·6 (9·9 to 11·4)	1 Neonatal disorders	7·3 (6·4 to 8·4)	–32·3 (–41·7 to –20·8)	–32·6 (–42·1 to –21·2)
2 Lower respiratory infections	8·7 (7·6 to 10·0)	2 Ischaemic heart disease	7·2 (6·5 to 7·9)	50·4 (39·9 to 60·2)	–28·6 (–33·3 to –24·2)
3 Diarrhoeal diseases	7·3 (5·9 to 8·8)	3 Stroke	5·7 (5·1 to 6·2)	32·4 (22·0 to 42·2)	–35·2 (–40·5 to –30·5)
4 Ischaemic heart disease	4·7 (4·4 to 5·0)	4 Lower respiratory infections	3·8 (3·3 to 4·3)	–56·7 (–64·2 to –47·5)	–62·5 (–69·0 to –54·9)
5 Stroke	4·2 (3·9 to 4·5)	5 Diarrhoeal diseases	3·2 (2·6 to 4·0)	–57·5 (–66·2 to –44·7)	–64·6 (–71·7 to –54·2)
6 Congenital birth defects	3·2 (2·3 to 4·8)	6 COPD	2·9 (2·6 to 3·2)	25·6 (15·1 to 46·0)	–39·8 (–44·9 to –30·2)
7 Tuberculosis	3·1 (2·8 to 3·4)	7 Road injuries	2·9 (2·6 to 3·0)	2·4 (–6·9 to 10·8)	–31·0 (–37·1 to –25·4)
8 Road injuries	2·7 (2·6 to 3·0)	8 Diabetes	2·8 (2·5 to 3·1)	147·9 (135·9 to 158·9)	24·4 (18·5 to 29·7)
9 Measles	2·7 (0·9 to 5·6)	9 Low back pain	2·5 (1·9 to 3·1)	46·9 (43·3 to 50·5)	–16·3 (–17·1 to –15·5)
10 Malaria	2·5 (1·4 to 4·1)	10 Congenital birth defects	2·1 (1·7 to 2·6)	–37·3 (–50·6 to –12·8)	–40·0 (–52·7 to –17·1)
11 COPD	2·3 (1·9 to 2·5)	11 HIV/AIDS	1·9 (1·6 to 2·2)	127·7 (97·3 to 171·7)	58·5 (37·1 to 89·2)
12 Protein-energy malnutrition	2·0 (1·6 to 2·7)	12 Tuberculosis	1·9 (1·7 to 2·0)	–41·0 (–47·2 to –33·5)	–62·8 (–66·6 to –58·0)
13 Low back pain	1·7 (1·2 to 2·1)	13 Depressive disorders	1·8 (1·4 to 2·4)	61·1 (56·9 to 65·0)	–1·8 (–2·9 to –0·8)
14 Self-harm	1·4 (1·2 to 1·5)	14 Malaria	1·8 (0·9 to 3·1)	–29·4 (–56·9 to 6·6)	–37·8 (–61·9 to –6·2)
15 Cirrhosis	1·3 (1·2 to 1·5)	15 Headache disorders	1·8 (0·4 to 3·8)	56·7 (52·4 to 62·1)	1·1 (–4·2 to 2·9)
16 Meningitis	1·3 (1·1 to 1·5)	16 Cirrhosis	1·8 (1·6 to 2·0)	33·0 (22·4 to 48·2)	–26·8 (–32·5 to –19·0)
17 Drowning	1·3 (1·1 to 1·4)	17 Lung cancer	1·8 (1·6 to 2·0)	69·1 (53·1 to 85·4)	–16·2 (–24·0 to –8·2)
18 Headache disorders	1·1 (0·2 to 2·4)	18 Chronic kidney disease	1·6 (1·5 to 1·8)	93·2 (81·6 to 105·0)	6·3 (0·2 to 12·4)
19 Depressive disorders	1·1 (0·8 to 1·5)	19 Other musculoskeletal	1·6 (1·2 to 2·1)	128·9 (122·0 to 136·3)	30·7 (27·6 to 34·3)
20 Diabetes	1·1 (1·0 to 1·2)	20 Age-related hearing loss	1·6 (1·2 to 2·1)	82·8 (75·2 to 88·9)	–1·8 (–3·7 to –0·1)
21 Lung cancer	1·0 (1·0 to 1·1)	21 Falls	1·5 (1·4 to 1·7)	47·1 (31·5 to 61·0)	–14·5 (–22·5 to –7·4)
22 Falls	1·0 (0·9 to 1·2)	22 Self-harm	1·3 (1·2 to 1·5)	–5·6 (–14·2 to 3·7)	–38·9 (–44·3 to –33·0)
23 Dietary iron deficiency	1·0 (0·7 to 1·3)	23 Gynaecological diseases	1·2 (0·9 to 1·5)	48·7 (45·8 to 51·8)	–6·8 (–8·7 to –4·9)
24 Interpersonal violence	0·9 (0·9 to 1·0)	24 Anxiety disorders	1·1 (0·8 to 1·5)	53·7 (48·8 to 59·1)	–0·1 (–1·0 to 0·7)
25 Whooping cough	0·9 (0·4 to 1·7)	25 Dietary iron deficiency	1·1 (0·8 to 1·5)	13·8 (10·5 to 17·2)	–16·4 (–18·7 to –14·0)
27 Age-related hearing loss	0·8 (0·6 to 1·1)	26 Interpersonal violence	1·1 (1·0 to 1·2)	10·2 (3·2 to 19·2)	–23·8 (–28·6 to –17·8)
29 Chronic kidney disease	0·8 (0·8 to 0·9)	40 Meningitis	0·6 (0·5 to 0·8)	–51·3 (–59·4 to –42·0)	–57·2 (–64·4 to –48·6)
30 HIV/AIDS	0·8 (0·6 to 1·0)	41 Protein-energy malnutrition	0·6 (0·5 to 0·7)	–71·1 (–79·6 to –59·7)	–74·5 (–82·0 to –64·5)
32 Gynaecological diseases	0·8 (0·6 to 1·0)	46 Drowning	0·5 (0·5 to 0·6)	–60·6 (–65·2 to –53·6)	–68·2 (–71·9 to –62·8)
34 Anxiety disorders	0·7 (0·5 to 1·0)	55 Whooping cough	0·4 (0·2 to 0·7)	–54·5 (–74·6 to –16·9)	–56·3 (–75·6 to –20·3)
35 Other musculoskeletal	0·7 (0·5 to 1·0)	71 Measles	0·3 (0·1 to 0·6)	–89·8 (–92·3 to –86·8)	–90·4 (–92·8 to –87·5)

Figure 1.2: Leading 25 Level 3 causes of global DALYs and percentage of total DALYs (1990 and 2019), and percentage change in number of DALYs and age-standardised DALY rates from 1990 to 2019 for both sexes combined for all ages (GBD Study 2019)

Although often interchanged with Acute Respiratory Infections (ARIs), the term RTIs also covers latent infections like tuberculosis. Diagnosis based solely on clinical presentation is often challenging due to the cardinal symptoms of respiratory disease - dyspnea and cough [8]. Therefore, molecular or imaging tests are often required for confirmation [9, 10].

Patients with RTIs typically experience symptoms such as cough, shortness of breath, expectoration, runny nose or congestion, loss of sense of smell or taste, sore throat, sinus pain, voice failure or hoarseness, and wheezing. In addition, patients may also experience other associated symptoms such as general symptoms like asthenia, fever, headache, chest pain, musculoskeletal symptoms like arthralgia and myalgia, and gastrointestinal symptoms like abdominal pain, chills, diarrhoea, nausea and vomiting.

A variety of microorganisms including viruses, bacteria and fungi can cause RTIs. Viruses account for nearly 80% of acute RTIs with influenza, parainfluenza, human respiratory syncytial virus and human adenovirus being the most common [11, 12]. However, improved detection methods have highlighted the significant role of rhinoviruses and coronaviruses in viral respiratory diseases [13, 14]. In both URT and LRT infections, the most prevalent bacterial pathogens include *Streptococcus pneumoniae*, *Chlamydophila pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* and *Legionella pneumophila* [15]. Fungal respiratory tract infections (RTIs) pose a substantial clinical challenge, particularly in patients with compromised immune systems. The primary causative agents of these infections are Aspergillus, Cryptococcus, and Pneumocystis.

1.3 Transmission and Dynamics of Respiratory Pathogens

The transmission of respiratory pathogens, predominantly viruses, can occur through three primary routes as outlined by the Centers for Disease Control Prevention (CDC) and the World Health Organization (WHO): contact, droplet, and airborne transmission [16–18].

- **Contact transmission** involves the direct or indirect transfer of virus-laden respiratory secretions from an infected individual to a susceptible individual.
- **Droplet transmission** occurs when virus-laden respiratory droplets expelled from an infected individual are deposited on the mucosal surfaces of a susceptible individual.
- **Airborne transmission** involves the generation of fine airborne respiratory droplets containing the virus during exhalation by an infected individual or medical aerosol-generating procedures performed on an infected individual. These droplets can then be inhaled by a susceptible individual.

$$\frac{dx}{dt} = k - ux - \beta xy \tag{1}$$

$$\frac{dy}{dt} = y(\beta x - u - v) \tag{2}$$

In the basic models of infection dynamics developed by R.M. Anderson, R.M. May, and M.A. Nowak, uninfected and infected hosts are represented by x and y, respectively. The constant immigration rate of uninfected hosts is denoted by k and their natural death rate by u (Equation 1) [19, 20].

Hosts that have been infected propagate the pathogen to those that are not infected at a rate symbolized by βxy. Here, β is the rate constant that typifies the infectivity of the pathogen. The mortality rate of infected hosts increases to u + v, where v is the parameter that represents the virulence, or harmfulness, of the infection (Equation 2) [19, 20].

$$R_0 = [\beta/(u+v)]\left(\frac{k}{u}\right) \tag{3}$$

The basic reproductive ratio, also known as the basic reproduction number (R_0), is characterized as the mean count of infected contacts for each infected individual. On a population scale, if R_0 exceeds one, it signifies that a virus will persist in propagating among vulnerable hosts in the absence of environmental alterations or external measures. Conversely, if R_0 is less than one, it suggests that the virus will ultimately die out on an epidemiological level given those particular conditions (Equation 3). [19–21].

Field observations have estimated consistent R_0 values for different viral pathogens despite uncertainties. For respiratory pathogens such as SARS coronavirus and H1N1 influenza, R_0 values typically range from 2 to 5. Another highly contagious virus with a high R_0 value is measles, which has an R_0 value that is often cited to be between 12-18 [22]. It's important to note that R_0 values can change over time due to mutations in the viral genome. These changes can affect the virus's ability to spread and persist in a population [19].

As evidenced by the rapid global spread of SARS-CoV-2 and the ensuing pandemic, respiratory infections with high R_0 values are prime candidates for causing epidemics or pandemics. In fact, some of the most significant pandemics of the 21st century have been caused by respiratory pathogens, particularly viruses.

1.4 Outbreaks of Respiratory Infections: Historical Overview

1.4.1 The 2002-2003 SARS Outbreak

In November 2002, a severe form of pneumonia was identified in several patients in Foshan, a city in Guangdong Province, China. The symptoms exhibited by these patients included fever and respiratory distress [23–25]. Following this, disease clusters were detected in seven municipalities in southern China. The virus was introduced into Hong Kong in February 2003 when a doctor from Zhongshan University in Guangdong Province traveled there for a wedding. He unknowingly transmitted the virus to several guests at the Metropole Hotel, marking the beginning of the virus's introduction into Hong Kong and its international spread [23–25]. The causative agent, SARS-CoV-1, was isolated by three laboratories in March 2003 using classical virological methods. From late 2002 to late 2003, the virus caused approximately 8,000 illnesses and 700 deaths in 29 countries before it finally disappeared [23, 26].

1.4.2 The 2009 H1N1 Flu Pandemic

In 2009's spring, the H1N1 strain of the influenza A virus emerged. This novel H1N1 infection was first detected in California on April 15th and quickly spread throughout the U.S. Soon after initial flu outbreaks were noted in North America in April 2009, this new flu strain began to spread internationally [26]. By June 2009, the WHO declared it a global pandemic, with 74 countries and territories reporting laboratory-confirmed cases. This strain got its classification as influenza A (H1N1)pdm09. Symptoms of this flu included fever, cough, a sore throat, nasal congestion, body discomfort, headaches, chills, and tiredness. The CDC provided data suggesting that in the virus's first year, it led to the deaths of an estimated 151,700 to 575,400 individuals globally. It was reported that about 80% of these deaths were in people below 65 years old. By August 10, 2010, the WHO marked the end of the global 2009 H1N1 flu pandemic [27]. Yet, the (H1N1)pdm09 strain is still present as a seasonal flu, causing sickness, hospital stays, and deaths annually.

1.4.3 The 2009-2010 West African Meningitis Outbreak

In January 2009, a bacterial meningitis was diagnosed in several patients in the Zinder Region of southern Niger, with symptoms such as fever, headache, and a stiff neck [26, 28]. The isolated strain was identified as *Neisseria meningitidis* (Nm) serogroup A [29]. This marked the onset of the 2009-2010 West African meningitis outbreak that affected Burkina Faso, Mali, Niger, and Nigeria [30]. Over 85% of the cases were concentrated in a specific region covering parts of Northern Nigeria and Niger. The outbreak resulted in a total of 13,516 infections and 931 deaths [31]. Nigeria faced the brunt of the outbreak, with more than half of the reported cases and deaths. To curb the spread, large-scale vaccination campaigns were initiated, utilizing almost a third of the global emergency vaccine reserve for this particular bacterial strain [29, 32].

1.4.4 The 2012 Middle East Respiratory Syndrome Coronavirus Outbreak

In June 2012, a novel coronavirus responsible for Middle East Respiratory Syndrome (MERS) was discovered in a patient in Jeddah, Saudi Arabia. This marked the start of the 2012 MERS Coronavirus Outbreak, which significantly affected several Middle Eastern countries, leading to the coining of the name "MERS" [33]. This virus, referred to as MERS-CoV, caused symptoms such as fever, cough, breathing difficulties, and occasionally complications like pneumonia and gastrointestinal issues [33]. By 2021, instances of the virus had been recorded in 24 nations, including Iran, Saudi Arabia, UAE, Jordan, Qatar, South Korea, Oman, UK, Kuwait, and Germany [26, 34]. WHO data suggests that around 35% of reported MERS cases have been fatal [35]. MERS-CoV jumps between animals and humans, primarily from infected dromedary camels to humans. Studies also show that the virus can spread between humans, especially in close contact settings like hospitals [36].

1.5 Respiratory Tract Infections in Travellers: Prevalence and Risk Factors

Travellers are at an increased risk for respiratory infections due to their exposure to crowded environments during transportation, sightseeing, and mass gatherings. However, the full extent of travel-related respiratory illnesses remains uncharacterized, and existing studies are outdated [37, 38]. The reported prevalence of respiratory symptoms among travellers varies, with some studies indicating rates as low as 1% among travellers arriving at US airports, while others report rates as high as 93% among Hajj pilgrims [39–41].

Common RTIs in travellers often reflect those found in the general population. Travellers don't frequently encounter tropical respiratory diseases [42, 43]. URTIs are more common than LRTIs, and the culprits often include local pathogens like flu viruses [43, 44]. It's noted that respiratory viruses are a common cause of fever in travellers, with rates ranging from 2.8% to 15% [45–48]. Other viruses, including rhinoviruses, adenoviruses, and RSV-A, are also prevalent in travellers [49].

Certain groups of travellers or specific destinations present a greater risk for these infections. For instance, tourists are at a higher risk than other types of travellers such as visitors of friends and relatives (VFRs) or immigrants [50]. This could be due to their exposure to crowded places and different pathogens. There are also notable outbreaks linked to air travel or cruises because of the confined spaces [51–55]. Respiratory illnesses are also common during mass gatherings events, including religious and sports events [56]. Interestingly, some studies indicate that men might have a reduced risk of certain respiratory infections, including pneumonia and bronchitis, but more research is needed to confirm these findings.

1.6 Leveraging Technology in Epidemiological Surveillance of Respiratory Infections

Traditionally, epidemiological surveillance relied solely on reported cases, a prime example being Dr. John Snow's investigation of the 1854 cholera outbreak in Soho, London. By mapping the cholera cases, he discovered a concentration around the Broad Street water pump, thereby identifying the epidemic's source [57, 58]. While this case study remains a significant milestone, modern technology enables us to track cases with greater precision.

An example of contemporary technology being harnessed is seen in how Twitter was employed to monitor respiratory infections. During the Influenza A H1N1 outbreak in the United States, researchers examined tweets to ascertain the public's feelings about H1N1 and to track the disease's spread. This investigation showed that Twitter was a reliable tool for capturing the general public's focus and worries related to health issues. Additionally, predictions of influenza-like symptoms (ILI) based on discussions on Twitter closely reflected the actual reported rates of the disease, highlighting the capacity of social media to provide insightful data for public health [59].

Another technological advancement is the use of governmental contact tracing apps like SwissCovid during the COVID-19 pandemic. These apps employ Bluetooth proximity technology to monitor and mitigate COVID-19 spread by organizing medical follow-up for patients and providing citizens with direct guidance on controlling the disease. The SwissCovid app identified individuals who had close contact with coronavirus-infected individuals and rapidly notified them if there was an infection risk. Similarly, 22 European public health authorities launched national tracing and warning apps to prevent coronavirus spread. These voluntary, privacy-preserving, and secure apps alert citizens who have been in close proximity with COVID-19 persons, demonstrating technology's potential to offer valuable public health insights and aid in COVID-19 prevention [60].

Epidemiological surveillance of mobile populations presents a multifaceted challenge. The majority of studies in the literature employ convenience sampling methods, focusing on participants who sought counseling prior to their trip or returned ill. Consequently, events transpiring during the trip in the host country remain under-studied, leading to an unclear understanding of the burden of respiratory infections in travellers.

While there are challenges, monitoring systems for returning sick travellers have been set up. Since 1995, GeoSentinel, a group of clinics specializing in travel and tropical medicine, has played a key role in tracking the health trends of travellers and refugees. However, a limitation of GeoSentinel and the daughter network of European clinics "EuroTravNet" is that they rely on reports from specific clinics who see mainly severely ill patients. These clinics only see a limited number of the returning ill travellers and importantly there are no denominator data. For these reasons GeoSentinel data are not ideal tofully grasp the extent of respiratory infections among the global traveling community.

1.7 Smartphone Applications: The Next Frontier in Traveler Health

In an effort to study mobile populations during their trip, researchers have turned to mobile phones. A study in 2014 investigated the potential of a smartphone application for tracking traveler health behavior and collecting infectious disease data during the Hajj pilgrimage. The study utilized a longitudinal design with an iPhone app featuring questionnaires for three distinct phases: pre-Hajj, during Hajj, and post-Hajj. The findings underscored the feasibility of using a mobile application for conducting prospective surveys and collecting data on travel-associated infections and traveler compliance with prevention measures. With a response rate exceeding 50%, this innovative approach showed promise [61].

Another novel approach to tracking travellers and their behavior during their trip was embodied by the Tracking Of Urgent Risks In Swiss Travellers (TOURIST2) study. This study aimed to monitor urgent risks in Swiss travellers to six travel destinations using a smartphone application. The study reported on the feasibility of using a new travel application for real-time data monitoring during travel in a cohort of travellers to three continents. The app was used to collect behavioral and health data from healthy travellers, elderly travellers and individuals with chronic diseases traveling to , Brazil, Thailand, Tanzania, India, China and Peru between September 2017 and January 2019. This study underscores the potential for using technology to track travellers and their behavior during their trip, offering valuable insights into travel-associated risks and traveler compliance with prevention measures [62].

1.8 Project Objectives

The primary objective of this PhD thesis was to explore respiratory tract infections (RTIs) in travellers using a mobile phone application named Infection Tracking in Travellers (ITIT). Funded by the Swiss National Science Foundation (SNF) and led by Prof. Dr. Patricia Schlagenhauf, this public health, project aimed to assess illness patterns during and after travel. By integrating geolocation and weather data with traveler symptoms, this innovative approach to infection surveillance leveraged the traveler for bottom-up data input, thereby creating extensive datasets.

Study I conducted a systematic review of the literature to gain a deeper understanding of the ethical considerations in travel health applications. This review informed the development of the ITIT app, ensuring it adhered to these considerations.

Studies Study II, Study III, and Study IV shared several objectives:

- To evaluate the range of in-travel infection symptoms encountered by different groups of travellers.
- To identify sex and age-specific profiles of respiratory infections.
- To assess differences in the epidemiology of respiratory infections based on geolocation, environmental data, and traveler symptoms.
- To investigate the prevalence of RTI, their risk factors, and impact on Quality of Life.
- To follow up on sequelae of respiratory infections

Study II systematically reviewed the literature to address these points. Study III tested the ITIT app with a pilot project involving 50 participants. Following revisions to the app based on the pilot project's results, Study IV assessed the first 500 participants to obtain preliminary results.

This PhD thesis also extended its focus to SARS-CoV-2 respiratory infections with Study V that tracked COVID symptoms remotely using a different application.

1.9 ITIT Application content

The ITIT study aims to recruit over 10,000 travellers in Switzerland and Europe. Although there is no traditional sample size calculation for this analysis, previous studies have indicated that a sample size of 10,000 travellers allows for a robust analysis [63].

Data for the ITIT project are collated using a smartphone application, utilizing daily symptom questionnaires. These questionnaires are formulated based on the most frequently reported symptoms by travellers in previous studies, encompassing four health systems (gastrointestinal symptoms, respiratory symptoms, skin infections and rashes, fever, pain, and myalgia). A subsequent questionnaire is dispatched to all participants who reported fever, pain, rash, or red eyes. Any participant who reports a confirmed arboviral infection or malaria receives a standardized invitation to become part of a study cohort examining the long-term consequences of these infections. Participation from travelers is promoted with generic information adhering to WHO International Travel and Health guidelines.

The application isuser-friendly and provides published outbreak alerts from the WHO. This research is aimed at characterizing the profiles of respiratory infectious diseases in travelers based on age, sex, travel purpose, location, climate, and environmental factors. It holds the potential to transform surveillance by facilitating bottom-up reporting of illness symptoms by travelers.

1.10 Statistical Plan

The fundamental premise of this study is that demographic characteristics (such as sex, age), exposure area, and travel purpose are associated with varying types and severity of travel-related infections. The primary endpoint is the overall incidence, severity, and duration of health problems during travel.

Given the nature of the data (daily collection) and potential correlation between individual data points, longitudinal analysis methods such as multilevel models are employed to assess intra- and inter-individual variability - specifically, the duration and intensity of symptoms among travellers. These models respect the ordinal characteristics of the outcomes (symptoms).

To visualize reported symptoms by location, a world map displays the number of cases and symptom intensity by country. When sufficient data are available, a cluster analysis for outbreaks within countries will be conducted.

To assess the long-term disease burden in returning travelers, various classification models such as random forest, penalised logistic regression, XGBoost, decision tree (CART), and k-Nearest Neighbours (k-NN) are compared based on their performance (AUC score) in predicting the impact of symptoms on daily activities. The results are presented in a forest plot.

Missing data in this study arises from participant non-compliance (e.g., missing surveys) or technical issues (e.g., missing geotags for the daily survey). Participants who have submitted at least one daily survey are considered to have completed the study. The incidence of health events during travel is calculated using completed travel days. As there is no reason to believe that surveys would not be missed at random, this approach would be the most conservative and would tend to bias the results toward the null value. In case of a largeamount of missing data, multivariate Imputation by Chained Equations (MICE) is applied to the optimal models and displayed in the model result. The chosen methods accounts for the clustering of participants within their respective trip.

To minimize missing data, a daily pop-up reminder message is included in the ITIT app for participants during their trip. The app is designed to be simple and user-friendly to encourage participation for just a few minutes each day. However, this study's large sample size is intended to account for dropouts while still allowing for robust analysis. All analyses in this thesis are performed using R statistical software.

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2
Study I

Mobile apps for travel medicine and ethical considerations: A systematic review

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Contents

2.1 Abstract

Background: The advent of mobile applications for health and medicine will revolutionize travel medicine.Despite their many benefits, such as access to real-time data, mobile apps for travel medicine are accompanied by many ethical issues, including questions about security and privacy.

Methods: A systematic literature review as conducted following PRISMA guidelines. Database screening yielded 1795 results and seven papers satisfied the criteria for inclusion. Through a mix of inductive and deductive data extraction, this systematic review examined both the benefits and challenges, as well as ethical considerations, of mobile apps for travel medicine.

Results: Ethical considerations were discussed with varying depth across the included articles, with privacy and data protection mentioned most frequently, highlighting concerns over sensitive information and a lack of guidelines in the digital sphere. Additionally, technical concerns about data quality and bias were predominant issues for researchers and developers alike. Some ethical issues were not discussed at all, including equity, and user involvement.

Conclusion: This paper highlights the scarcity of discussion around ethical issues. Both researchers and developers need to better integrate ethical reflection

at each step of the development and use of health apps. More effective oversight mechanisms and clearer ethical guidance are needed to guide the stakeholders in this endeavour.

2.2 Introduction

Travel, whether for leisure, business, or visiting friends and relatives (VFR) is an important global phenomenon, with significant impacts on spending, employment, and also health. In 2019, there were 15 billion international inbound tourists, with Europe having the largest number of international tourists and the most spending on tourism [1, 2]. With the growth of international travel, however, comes an increased risk to traveler health, and of the possibility of the spread of infections to new areas. Travelers may be at risk of contracting illnesses such as malaria, traveler's diarrhea, arboviruses (such as dengue, Zika, and chikungunya), sexually transmitted infections, and more recently, the novel coronavirus SARS-CoV-2 [3–6].

Travel medicine plays an important role in preventing and treating travel-related illnesses. In Europe, travel medicine is a diverse field with a variety of national and local guidelines, and is administered by a wide range of health professionals, including nurses, general practitioners, travel clinics, and pharmacists [2]. Prevention is key for maintaining traveler health, and can include vaccinations, prophylaxis, travel safety information, insect bite prevention, and more [7]. Also relevant is the role of travelers as sentinels for infection and in surveillance of imported infections associated with travel. As travel increases and diversifies in destinations, and numbers and types of travelers, so too must travel medicine respond to the changing landscape of travel.

One method that has shown promise is the use of smartphone apps, or mHealth apps [8]. Monitoring traveler health behavior as well as encountered risks has become easier and more reliable due to advances in the quality of mobile health technology and widespread use of smartphones, allowing for real-time data collection [9, 10]. For instance,in the context of the COVID-19 pandemic, apps for digital contact tracing, and potentially for storing individuals' vaccination certificates, became popular across Europe and beyond [11, 12]. An ambitious new project called Illness Tracking in Travellers (ITIT) aims to collect data on traveler illness in collaboration with the World Health Organisation (WHO), with a goal of facilitating rapid public health responses [13].

However, many travel medicine apps are not up to date, lack accurate and evidence-based content, or were not developed with the involvement of health professionals [14]. This is consistent with the broader literature on health apps [15–17]. Research has shown that questions of data security, confidentiality, liability, and trust are at the forefront of the discussion about health apps (including those developed to fight COVID-19), despite their many advantages [15, 18–20]. Effectiveness and accessibility are also mentioned frequently as reasons for the use or rejection of health apps [21, 22]. Equity of access is another important ethical issue. Although the average number of mobile phone subscriptions worldwide was 104 per 100 people in 2018 [23], certain populations are underrepresented, including older individuals and those with a lower socioeconomic status [24, 25]. This information is particularly relevant for studies of travel health apps: despite their intention to collect information from a variety of settings and population groups, these studies might be biased towards subgroups already owning and comfortably using mobile devices [26]. These issues are important to address in order to avoid bias. User trust is another important issue and lack of trust can result in poor uptake [27].

The goal of this systematic review is to evaluate ethical issues around mobile health apps for travelers, identify important deficits, and suggest key ethical areas to address in future travel medicine apps.

2.3 Methods

2.3.1 Identification and selection of studies

The systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [28] and registered in the Prospero database (CRD42021231857). A systematic search of the Medline, Scopus, Web of Science, Embase, IEEE Xplore, Science Direct, Cochrane Central Register of Controlled Trials (CENTRAL), SSRN, and medrXiv databases was performed on January 7th, 2021 by a librarian scientist. The search strings can be seen in Appendix A.

Titles and abstracts were imported into the reference manager software Endnote20ő (Clavirate, 36T3 Boston, MA 02210), and duplicates were removed. Titles and abstracts were then imported into the knowledge synthesis software Rayyan QCRI [29] and examined for eligibility by two independent reviewers, with the consultation of a third in case of disagreement. Finally, the full text of the remaining studies was examined for relevance, and relevant studies were included in this review (see Appendix B for the excluded papers list) The reference lists of included papers were examined for additional relevant studies not included in the initial search. A team of three co-authors completed the abstract screening, full-text review, and data extraction. Any disagreement among the authors was resolved through discussion.

2.3.2 Eligibility criteria

Only studies meeting the inclusion criteria were considered. Reviewed studies were written in English, German, French, or Italian, and published until the 31st December 2020. Preprints, dissertations, and peer-reviewed studies with all study designs (qualitative, mixed methods, quantitative) were included, while books, conference abstracts, editorials, and papers without an available full text were excluded. Duplicates and irrelevant papers were also excluded. In order to be considered relevant, papers had to report on mobile phone apps for travel medicine for travelers over eighteen (international and intranational), and these apps must have been developed for the primary purpose of traveler health/travel medicine. Apps for children and youth were excluded, as well as apps not designed specifically for travel medicine, even though they may still collect data useful for travel medicine research (such as social media apps collecting epidemiological data), or may be used in some way by travelers (such as holiday booking apps, apps for tourist leisure activities). Reference to ethical implications of developing and using mobile applications for travel medicine was an additional inclusion criterion. Reasons for exclusion from the review were noted in Rayyan QCRI [29].

2.3.3 Data extraction

The primary outcome was ethical considerations of the development and use of mobile phone apps for travel medicine purposes, and the secondary outcome was the opportunities and challenges in ethical considerations. Relevant information was extracted through a deductive coding process. In consultation, all authors agreed on a list of categories to code the studies accordingly. When an ethical consideration included in the text could not be coded under any existing category, it was temporarily designated "unclassified". Subsequently, the authors decided whether this code should generate a separate category (introduced through an inductive process) or be grouped under an existing one. The extracted information was presented in tabular form using Excel software (Appendix C).

2.3.4 Risk of bias assessments

Quality assessment of the studies was conducted simultaneously. At the study level, quality was assessed with different tools according to the study design (Randomized trials – Cochrane risk of bias tool, Observational studies – STROBE, Narrative articles – SANRA) [30]. At the outcome level, we assessed the types of reasons supporting each ethical statement: supported by empirical evidence, justified by rationally articulated arguments (potentially supported by the literature), or uncorroborated (without an explicit justification). This categorization allowed for higher precision in identifying the gaps in the ethical reflection on travel medicine apps [31]. The quality assessment (recorded in Appendix C) was once again conducted independently by two authors, and disagreement was resolved through discussion with a third.

2.3.5 Data synthesis

All papers that met the eligibility criteria were included in the narrative synthesis [32]. Similarities and differences across studies were analyzed, and homogeneous studies were clustered. Study characteristics, type of intervention adopted, context of the intervention, opportunities and challenges brought by the intervention, and ethical considerations of developing and adopting mobile apps for travel medicine purposes were all considered in the synthesis. As a qualitative synthesis, the findings were clustered thematically according to the reasons used to justify the ethical considerations.

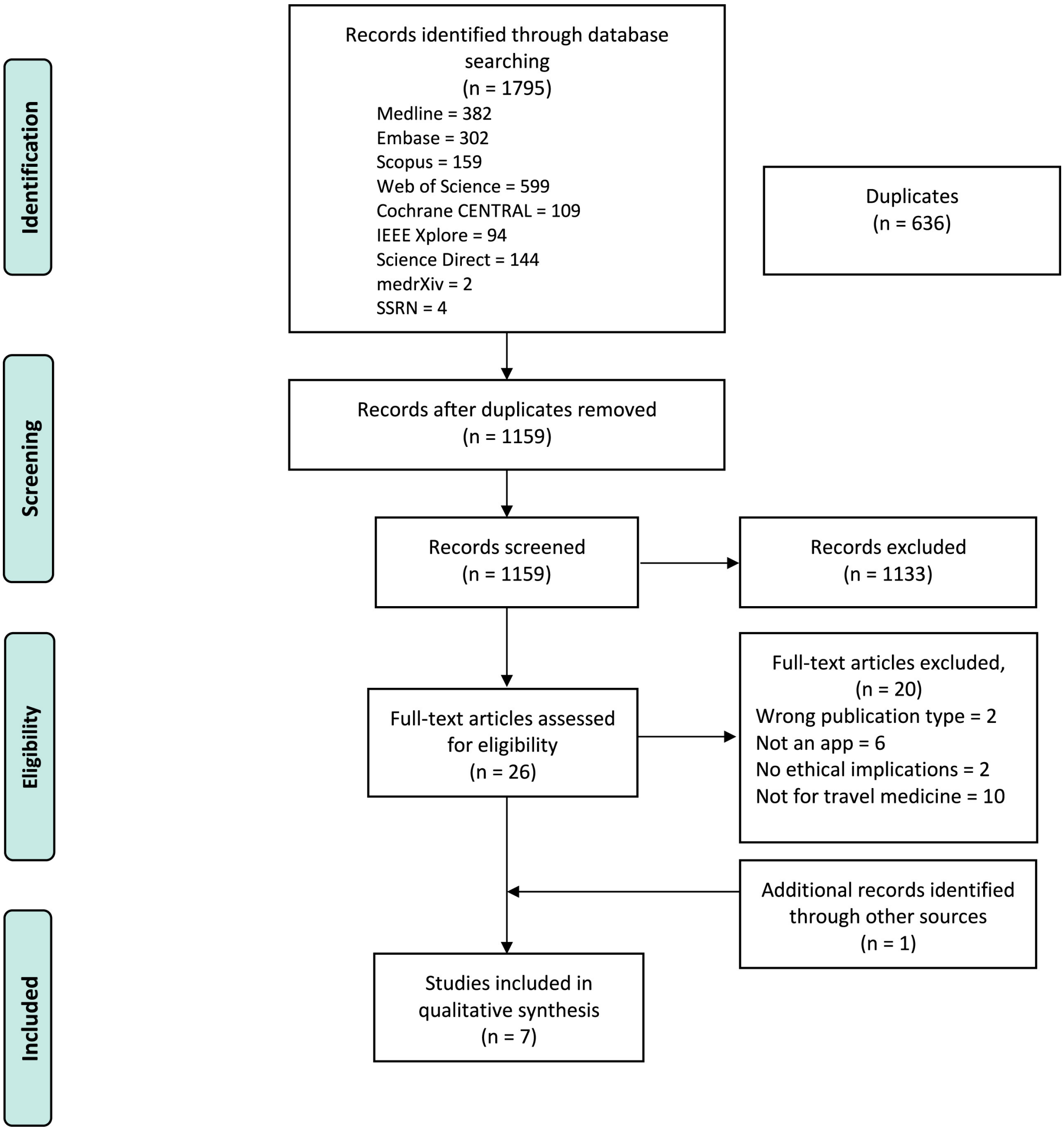

Figure 2.1: PRISMA flowchart of identification and selection of studies to be included in the systematic review.

2.4 Results

A total of 1795 studies were found through the literature search. Of these, 636 were duplicates, and 1133 were excluded through the abstract screening. The full text of the remaining 26 papers were screened, and of these, six were included. In addition, one paper was found through the screening of reference lists of the included papers, resulting in seven papers being included in the review. Figure 2.1 provides an overview of the screening process.

Table 2.1: Characteristics of included papers.

Author	Year	Title	Journal	Study Type	Field
Baroutsou et al.	2020	TOURIST2 Tracking of urgent risks in swiss travelers to the 6 main travel destinations Feasibility and ethical considerations of a smartphone application-based study	Travel Medicine and Infectious Disease	Cohort Study	Epidemiology
Farnham et al.	2018	Streaming data from a smartphone application: A new approach to mapping health during travel	Travel Medicine and Infectious Disease	Cohort Study	Epidemiology
Du et al.	2020	COVID-19 Contact Tracing Apps: A Technologic Tower of Babel and the Gap for International Pandemic Control	JMIR MHealth and UHealth	Qualitative Analysis	Epidemiology
Lai et al.	2019	Measuring mobility, disease connectivity and individual risk: a review of using mobile phone data and mHealth for travel medicine	Journal of Travel Medicine	Qualitative Analysis	Epidemiology
Subramaniyaswamy et al.	2018	An ontology-driven personalized food recommendation in IoT-based healthcare system	Journal of Supercomputing	Qualitative Analysis	Computing
Sethia et al.	2018	Smart health record management with secure NFC-enabled mobile devices	Smart Health	Qualitative Analysis	Travel Medicine
Seed et al.	2016	Identification and review of mobile applications for travel medicine practitioners and patients	Journal of Travel Medicine	Brief Communication/ Qualitative Analysis	Travel Medicine

Table 2.2: Quality rating of papers included in the systematic review.

Paper	Quality Rating System	Quality Rating
Baroutsou et al., 2020	STROBE[a]	21/22
Farnham et al., 2018	STROBE[a]	20/22
Du et al., 2020	SANRA[b]	10/12
Lai et al., 2019	SANRA[b]	11/12
Subramaniyaswamy et al., 2018.	SANRA[b]	9/12
Sethia et al., 2018	SANRA[b]	10/12
Seed et al., 2016	SANRA[b]	9/12

[a] Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist was created to help authors submit high-quality observational studies by grading them on a 22-point scale.
[b] Scale for the Assessment of Narrative Review Articles (SANRA) aimed to improve the quality of narrative reviews by rating them on a 12-point scale.

Of the seven included papers, two were cohort studies and five were qualitative analyses or narrative reviews. Characteristics of included papers can be found in Table 2.1. The two cohort studies described the same app called the Tourist app, which was pilot tested in the 2018 paper [33].The 2020 paper focuses on novelties and upgrades of the app, as well as participant willingness to use the app. Three papers described specific apps for travel medicine: Du, Raposo, and Wang [34] (contact tracing), Subramaniyaswamy et al. [35] (food recommendations while travelling), and Sethia, Gupta, and Saran [36] (electronic health record access while travelling). Finally, two papers provided a review of several apps. Seed et al. [14] offered an overview of travel medicine apps available in 2016, and Farnham et al. [37] reviewed the literature on benefits and challenges of travel medicine mHealth.

All included papers were rated for quality using the STROBE guidelines for the cohort studies, and the SANRA guidelines for the qualitative/narrative analyses (Table 2.2). The two cohort studies and the paper by Lai et al. [9] had the highest quality ratings, while the papers by Seed et al. [14] and Subramaniyaswamy et al. [35] had lower scores.

2.4.1 Benefits and challenges

Each paper mentioned opportunities and challenges of using mobile apps for traveler health, with reference to travel app users, researchers, and developers (Figure 2.2). The most commonly stated opportunity of travel medicine apps was to collect real-time data, thereby reducing recall bias and allowing users to access resources when needed. This was followed closely by the accuracy and precision of the data and easy access to information and resources, which are also related to reduced recall bias. Several papers mentioned linked geolocation data as a benefit of the apps, as well as the possibility of larger sample sizes and reduced costs. Geolocation benefits both researchers, enabling them to link location to risk events

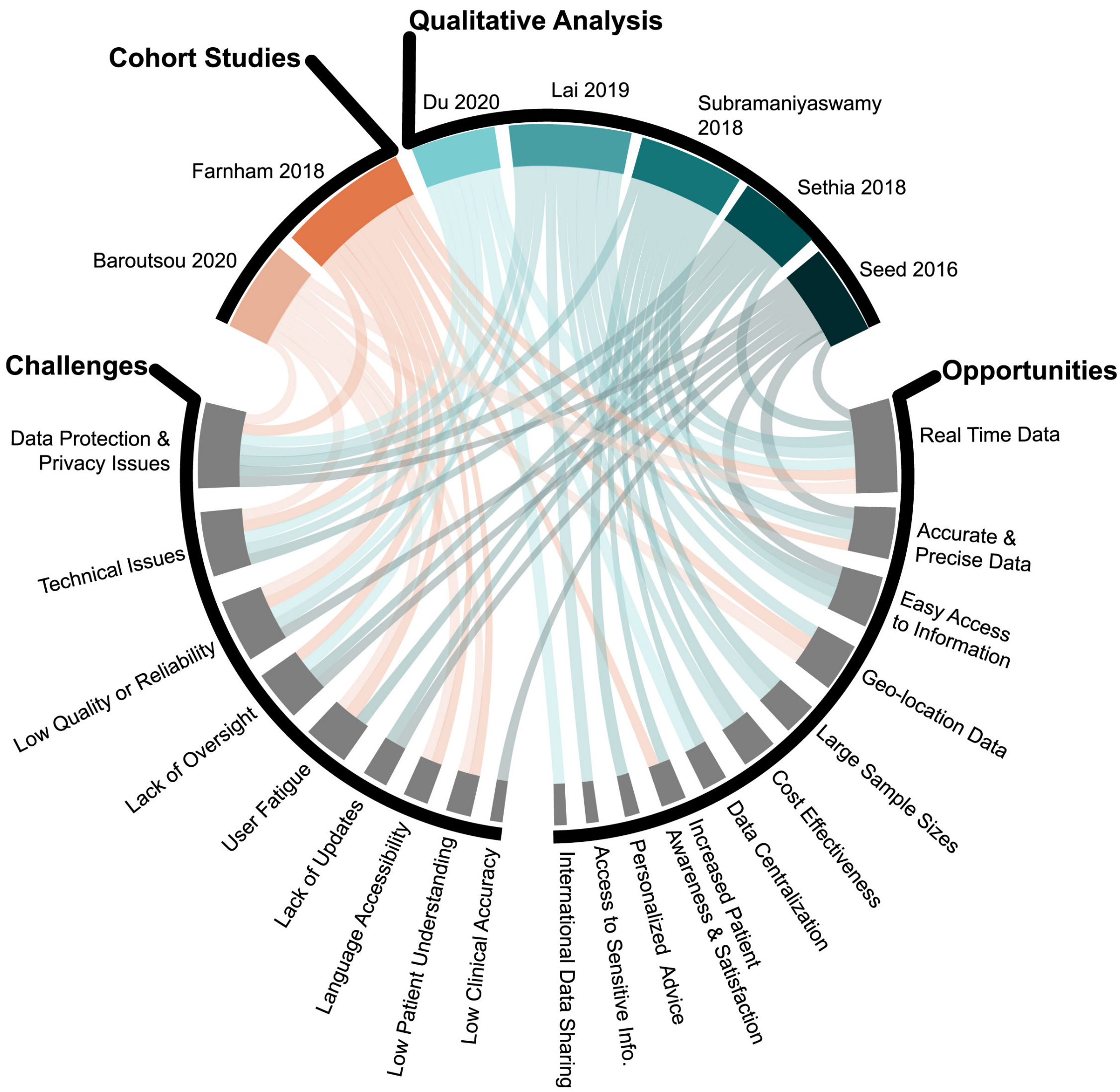

Figure 2.2: Challenges and opportunities identified for mobile apps used for travelers' health.

[37] or examine contact between users (as in COVID tracking apps) [34], and users, allowing for personalized information based on location [35]. Finally, opportunities mentioned once or twice included personalized advice, data decentralization, and easier international data sharing. Conversely, all of the papers recognized data protection and privacy issues as a challenge for travel health apps. Other potential weaknesses included technical issues, low-quality data, and low reliability. The lack of clear governance or oversight during app development was also highlighted as troublesome. Frequently mentioned challenges associated with mobile travel health apps included potential for user fatigue due to data overload, language accessibility concerns, lack of updates leading to outdated information, and low traveler understanding. The mentioned opportunities and challenges of mobile apps for traveler health are presented in Figure 2.2.

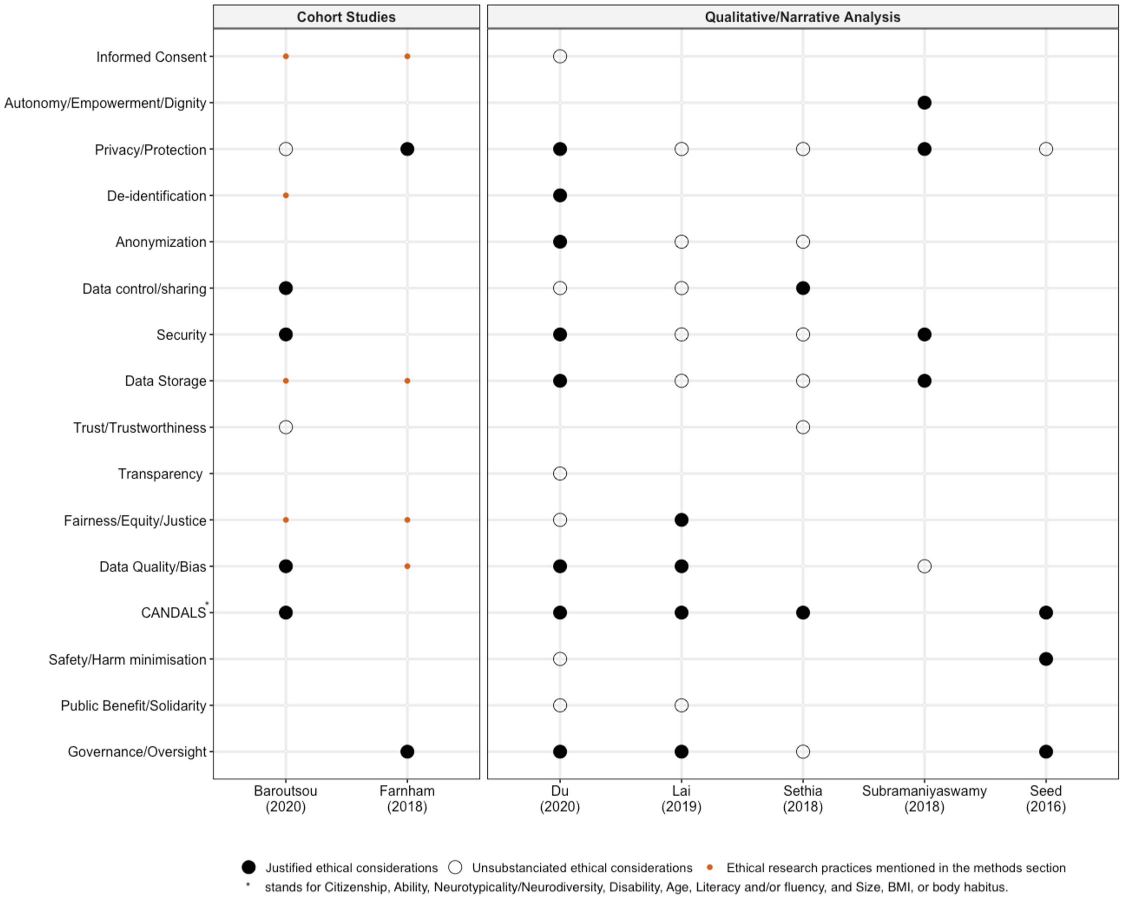

Figure 2.3: Cleveland's Dot Plots of sixteen ethical considerations identified in the papers included in the systematic review.

2.4.2 General ethical issues

In five of the seven papers, a full section was dedicated to discussion of ethical issues, while two papers discussed ethical issues only briefly, devoting less than a paragraph to the topic. Sixteen distinct ethical issues were touched upon across all papers. However, despite the emphasis on ethical considerations, almost half were not explored in detail, with no justification of their relevance provided in the text. Instead, many issues were mentioned in passing in the methods section (Figure 2.3). More recently published papers tended to discuss a greater number of ethical issues and examine them in more detail than those published a few years ago. Furthermore, the recently published papers were more likely to contain evidence-based justification or stronger theoretical arguments in support of their ethical reasoning, in comparison with the older papers (Figure 2.4). In fact, only the cohort study by Baroutsou et al. [8] had evidence-based reasons concerning topics such as secondary use of data, institutional trust, and age or chronic disease status of participants.

Looking more closely at the ethical considerations mentioned, privacy issues were most frequently discussed, being addressed by all of the papers, followed

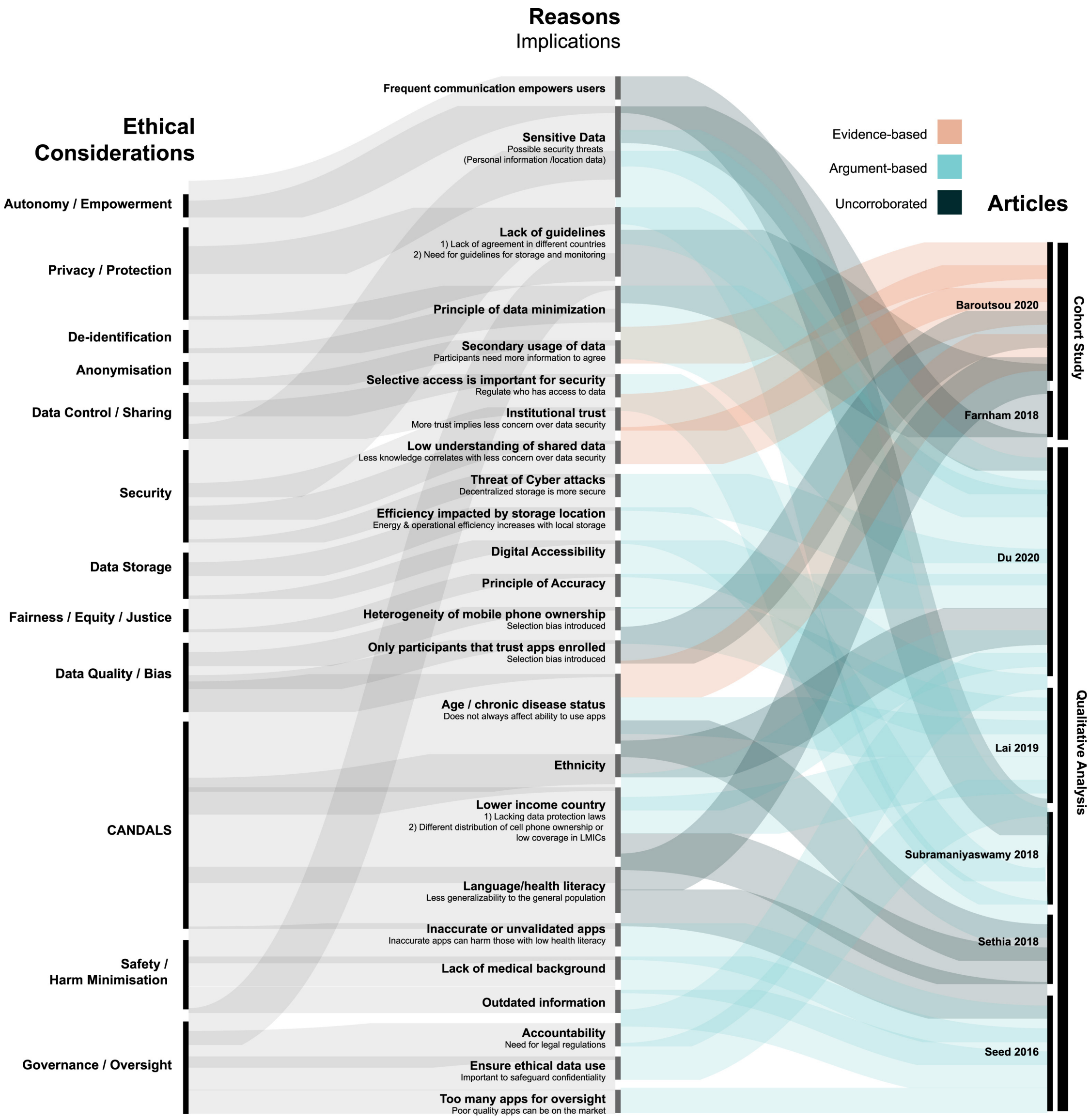

Figure 2.4: Types of reasons justifying the ethical considerations and their implications.

closely by issues included in the "CANDALS" classification [38] (Citizenship, Ability, Neurotypicality/Neurodiversity, Disability, Age, Literacy and/or fluency, and Size, BMI, or body habitus.) The papers discussed how age, disease status, ethnicity, lower-income country status, and health literacy can impact the adoption and usability of mobile health apps by individuals across countries, social classes, and cultures. Another frequently mentioned ethical issue was data storage, in relation to both data security (risk of cyber-attacks) and efficiency (e.g., saving energy in resource limited settings). Conversely, the least discussed ethical issues included transparency, autonomy, and individual traveler empowerment.

2.4.3 Cohort studies

Both cohort studies focused on the importance of protecting user privacy, an increasingly relevant topic for the general public. The 2018 paper by Farnham et al. [37] highlighted the lack of clear guidance at an international level, rendering it difficult to develop apps compliant with privacy laws across countries. The 2020 paper by Baroutsou et al. [8] goes beyond privacy issues, discussing the ethical implications of sharing data for secondary purposes, through surveying participant opinions of this topic before and after the study, and examining their reasoning. This highlights the importance of trust in the institutions responsible for app development, to engage app users and address data security concerns.

Looking at additional ethical issues taken into account in the research methodology, Baroutsou et al. [8] mentioned e-consent forms and data de-identification and storage, as well as the concept of fairness, e.g., providing mobile devices to participants without access to one. They reflected further on data bias, as only individuals already interested in the app took part in the cohort study.

2.4.4 Qualitative/narrative papers

The paper by Du, Raposo, and Wang [34] highlighted the greatest number of ethical concerns of all the included papers. Particularly, the paper discussed the data de-identification and anonymization as ways to preserve user privacy, as per the principle of data minimization. This paper also mentioned data security with regard to collection, storage, and use of sensitive data, as well as to individual harms that could emerge from a data breach. More specifically, it examined GPS location data used by apps such as those developed for COVID tracing, and the harms related to the potential theft of this information.

The qualitative papers mention ethical considerations not considered in the cohort studies, such as transparency, public benefit, solidarity, safety, and harm minimization. Concerning the last point, Seed et al. mentioned inaccuracy, lack of a medical background, and outdated information due to a lack of updates as potential sources of harm for people using travel medicine apps, especially those with low health literacy. Sethia, Gupta, and Saran [36] examined data control, emphasizing the importance of selective access to data for data security, and the importance of regulating data access. Furthermore, data quality (and its link to bias) was a concern mentioned by Lai et al. [9], Du, Raposo, and Wang [34] and Subramaniyaswamy et al. [35]. Inaccurate data collection or heterogeneity of mobile phone ownership may result in selection bias, which can negatively affect data analysis and provide inaccurate feedback to users. The majority of the qualitative papers also mentioned issues of data governance, specifically the lack of adequate oversight for mHealth apps in the field of travel medicine. Du et al. stressed the need for legal regulation to address accountability [34], in the case of a security breach or inaccurate recommendations made by an app. Lai et al. [9] recommended introducing oversight to ensure that privacy is taken into account during travel medicine app development. Finally, Seed et al. [14] reflected on the exponential number of apps developed in recent years, and the lack of effectiveness of current oversight mechanisms to keep pace with this rapidly evolving sector.

2.5 Discussion

This review found that privacy is the most pressing ethical issue for travel medicine apps. This may be partially explained by researcher and developer concerns about compliance with privacy and security regulations. These concerns are justified, due to the lack of clear ethical standards and data regulation at the international level [39]. Apart from the General Data Protection Regulation in Europe, there are no defined minimum global standards for storage and sharing of personal data for secondary purposes [40, 41]. Medical travel apps (as all health apps) must comply with each individual country's privacy law [37]. Baroutsou et al. [8] showed that trust in the institutions developing and implementing health apps can reduce user fears about data security and confidentiality. It is therefore essential to develop international data governance standards, endorsed by a variety of stakeholders, that not only guide researchers when developing their applications, but also increase user trust in the technology [42].

Given the types of papers assessed (cohorts and papers describing app development) it is not surprising that data quality and bias were also predominant issues. As the papers were written from the perspectives of app developers and researchers, concerns about potential biases and other technical issues were highlighted over issues that might have been emphasized by ethicists. Examining data quality in more detail, self-reported user data introduces two issues of ethical relevance. The first is data accuracy. Although real-time self-reporting of data can reduce recall bias, positively influencing data quality, researchers can struggle to verify whether the information provided is precise, complete, and mirrors reality. For this reason, using GPS and metadata collected directly through the phone (without user input) might compensate for potential errors and biases. The ability to access these data represents a significant advantage of travel applications over other travel medicine strategies. Nevertheless, rigorous data quality control is still required. The second issue is data representativeness. Our analysis showed that effort should be made to include minorities as well as other population subgroups (CANDALS) in the design and deployment of health apps, as factors such as age, language and health literacy, or living in a lower-middle income country play a role in app use [9, 36]. Selection bias introduced due to the heterogeneity of mobile phone ownership or user comfort with mobile technology directly affects data quality. This in in turn may give incorrect or misleading feedback to users, which is particularly problematic for travel medicine apps, when user health is at stake.

Conversely, researchers dedicated only minimal attention to issues of equity and justice. Although a few articles [9, 37] discussed accessibility through lending a mobile phone or SIM card to participants, no reference is made to the social implications of these applications, or whether they extend access to health information in an equitable way to all population groups.

Similarly, though the apps are used by individuals with various needs and health concerns, it can seem that researchers developed these tools without adequately considering the context, resulting in a "one size fits all" application. Only the more recent cohort study considered engaging users in the app development process and receiving feedback. Following on this point, it is important to note that informed consent, central to mHealth literature, has scarcely been discussed. Informed consent is mentioned in the cohort study methodology without further development, though their protocols reference it often. Of the qualitative studies, informed consent is only briefly referenced in Du, Raposo, and Wang [34]. Many of the papers seem to view informed consent more as a task to be completed to avoid legal repercussions, than as a real ethical concern. However, in the interest of increasing trust, researchers should engage users. This might include clearly communicating the app's objectives and addressing the data confidentiality concerns of users. Moreover, researchers should focus on user satisfaction, providing an app that is intuitive and accessible on multiple platforms. Finally, it could be important not only to be transparent about the user's consequences from using the app, but also to stress the benefit for the broader community. As with COVID-19 digital contact tracing apps the notification of a potential close encounter with a COVID-19 positive individual might result in limiting individual freedoms (e.g., limiting freedom of movement with quarantine). However, this downside for the app user could be justified in light of a collective benefit. If researchers succeed in increasing willingness to use the app, they may also indirectly increase the quantity and quality of data that they collect.

Accompanying the user on their journey, travel medicine apps can offer individualized advice although this would mean that the app becomes a "medical device" and would thus require regulation. However, whether or not these apps are actually effective in providing timely advice and suggestions was not discussed in the papers evaluated here. On the contrary, as pointed out in Seed et al. [14], there is potential for harm due to a lack of medical background of app developers and app users and poor data accuracy. This should be considered carefully by researchers, as it may negatively influence user willingness to adopt the apps, especially those that collect highly sensitive data [18]. More research is needed to evaluate the ethical and societal implications of travel medicine apps Simultaneously, future policies should provide detailed guidance about user experience and public involvement at each phase of app development, strategies for risk prevention and mitigation before releasing the apps, and transparent data collection, usage, and storage.

2.6 Strengths and limitations

This is the first systematic review to examine the important and quickly growing topic of ethical aspects of travel medicine apps. A major strength of this work is the evaluation of key health equity stratifiers using the CANDELS classification to show how age, disease status, ethnicity, lower-income country status, and health literacy can impact the adoption and usability of mobile health apps by individuals across countries, social classes, and cultures. In the modern age, digital technology will play an expanding role in travel, emphasizing the importance of analyses such as this one. One limitation of this review is the quality of ethical assessment within the selected papers. Although the seven included papers matched the inclusion criteria and were of good quality, the depth of ethical assessment was often superficial, with only a short section devoted to ethics and little evidence to support the issues discussed. This reinforces the need for more research into ethical issues surrounding travel medicine apps, and health apps in general. Another limitation of this analysis is the inclusion and analysis of both cohort and qualitive studies, even though they employ different methodologies. However, the discussion of ethical issues can occur across all study designs, leading to comparability, and the quality assessment of the selected studies indicates strong results across study types. A final limitation is the use of a qualitative thematic methodology to extract ethical issues. This procedure might be subject to subjective biases, which were addressed by 1) having an inductive table of ethical issues and using a deductive approach to collect the issues, and 2) having multiple researchers working in parallel. However, it is not possible to completely rule out bias in the data extraction.

2.7 Conclusion

This systematic review identified 1159 unique articles of which seven (0.6%) met our pre-defined inclusion criteria. We found that although some ethical issues are widely debated (privacy, security and data quality), many are just mentioned (justice, fairness, risk assessment), and some are disregarded (effectiveness, user involvement). While it is true that travel applications constitute a relatively new approach to collecting data and engaging users, this result revealed gaps that exist regarding ethical considerations in travel medicine literature. These gaps highlight the need for developers and researchers working with travel medicine apps to do a careful risk-benefit assessment, not only exploring potential risks, but employing strategies to mitigate such risks. In light of the fast-evolving landscape of digital health and health apps, oversight mechanisms should be updated to support researchers and developers in making ethically aligned choices.

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2.9 Supporting Informations

2.9.1 Appendix A

Search strings by database. Available at: https://ars.els-cdn.com/content/image/1-s2.0-S1477893921001848-mmc1.docx

2.9.2 Appendix B

List of Papers Excluded at Full Text Review. Available at: https://ars.els-cdn.com/content/image/1-s2.0-S1477893921001848-mmc2.docx

2.9.3 Appendix C

Papers quality assessment. Available at: https://ars.els-cdn.com/content/image/1-s2.0-S1477893921001848-mmc3.xlsx

3

Study II

Travel-related respiratory symptoms and infections in travellers (2000—22): a systematic review and meta-analysis

Thibault Lovey, Robin Hasler, Philippe Gautret, Patricia Schlagenhauf

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Contents

3.1 Abstract

3.1.1 Background

Respiratory tract infections (RTIs) are common in travellers due to the year-round or seasonal presence of respiratory pathogen and exposure to crowded environments during the itinerary. No study has systematically examined the burden of RTI infections among travellers. The aim of this systematic review and meta-analysis is to evaluate the prevalence of RTIs and symptoms suggestive of RTIs among travellers according to risk groups and/or geographic region, and to describe the spectrum of RTIs.

3.1.2 Methods

The systematic review and meta-analysis was registered in PROSPERO (CRD42022311261). We searched Medline, Embase, Scopus, Cochrane Central, Web of Science, Science Direct and preprint servers MedRxiv, BioRxiv, SSRN and IEEE Xplore on 1 February 2022. Studies reporting RTIs or symptoms suggestive of RTIs in international travellers after 1 January 2000 were eligible. Data appraisal and extraction were performed by two authors, and proportional meta-analyses were used to obtain estimates of the prevalence of respiratory symptoms and RTIs in travellers and predefined risk groups.

3.1.3 Findings

A total of 429 articles on travellers' illness were included. Included studies reported 86841 symptoms suggestive of RTIs and 807632 confirmed RTIs. Seventy-eight percent of reported respiratory symptoms and 60% of RTIs with available location data were acquired at mass gatherings events. Cough was the most common symptom suggestive of respiratory infections, and the upper respiratory tract was the most common site for RTIs in travellers. The prevalence of RTIs and respiratory symptoms suggestive of RTIs were 10% [8%; 14%] and 37% [27%; 48%], respectively, among travellers. Reporting of RTIs in travellers denoted by publication output was found to correlate with global waves of new respiratory infections.

3.1.4 Interpretation

This study demonstrates a high burden of RTIs among travellers and indicates that travellers' RTIs reflect respiratory infection outbreaks. These findings have important implications for understanding and managing RTIs among travellers.

3.2 Introduction

After a 70% drop in traveller arrivals in 2019 due to the COVID-19 pandemic, international travel appears to be rapidly recovering. Most countries have relaxed their entry requirements and reopened their borders. The UN World Tourism Organization reports that arrivals in the first 7 months of 2022 have reached 57% of pre-pandemic levels, due in part to increased vaccination rates and a manageable number of COVID cases.[1]

Although the COVID-19 pandemic has turned into an endemic, non-severe infection in most areas, the risk of respiratory infectious disease persists. Exposure to crowded environments, such as encountered during transportation, sightseeing, mass gatherings, and the year-round or seasonal presence of respiratory pathogens in frequently visited areas make travellers particularly vulnerable to respiratory infections. The full spectrum of travel-related respiratory illness is rarely described and studies are dated.[2, 3] The estimated prevalence of respiratory symptoms among travellers varies widely. For example, it ranges from less than 1% among travellers arriving at US airports to more than 39% among French medical students travelling abroad and up to 93% of Hajj pilgrims.[4–6] The prevalence is equally high in confirmed respiratory tract infections (whether diagnosed medically or by molecular methods).

RTIs in travellers often resemble those in the local population, and tropical respiratory illnesses remain rare in travellers.[7, 8] Thus, as in the general population, upper respiratory tract infections (URTIs) are more common than lower respiratory tract infections (LRTIs).[9] Pathogens circulating in the local population, such as respiratory viruses, are frequently detected in travellers.[8] Influenza is the most common virus, with an estimated prevalence of 2.8% and up to 15% among travellers with fever.[10–13] Travellers are particularly affected by the H3N2 variant and to a lesser extent by the H1N1 or B group variants.[10] Other viruses commonly found in travellers include rhinoviruses, adenoviruses and respiratory syncytial virus type A.[14] Typical or atypical bacteria are also common and fungi are sometimes detected, notably histoplasmosis.[15]

Certain groups of travellers or specific locations have an increased risk of respiratory infections. For example, tourists have a higher risk of respiratory infections than immigrants, visitors of friends and relatives (VFRs), and expatriates ($P<0.0001$).[16] Outbreaks of respiratory infections are commonly reported in relation to air travel or on ships with their confined spaces.[17–21] Respiratory infections also occur at mass gatherings, especially religious and sporting events with large crowds, and account for up to 40% of all illnesses reported during such events.[22] However, some respiratory infections are limited to certain travel groups.

To date, there are no systematic reviews or global studies that provide information on the complete range of respiratory illness in travellers by specific groups of travellers. We therefore aimed to conduct a systematic review and meta-analysis of studies published between 2000 and 2022, taking into account different regions and risk groups to obtain reliable prevalences. The main objective of this study was to estimate the prevalence of respiratory symptoms and RTIs among all travellers stratified by specific regions and/or risk groups. As a secondary objective, we examined the types of symptoms indicative of RTIs and confirmed RTIs that occurred in travellers and assessed the difference in risk for the two important factors of age and sex.

3.3 Methods

This systematic review follows the PRISMA 2020 guidelines and has been registered in the PROSPERO database (CRD42022311261).

3.3.1 Eligibility criteria

Studies that reported at least one case of respiratory infection or respiratory symptoms in travellers were included.

Respiratory infections or respiratory tract infection (RTIs) were broadly defined as infections affecting at least one segment of the respiratory tract (either as the site of infection or the route of transmission). Only confirmed respiratory infections were considered, i.e. cases diagnosed either by clinical examination (including history, clinical examination and complementary tests) or by molecular methods (such as PCR or serology). Respiratory infections caused by viruses, bacteria including mycobacteriaceae, and fungi were evaluated.

In addition, respiratory symptoms were defined as a group of symptoms suggestive of the presence of RTIs. Cough, dyspnoea, expectoration, loss of sense of smell or taste, rhinitis/runny nose/congestion, sinus pain, sore throat, voice failure/hoarseness and wheezing were considered symptoms of RTIs in our article.

Only adult travellers who had crossed at least one international border were studied. Cases of respiratory infections or symptoms that occurred during specific occasions such as mass gatherings, air travel, cruises or on commercial vessels were considered and stratified by specific groups. Considering the limited number of reported respiratory infections among participants in various mass events outside the Hajj (Saudi Arabia), including events such as AsiaWorld-Expo (Hong Kong SAR), Bb Fard (Pakistan), Easter Festival (Austria), Eco-Challenge (multiple countries), EXIT Festival (Serbia), Grand Magal of Touba (Senegal), Rock Werchter (Belgium), Sojourn (Germany), Sziget Festival (Hungary), Tablighi Jamaat (India), Umrah (Saudi Arabia), Universiade (Serbia), Winter Olympics and Paralympics (2002, USA) and World Youth Day (2008, Australia), we grouped them into a single risk category in our study and referred to them as Mass gathering events. For air travel and cruise ships, no distinction was made between crew members and other passengers. Special categories were also defined for refugees and asylum seekers. Settled immigrants, already established in the country of reporting, were excluded. Studies that used genome sequencing or mathematical models to estimate the country in which respiratory infection was acquired or to predict new cases were excluded.

Studies in English, French, Spanish and German that reported cases between 1 January 2000 and 31 January 2022 were reviewed, including those whose recruitment period began before 2000 but included cases from the period of interest. Preprints, conference abstracts and peer-reviewed studies such as randomized controlled trials (RCTs), cohort studies, case–control studies, cross-sectional studies, case series, case reports, prevalence studies and systematic reviews were considered for eligibility. Reviews, editorials, opinion pieces, essay summaries, books and articles for which full text was not available were excluded. Commentaries, short communications and letters to the editor that did not report original cases were also excluded.

3.3.2 Information sources

A systematic search was conducted on 1 February 2022 in the bibliographic databases Medline, Embase, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Science Direct and the preprint servers MedRxiv, BioRxiv, SSRN and IEEE Xplore (TL). All strings were recorded and can be found in the Appendix A.

3.3.3 Selection process

The results of the various strings were imported into Endnote20 Reference Manager (Clavirate, Boston, MA 02210) to achieve deduplication. The references were then transferred to the knowledge synthesis software Rayyan QCRI. All studies were checked for eligibility first by title and abstract and then by full text. All references of included studies and excluded reviews were also reviewed. The screening processes were performed simultaneously by two different blinded authors (T.L., R.H.). Pooling was performed at the end of each round, and a third author (P.S.) was involved in the decision in case of disagreement. Reasons for exclusion were recorded for each excluded study in Rayyan QRCI and reported in the PRISMA flowchart.

3.3.4 Data collection

For each article in which at least one respiratory symptom and/or confirmed respiratory infection was reported, the total number, the sex stratification, the age group, the size of the study population, and the type of respiratory symptom or respiratory infection and possible accompanying symptoms were recorded. The country where the respiratory symptom or infectious respiratory disease was detected and the location where it was acquired were also noted. Age groups were defined in four categories, Child/Youth (0–19 years) to accommodate included papers where young adults were included in 'child' categories, Adult (20–39 years), Middle-aged Adult (40–59 years) and Senior Adult (60+ years). When only the percentage or prevalence per 1000 persons was reported, the data were converted to absolute numbers. If this was not possible, the study was excluded. The extraction process was performed manually twice per study in two different Google sheets before they were merged (T.L.).

3.3.5 Bias assessment

We used the JBI Critical Appraisal Tools[23] to evaluate our studies. These tools were developed by an independent, non-profit research organization at the Faculty of Health and Medical Sciences, University of Adelaide, Australia, and include a specific checklist for each study design. Studies were scored simultaneously by two blinded authors (T.L., R.H.), and a mean score was calculated. Scores are expressed as a percentage of the maximum possible score and can therefore be easily compared between different types of studies. Interpretations in the literature differ, but it is reasonable to assume that a score above 70% indicates a low risk of bias, a score between 50% and 70% indicates a medium risk of bias, and a score below 50% indicates a high risk of bias.

3.3.6 Data synthesis

All studies that met the inclusion criteria were included in the descriptive analysis. The absolute number of cases of respiratory infections, respiratory symptoms, and the number of cases by UN region or specific category and the distribution by sex and age were calculated. Maps were generated for respiratory infections, respiratory symptoms and major respiratory infection outbreaks in the past 20 years (H1N1, MERS-CoV, SARS-CoV-1, SARS-CoV-2), with absolute numbers of cases calculated for the 17 subregions of the UN geoscheme. Studies that reported only positive cases, had no reference population or whose reference population was not exclusively travellers were excluded from the meta-analysis. No studies were excluded due to a high risk of bias—only those identified by three unsupervised learning algorithms (k-means, DBSCAN and Gaussian mixture models) in the graphic display of study heterogeneity (GOSH) graphs. The meta-analysis of proportions was calculated with a logistic regression model using the maximum likelihood estimator for tau2, the Hartung–Knapp adjustment for the random effects model and a logit transformation. A significance level of 0.05 was used for all statistical tests. All analyses were performed with the statistical program RStudio (version 2022.07.1).[24]

3.3.7 Role of the funding source

There was no funding source for this study.

3.4 Results

Database searches yielded 2042 articles, of which 204 were identified as duplicates and 1234 were excluded after review of titles and abstracts. Of the remaining 602 articles, 19 full texts could not be found and 583 were screened for eligibility. After the second screening, 268 articles were included. Based on their references and the references of the excluded journals, 340 new studies were identified. Of these, an additional 161 studies were included, bringing the total number of included studies to 429. An overview of the screening process and reasons for exclusion during full-text screening is provided in Figure 3.1 and the full list of included studies can be found in the Appendix B.[25]

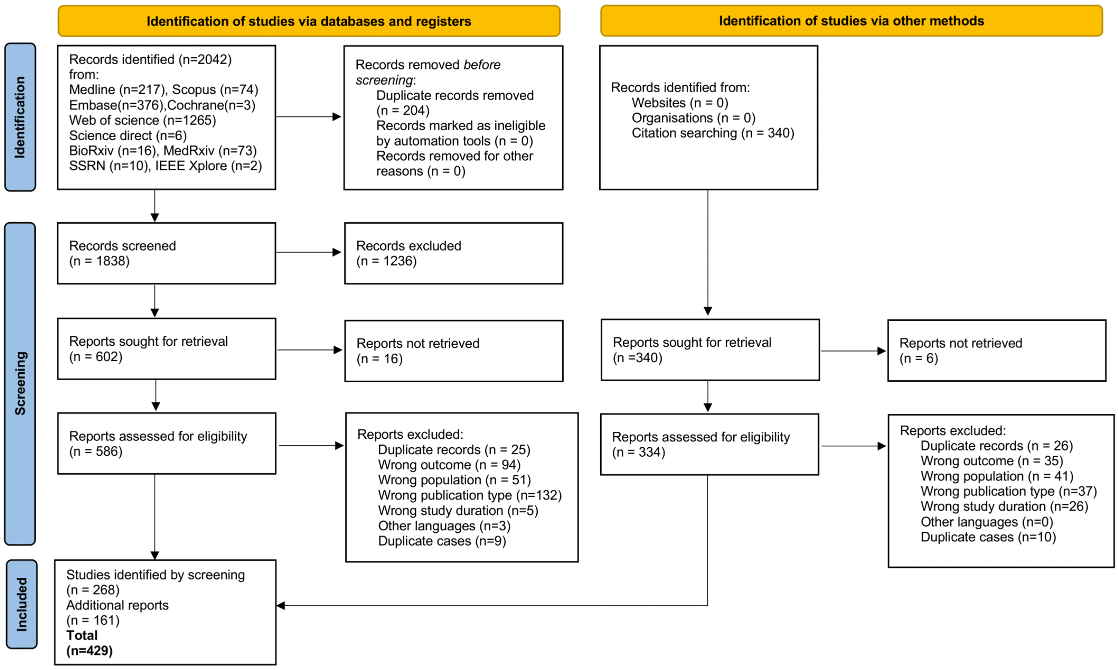

Figure 3.1: PRISMA flow diagram 2020

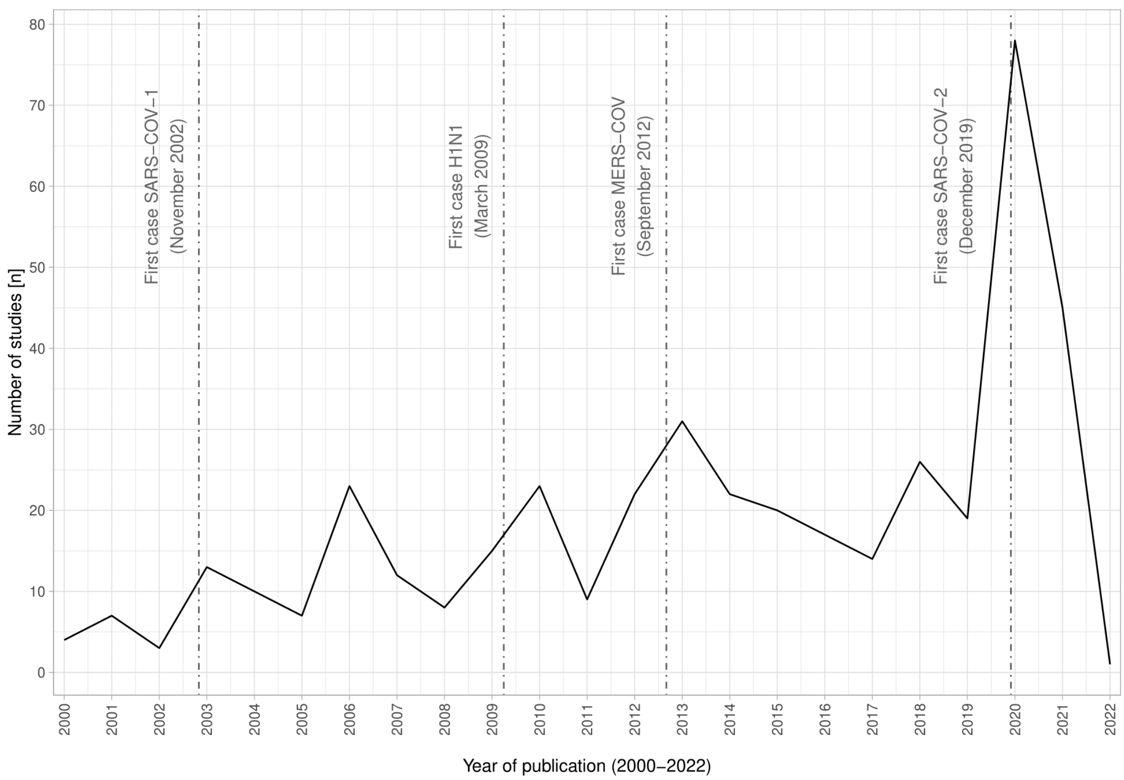

Figure 3.2: Time-series plot of the absolute annual frequency of included studies with the date of the first observed case of the four epidemics/pandemics of respiratory infections of the twenty-first century

Table 3.1: Table showing the total number of studies by study design JBI score, number of respiratory cases and symptoms, and distribution by region, specific group, sex and age category

Characteristic	Overall		Randomized Controlled Trials (RCTs)		Cohort Studies		Cross-sectional Studies		Casecontrol Studies		Case Reports		Case Series		Prevalence Studies	
Number of studies (n)	429		2		17		284		2		57		55		12	
JBI Critical Score (%)																
Mean (SD)	77 (15)		63 (3)		72 (9)		78 (15)		92 (11)		77 (19)		73 (15)		78 (16)	
Range	25, 100		62, 65		59, 91		44, 100		85, 100		25, 100		45, 100		39, 100	
	Symptoms[a]	Cases[b]	Symptoms[a]	Cases[b]	Symptoms[a]	Cases[b]	Symptoms[a]	Cases[b]	Symptoms[a]	Cases[b]	Symptoms[a]	Cases[b]	Symptoms[a]	Cases[b]	Symptoms[a]	Cases[b]
Total (n)	86841	807632	676	324	499	2773	82791	798451	1310	32	61	90	290	2863	1214	3099
UN Region																
Africa	250 (2%)	4233 (3%)	N/A	N/A	N/A	284 (24%)	219 (2%)	3872 (3%)	N/A	N/A	7 (12%)	13 (14%)	24 (10%)	64 (3%)	N/A	N/A
Americas	1166 (8%)	5263 (4%)	N/A	N/A	N/A	59 (5%)	524 (5%)	4955 (4%)	N/A	N/A	12 (20%)	20 (21%)	13 (5%)	201 (9%)	617 (51%)	28 (3%)
Asia	687 (5%)	19812 (14%)	N/A	N/A	N/A	195 (16%)	632 (6%)	18242 (14%)	N/A	N/A	32 (54%)	34 (36%)	23 (10%)	1340 (57%)	N/A	1 (0%)
Europe	59 (0%)	11167 (8%)	N/A	N/A	N/A	93 (8%)	14 (0%)	10485 (8%)	N/A	N/A	2 (3%)	3 (3%)	43 (18%)	586 (25%)	N/A	N/A
Oceania	1 (0%)	788 (1%)	N/A	N/A	N/A	N/A	N/A	787 (1%)	N/A	N/A	1 (2%)	1 (1%)	N/A	N/A	N/A	N/A
Specific Cases																
Airplane	93	451	N/A	N/A	N/A	9	47	375	N/A	N/A	N/A	1	17	37	29	29
Cruise or Merchant Vessel	465 (3%)	2478 (2%)	N/A	N/A	N/A	N/A	351 (3%)	1629 (1%)	N/A	N/A	3 (5%)	3 (3%)	111 (47%)	56 (2%)	N/A	790 (93%)
Refugee and Asylum-Seeker	341 (2%)	11179 (8%)	N/A	N/A	N/A	N/A	340 (3%)	11157 (8%)	N/A	N/A	1 (2%)	3 (3%)	N/A	19 (1%)	N/A	N/A
Mass gatherings events[b]	11033 (78%)	81862 (60%)	676 (100%)	337 (100%)	248 (100%)	542 (46%)	8229 (79%)	80897 (61%)	1310 (100%)	32 (100%)	1 (2%)	16 (17%)	7 (3%)	38 (2%)	562 (47%)	N/A
Age Distribution																
Child/Young	50 (3%)	8359 (34%)	N/A	N/A	N/A	N/A	48 (4%)	8337 (34%)	N/A	N/A	1 (2%)	1 (2%)	1 (1%)	21 (10%)	N/A	N/A
Adult	202 (13%)	7928 (32%)	N/A	N/A	12 (57%)	NA (NA%)	135 (10%)	7816 (32%)	N/A	N/A	15 (29%)	18 (31%)	40 (49%)	94 (47%)	N/A	N/A
Middle Age Adult	108 (7%)	5318 (22%)	N/A	N/A	N/A	N/A	65 (5%)	5250 (22%)	N/A	N/A	19 (37%)	20 (34%)	24 (30%)	48 (24%)	N/A	N/A
Senior Adult	1161 (76%)	2844(12%)	N/A	N/A	9 (43%)	N/A	1119 (82%)	2769 (11%)	N/A	18 (100%)	17 (33%)	20 (34%)	16 (20%)	37 (18%)	N/A	N/A
Unknown	85322	783183	676	324	478	2773	81424	774279	1310	14	11	31	209	2663	1214	3099
Gender Distribution																
Female	858 (47%)	18822 (40%)	N/A	N/A	N/A	106 (26%)	789 (47%)	18541 (40%)	N/A	12 (38%)	17 (33%)	20 (33%)	52 (44%)	143 (37%)	N/A	N/A
Male	986 (53%)	28220 (60%)	N/A	N/A	N/A	303 (74%)	886 (53%)	27609 (60%)	N/A	20 (62%)	35 (67%)	41 (67%)	65 (56%)	247 (63%)	N/A	N/A
Unknown	85025	760590	676	324	499	2364	81142	752301	1310	N/A	11	29	173	2473	1214	3099

[a] Includes cases of AsiaWorld-Expo, Bb Fard, Easter Festival (Carinthia), Eco-Challenge, EXIT Festival, Grand Magal of Touba, Hajj, Rock Werchter, Sojourn, Sziget Festival, Tablighi Jamaat,Umrah, Universiade, Winter Olympic & Paralympic Games, World Youth Day

[b] Relative frequency (%)

The year of publication of included studies ranged from 2000 to January 2022, with most studies (n=78) coming from 2020 and fewest from 2002 containing the fewest (n=3). The year 2022 cannot be compared because it included only the month of January. The largest difference between years was 2019 (n=19) and 2020 (n=78) with four times more studies than the previous year due to a large number of 2020 COVID-19-related publications. Figure 3.2 shows the number of included studies per year compared with the date of the first observed case of the four epidemics/pandemics of respiratory infections of the twenty-first century. Reporting of RTIs in travellers denoted by publication output s was found to correlate closely with global waves of new respiratory infections.

Of the 429 included studies, more than 66% (284/429) were cross-sectional studies and the remainder were RCTs (n=2), cohort studies (n=17), case–control studies (n=2), case reports (n=57), case series (n=55) and prevalence studies (n=12). The overall mean for the JBI critical score was 77% (SD 15), with a minimum score of 25% and maximum score of 100%. Randomized control trials have the lowest mean for the JBI critical score with 63% (SD 3) and case–control studies the highest one with 92% (SD 11). The study with the minimal JBI score overall 25% was a case report (Table 3.1).

Included studies reported 86841 symptoms suggestive of RTIs and 807632 confirmed RTIs. Of the reported respiratory symptoms with available information on the area of acquisition, 78% (11033/14095) occurred at mass gathering events. The most represented UN region for respiratory symptom acquisition was the Americas with 8% (1166/14095), while the Oceania region reported only one respiratory symptom in a case report. Respiratory symptoms were linked to airplanes, cruise ships/commercial vessels and refugees/asylum seekers in 93, 465 and 341 travellers, respectively. Of the confirmed respiratory illness cases with known area of acquisition, 60% (81862/137233) were from mass gatherings events and the most represented UN region of acquisition was Asia where 14% (19812/137233) of respiratory cases were acquired. Oceania was the least represented UN region with only 1% (788/137233) of confirmed cases. There were 451, 2478 and 11179 reported respiratory infection cases linked to airplanes, cruise ships/commercial vessels and refugees/asylum seekers, respectively. The sex ratio for respiratory symptoms was 1.15 male:1.00 female (men: 986/women: 858) and for respiratory infections this was 1.50 male and 1.00 female (men: 28220; women: 18822). Regarding age categories, 76% (1161/1521) of reported symptoms were in older adults (>60 years), whereas for respiratory infection cases the distribution was balanced among age categories. Missing data were common in the included studies particularly for sex and age. Place of acquisition was not reported in 84% (72746/86841) of reported respiratory symptoms, as well as in 83% (670399/807632) of reported respiratory tract infection cases. A high rate of missing data was found for both respiratory symptoms and confirmed RTI cases. Specifically, 98% (85322/86843) of the data was missing for the age category and 98% (85025/86869) for sex in respiratory symptoms. Similarly, 97% (783183/807632) of the data was missing for the age category and 94% (760590/807632) for sex in confirmed RTI cases (Table 3.1).

Of the 2163 respiratory symptoms for which UN regional location assignment was possible, 84% (1809/2163) could be assigned to the 17 UN subregional geoschemes. Latin America and the Caribbean was the subregion with the most travel-related

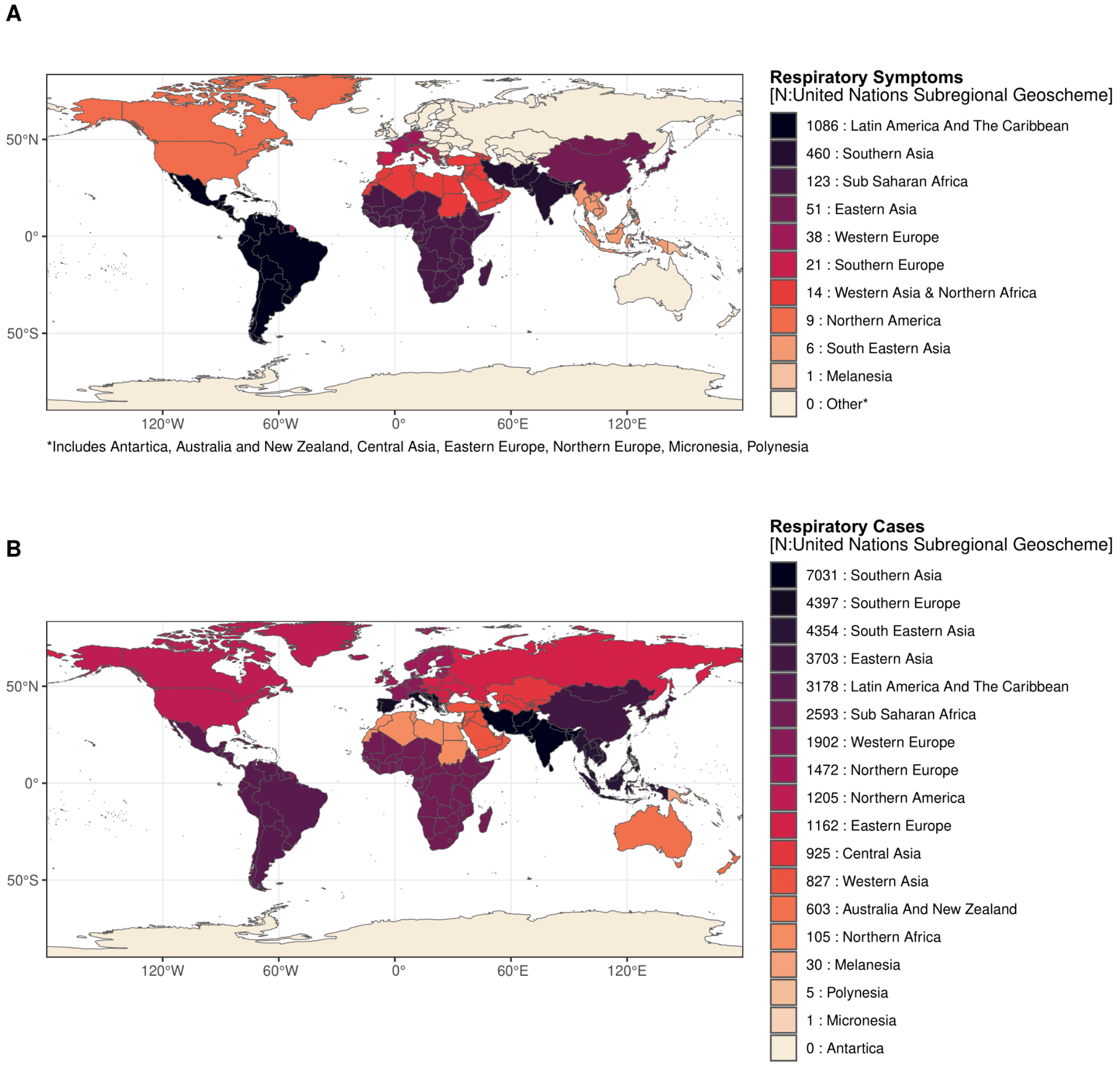

Figure 3.3: Cumulative cases from 2000 to 2022 for symptoms suggestive of respiratory illness (A) and respiratory infections (B) in the 17 United Nations subregional geoschemes. Note: Specific groups (Airplane, Cruise or Merchant Vessel, Refugee and Asylum-Seeker and Mass gatherings events) are not displayed

respiratory symptoms, with 60% (1086/1809) of reported respiratory symptoms. No reports of travel-related respiratory symptoms were found for other subregions such as Australia and New Zealand, Central Asia, Eastern Europe, Northern Europe, Micronesia, Polynesia and Antarctica (Figure 3.3A). Looking at respiratory tract infections, of the 41263 cases for which UN regional location was available, 81% (33493/41263) could be attributed to the 17 UN subregional geoschemes. For RTIs, South Asia was the subregion with the most reported cases of respiratory illness among travellers, and Micronesia and Antarctica were the least affected regions, with 1 and 0 cases, respectively (Figure 3.3B).

Cough was the most common respiratory symptom with 11206 reported cases among travellers, 76% of whom (8556/11206) contracted the symptoms at mass gatherings. Fever was commonly associated with respiratory symptoms (4309).

Common cold-like syndrome (CCLS) and Influenza-like Illness (ILI) were reported in 108841 and 50317 travellers, respectively. See the Appendix C for more details.

Medically diagnosed respiratory infections accounted for 126710 of the reported cases. Forty-nine percent (61553/ 126710) of these were URTI, followed by 29% (37014/126710) LRTI and 21% (26632/126710) mixed RTIs. Pharyngitis accounted for 51% (31396/61553) of LRTIs. Among LRTIs, pneumonia and tuberculosis were the most common, accounting for 43% (16063/37104) and 41% (15136/37104), respectively. More than 70% (10542/15136) of the TB cases were observed in the specific group of refugees and asylum seekers (Appendix D).

Respiratory infections detected by molecular diagnosis were mainly viruses (94%), followed by bacteria (6%) and fungi (<1%). Coronaviridae accounted for 54% (35117/65580) of the viruses detected, with SARS-CoV-2 accounting for 95% (33258/35117) of those. Orthomyxoviridae were also frequent (35%, 22683/65580), with H1N1 (A/H1N1) accounting for 22% (5091/22683) of the influenza viruses detected. Fifty-seven percent (2219/3863) of the bacteria were Gram-negative, with Haemophilus influenzae accounting for 49% (1081/2219) of the Gram-negative bacteria and 28% (1081/3863) of the total bacteria detected. For fungi, Candida albicans was the most frequent (Appendix E).

Global maps showing the absolute frequency of publications related to respiratory infections in travellers in the 17 United Nations subregional geoschemes for the four respiratory epidemics/pandemics of the twenty-first century are provided in the Appendix F.

3.4.1 Meta-analysis

Fifty-nine studies were included in the meta-analysis for respiratory symptoms, of which two were eliminated by the graphic display of heterogeneity (GOSH) analysis.[4–6, 15, 26–80] All included studies yielded a prevalence of respiratory symptoms in travellers of 37% [27%; 48%] for the years 2000 to 2022. Subgroup analysis shows that this estimate varies by exposure group, with the reported prevalence of respiratory symptoms in mass gatherings reaching 64% [51%; 75%], whereas after air travel only 8% [4%; 14%] of travellers had respiratory symptoms (Figure 3.4).

For respiratory infection cases, 111 studies were included in the meta-analysis, 9 of which were removed by the GOSH analysis.[4–6, 10, 15, 17–20, 22, 28, 31–37, 40, 43, 45, 46, 49, 51, 53, 54, 56, 58, 59, 64–66, 69, 72–74, 77, 79–153] The prevalence of confirmed respiratory illness among travellers was estimated to be 10% [8%; 14%]. Americas and mass gatherings were the groups at highest risk, with 21% [7%; 50%] and 18% [11%; 27%], respectively. Asia had a lower-than-average risk of 6% [2%; 14%] (Figure 3.5).

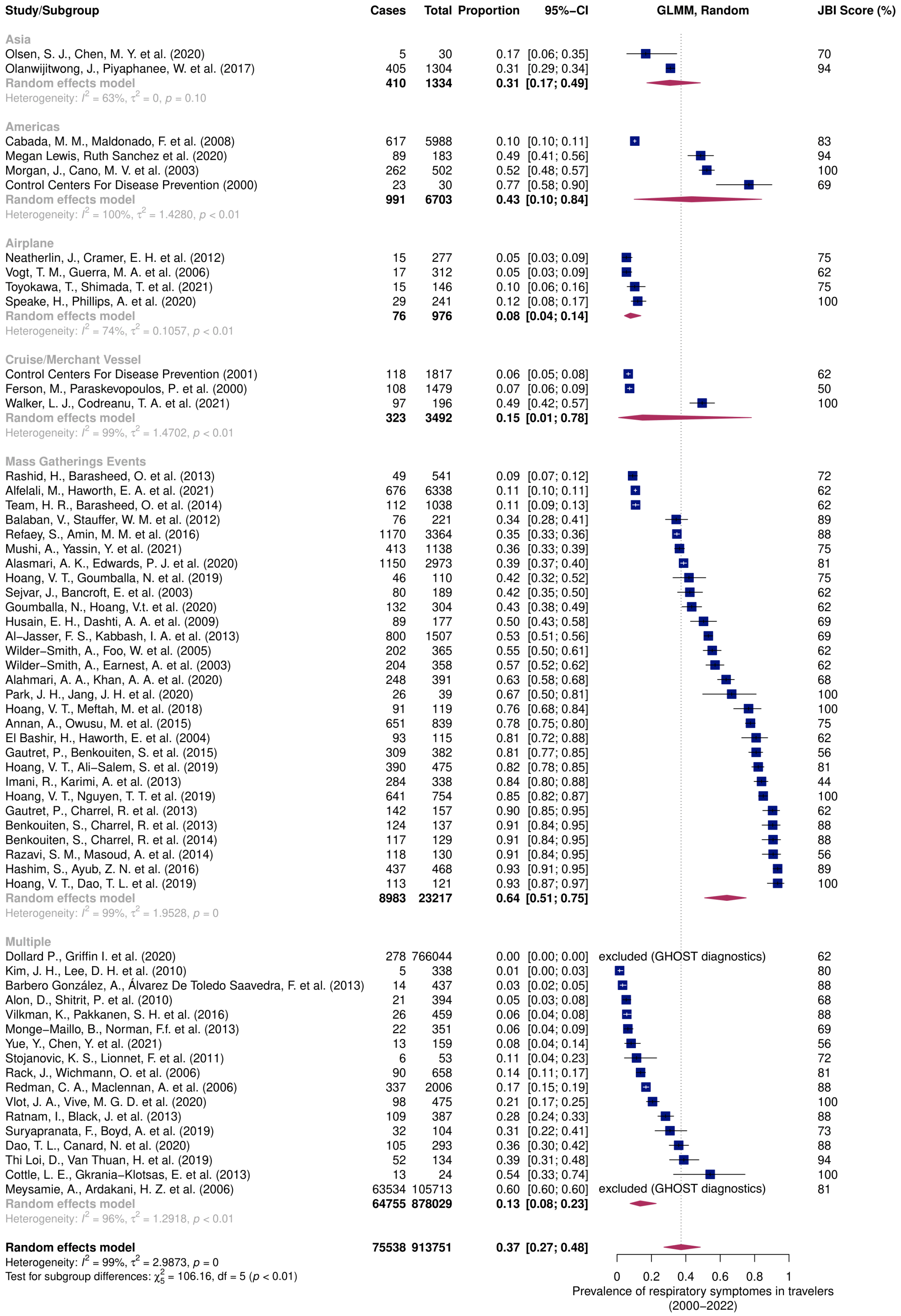

Figure 3.4: Meta-analysis estimating the prevalence of respiratory symptoms in travellers from 2000 to 2022 with subgroup analysis by UN region and specific groups

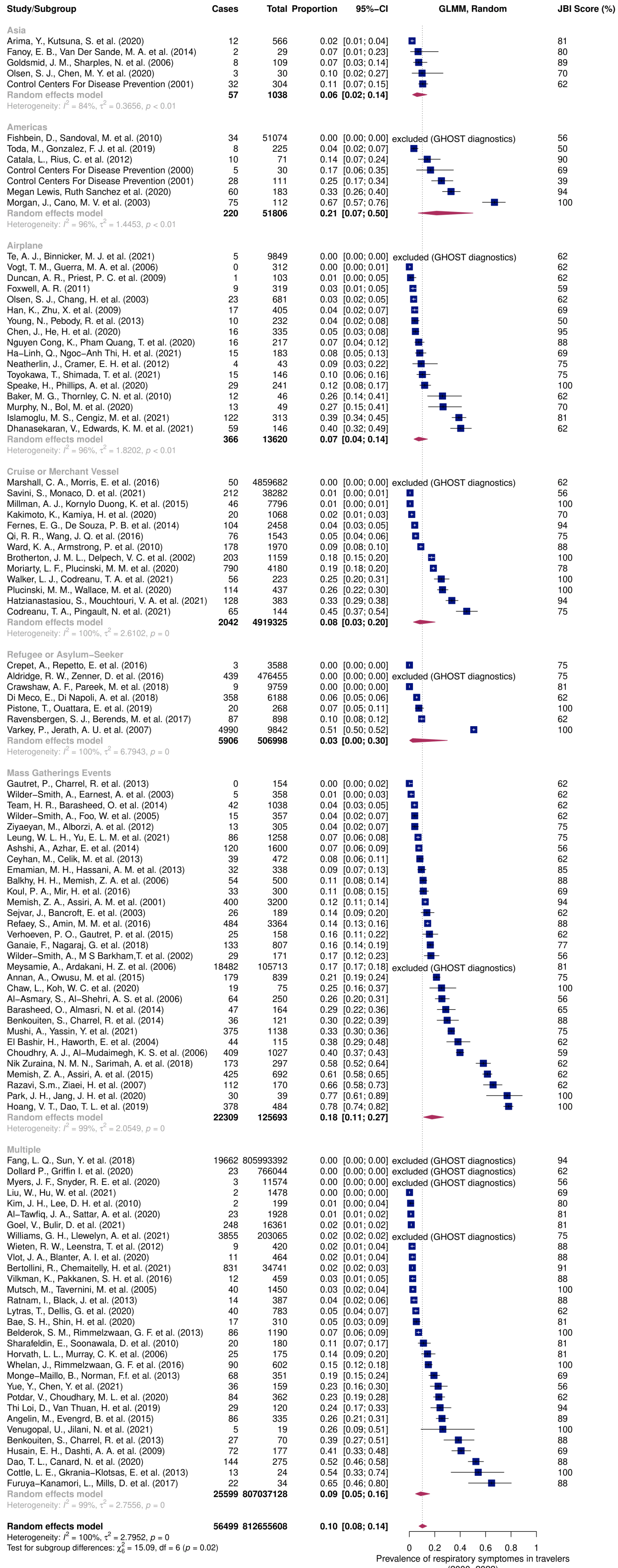

Figure 3.5: Meta-analysis estimating the prevalence of respiratory cases in travellers from 2000 to 2022 with subgroup analysis by UN region and specific groups

3.5 Discussion

This systematic review included 429 studies published between 2000 and January 2022 with an overall low risk of bias that reported respiratory symptoms or confirmed RTIs in travellers. We found a prevalence of respiratory symptoms and confirmed RTI cases of 37% [27%; 48%] and 10% [8%; 14%], respectively. This is the first meta-analysis to estimate global prevalences among travellers by region and specific area. These results demonstrate the high burden of respiratory infections among travellers regardless of risk group.

It is well known that mass gatherings are conducive to the spread of airborne diseases and that participants are therefore at high risk of suffering from respiratory symptoms and infections. In our study, the prevalence in mass gatherings was 1.7 and 1.8 higher than the overall prevalence for respiratory symptoms and infections, respectively, compared with other traveller groups. Furthermore, in absolute numbers, mass gatherings accounted for 60% of the reported cases of respiratory infections for which the area of acquisition was available, underscoring the risk of transmission during these events. Preventive measures, such as frequent changing of face masks, have been suggested to reduce respiratory transmission at mass gatherings. One study demonstrated a positive association between changing masks every 4 hours and fewer upper respiratory tract infections.[47] However, other studies have failed to provide clear evidence of the effectiveness of face masks against viral respiratory infections in this setting, possibly because of non-compliance with protocols.[42] In contrast to mass gatherings events, cases among airplane and cruise ship passengers were essentially limited to airborne viruses with SARS-CoV-2 and Influenza A virus accounting for most of the cases reported in our study.

The Americas, particularly the Latin America and Caribbean subregion, was the region with the highest absolute number of respiratory symptoms among travellers. The estimated prevalence of respiratory symptoms and confirmed RTIs is also higher than in other continents. However, the region with the highest absolute number of confirmed respiratory infections was Asia, particularly Southern Asia (Figure 3.3). This difference may be explained by the fact that mild respiratory symptoms or infections are underrepresented in the literature. Indeed, only 8–55% of travellers seek medical attention when they become ill during their trip, so mild respiratory symptoms or illnesses are more likely to go unreported.[154] In addition, most studies are from developed countries, so reported cases depend on the preferred destinations of these countries. In fact, Asia is the second most visited continent after Europe, with 360 million international tourist arrivals in 2019.

Most URTIs are caused by viral pathogens. In the last 22 years, 94% of the causative agents of RTIs in travellers reported in the literature were viruses. It is therefore not surprising that 49% of medically diagnosed infections in our studies were URTIs, compared with 29% LRTIs. Fever was found to be frequently associated with respiratory symptoms, confirming the findings of many studies, namely that respiratory infections are the most common cause of fever in travellers.[155–157] Influenza-like illness (ILI), defined by the Centers for Disease Control and Prevention as fever (temperature of 37.8řC or higher) and cough and/or sore throat, was frequently observed in certain areas of increased risk for respiratory virus transmission, such as cruises and mass gatherings. For example, in a 3-year prospective study, 33% of ill passengers and crew members were diagnosed with ILI.[158] In our systematic review, we found two cases of H5N1 infection in travellers. The first case was reported in November 2010 and involved a traveller returning from a poultry market in Shanghai.[159] The second case was reported in December 2013 and involved a Canadian traveller who had recently returned from a 3-week stay in Beijing.[160] Avian Influenza Weekly Update number 881, published on 3 February 2023, reports that a total of nine cases of H5N1 were reported in China during 2010–14.[161] These findings highlight the critical role of travellers as sentinels in detecting the spread of influenza and emphasize the importance of continuous surveillance of travellers to prevent respiratory infection outbreaks.

We observed that men were proportionately more often affected by respiratory symptoms and infections, which contrasts with other studies that have shown that the male sex is associated with a lower incidence of RTIs such as pneumonia and bronchitis.[162] Age appears to have a lesser impact on respiratory infections in our study that were previously described. However, due to the large number of missing values for age and sex, we were not able to statistically verify these differences and the results should therefore be interpreted with care. Further studies are needed to estimate the sex differences in respiratory infections among travellers.

The number of articles published annually on respiratory infections in travellers has been increasing since the 2000s, indicating a growing interest among researchers (Figure 3.2). While this positive trend may be partially attributed to factors such as improved diagnosis, the identification of new viruses and an overall increase in awareness, the positive cyclical pattern observed, with up to four times more publications in the year following the four respiratory virus epidemics/pandemics of the twenty-first century, cannot be explained by these factors alone. This cyclical pattern suggests that travellers are significantly affected by these viruses and reflect the global spread of respiratory infectious diseases. In addition, maps created using reported cases in the literature provide further evidence of this overlap with official maps reporting the total number of cases (Appendix F). Since 1995, GeoSentinel, a network of travel and tropical medicine clinics, has identified geographic and temporal patterns of morbidity among travellers, immigrants and refugees. However, GeoSentinel relies on the reporting of illness from specified travel and tropical medicine clinics and sees only a small proportion of ill returning travellers, which makes it difficult to assess the true impact of respiratory infections in the global mass of travellers. Therefore, new studies are using apps to track travellers' symptoms during travel to increase the accuracy of the data and to allow 'bottom up', real-time reporting of illness including respiratory illness. For instance, a pilot study that used an app called ITIT 'Illness Tracking in Travellers'[163] to capture travellers' symptoms during their travel showed that 67% of the symptoms reported during travel were symptoms suggesting respiratory illness or infections.[164]

An important limitation of our study is that in many cases reference populations were not available, so that only absolute numbers could be calculated in the descriptive analysis. Another potential limitation is that most studies used a convenience sampling method because of the difficulty of following travellers throughout their journey. Therefore, most studies included participants who sought counselling before the trip or ill returned travellers. This may introduce bias into prevalence estimates, such as underestimation. In addition, studies reporting only ill travellers cannot be included in the meta-analysis to estimate prevalence. Overrepresentation of traveller groups, such as Hajj pilgrims, or imbalance in the number of reported cases from countries where testing is more readily available may also confound the results and partially explain why species identification is not possible in most cases. Finally, some high-risk groups such as VFRs, immunocompromised travellers or business travellers, and sociodemographic factors such as obesity are missing from our risk categories, so the results in this paper cannot be generalized to such subgroups.

3.6 Conclusion

In summary, our systematic review and meta-analysis provide an estimate of the prevalences of respiratory symptoms and infections in travellers. In addition, we present the distribution of these infections across UN regions, specific groups of travellers and area of acquisition, as well as by sex. Respiratory symptoms and infections represent a significant burden for travellers and specific factors such as attendance at mass gatherings events increase the risk of infection. Travellers can act as sentinels and evaluations of traveller infections may be useful in identifying emerging respiratory infections of pandemic potential. Further studies are needed to better assess the true impact of these travel-acquired respiratory infections in terms of morbidity and quality-of-life impact. New digital tools such as mobile applications will allow researchers access to real-time data on travellers' illness throughout their journey and allow for rapid response to emerging respiratory infections.

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3.8 Supporting Informations

3.8.1 Appendix A

Search strings and number of articles retrieved per database. Available at: https://shorturl.at/vwHX8

3.8.2 Appendix B

The complete numbered, alphabetically sorted literature list of articles included in the systematic review and the number of reported cases with respiratory symptoms and/or respiratory cases. The reference population, if any, and stratification by age group and sex are also provided. In green and blue are the studies included in the meta-analysis for prevalence of respiratory symptoms and respiratory cases, respectively. Available at: https://shorturl.at/vwHX8

3.8.3 Appendix C

Absolute number of *specific respiratory symptom or symptoms associated with a respiratory symptom* by UN region or specific acquisition area. Available at: https://shorturl.at/vwHX8

3.8.4 Appendix D

Absolute number of *medically diagnosed* respiratory cases by UN region or specific acquisition area. Available at: https://shorturl.at/vwHX8

3.8.5 Appendix E

Absolute number of *molecularly diagnosed* respiratory cases by UN region or specific acquisition area. Available at: https://shorturl.at/vwHX8

3.8.6 Appendix F

Absolute frequency of respiratory infections cases in travellers for the four respiratory pandemics of the 21st century. Available at: https://shorturl.at/vwHX8

4
Study III

Infection tracking in travellers using a mobile app (ITIT): The pilot study

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Contents

4.1 Abstract

Background: Current surveillance of travellers' health captures only a small proportion of illness events. We aimed to evaluate the usability and feasibility of using an app to enable travellers to self-report illness.

Method: This pilot study assesses a novel mobile application called Infection Tracking in Travellers (ITIT) that records travel-related symptoms with associated geolocation and weather data. Participants were recruited in three Swiss travel clinics between December 2021 and March 2022. A feedback survey was used to examine app ease of use, and data from the app was used to examine travel and illness patterns as a proof-of-concept for the larger ITIT study.

Results: Participants were recruited from Zürich, Basel, and Geneva, with 37 individuals completing a total of 394 questionnaires in 116 locations in Asia, Africa, the Americas, and Europe. Illness symptoms were reported by 41% of participants, 67% of which were respiratory. The post travel questionnaire showed that all participants found the app easy to use and 63% said they would recommend it to others. Several users provided suggestions for improved usability.

Conclusion: The app fulfilled its function as a research tool linking infection symptoms with geolocation and climate data.

4.2 Introduction

As the COVID-19 pandemic has shown, illnesses contracted and spread through travellers can have wide reaching impact not only on the health of the individual traveller, but also on society as a whole. Travellers have long been exposed to a wide variety of infections ranging from arboviruses such as dengue, to diarrheal diseases, and parasites such as malaria [1]. When bringing these infections back into their home country, travellers can also cause local outbreaks, as recent dengue outbreaks in France and Spain have shown [2]. The tracking and reporting of these infections is important for travellers' health, and to identify and curtail outbreaks. However, much of current surveillance is top down, and relies on travellers seeking medical attention back in their home country, and on health care professionals and institutions reporting these infections to their respective public health authorities. This is time-consuming and misses many travellers with less severe symptoms, making timely outbreak detection more difficult. Therefore, it is of paramount importance to improve and supplement existing surveillance with bottom-up, participant-based surveillance, to identify outbreaks more quickly, and allow for more accurate prevalence predictions.

A promising area to achieve this is through mobile device-based applications. The number, and type of apps for health have exploded in recent years, with developments including apps for leprosy screening [3], tuberculosis treatment [4], HIV prophylaxis adherence [5], and a host of COVID tracking and reporting apps [6, 7]. There are also apps dedicated to outbreak surveillance, however, most of these focus only on a single disease, notably influenza or only cater to health care providers [8]. Other apps focus on traveller risks and behaviour with respect to non-infectious disease [9]. In contrast, the Infection Tracking in Travellers (ITIT) project is concerned only with infection acquired during travel. Mobile apps can also provide a breakthrough in low resources settings, making acquisition of data easier, and more complete [10]. However, with this technology also comes an increased need to focus on participant privacy and data protection in the digital sphere [11]. Keeping all of this in mind, we conceptualised and developed the ITIT app, a symptom-based surveillance app that will collect bottom-up, real-time information from travellers on a wide range of travel-related infections, keeping data protection and privacy and public health at the forefront.

The ITIT project combines self-reported symptoms from the ITIT app with GPS location and weather data to create a system of bottom-up real-time illness surveillance. This paper outlines the pilot project of the ITIT study, looking at a first cohort of 38 participants to examine the feasibility of the larger ITIT study, evaluate app functionality and user-interface, and data that will be collected in the larger study.

4.3 Materials and methods

This is the pilot project of a prospective, non-interventional, cohort study called Infection Tracking In Travelers (ITIT). The project is funded by the Swiss National Science Foundation. This study has been approved by the Swiss ethical committees (BASEC number 2020–02292) and has been registered in the database "ClinicalTrials.gov" (identifier NCT04672577) [12].

As incentives the app provides vetted travel health information from the WHO including Disease Outbreak News bulletins (DONs), and an e-library of travel health topics, as well as vaccination recommendations and requirements for each country [13].

4.3.1 Participant recruitment

Study participants were recruited between December 8, 2021, and March 31, 2022, at three different Swiss travel clinics in Zürich, Basel, and Geneva. The recruitment period ended when the sample size reached 50 pilot participants. Individuals were eligible for the study if they were over 18 years of age, travelled internationally for at least two days before the end of April 2022, and provided electronic informed consent.

Health care professionals at the various travel clinics were asked to introduce the study to eligible travellers during their pre-travel consultations. If interested, participants were informed of the study procedure and their contact information was recorded, along with the destination and dates of travel. Flyers with QR codes to download the ITIT application and describing the main study objectives were provided to interested participants and were freely available in the travel clinics (Figure 4.1).

4.3.2 Survey and mobile application

The ITIT app could be downloaded free of charge by participants from the Apple App Store and the Google Play Store. The content of this application is available in 9 different languages. When the application was first launched, participants were guided through the electronic consent form and asked to digitally sign it. Only participants who had given consent could access and respond to the daily survey. Consent to provide location data was optional and could be adjusted at any time in the app.

To actively participate in the study, participants were asked to complete a demographic questionnaire prior to their departure that included questions about age, sex, travel characteristics and health information. Then, during their trip, travelers were sent pop-up questionnaires at a specific time each day (6 p.m.) reminding them to complete the daily survey.

The daily survey consisted of self-reported, 5-point Likert scales describing the intensity of symptoms ranging from “none” to “medical attention”. Symptom types were grouped into 4 different categories (gastrointestinal, respiratory, skin and rashes, and general symptoms) and could be skipped by participants as needed. Two additional questions about the impact of symptoms on daily activities and general mood were asked of all participants who reported at least one symptom event.

Responses were stored locally in the internal memory of the participant’s smartphone and sent periodically via an SSL-secured http request to the ITIT platform hosted by a Google server in Zürich when Internet connectivity was available. The data were then enriched with climate data through programmatic queries based on collected parameters such as longitude, latitude, and time recorded during the survey.

All collected data were anonymized and could only be accessed through a dedicated dashboard restricted to the principal investigator and core team. ETHZ Health Ethics and Policy lab were closely involved in all aspects of the project that involved digital ethics [14]. Additionally, a systematic review was conducted prior to the study to better understand the ethical implications in developing an application for travel medicine [11].

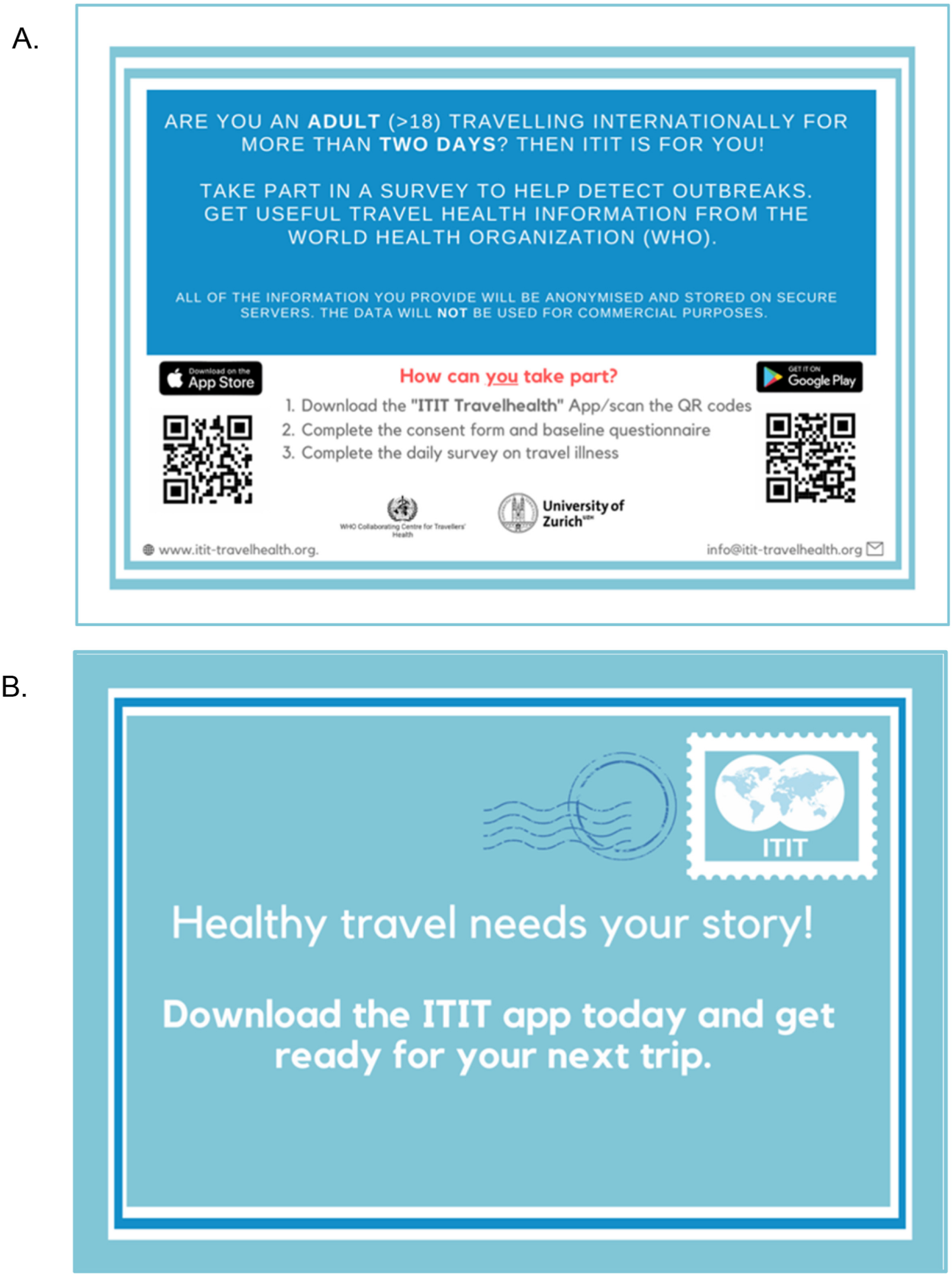

Figure 4.1: Recruitment flyer developed for the ITIT project. Printed as a postcard. A. Front B. Back.

4.3.3 Feedback questionnaire

Once all pilot study participants returned from their travels, a feedback form was emailed with the collected contact information. All participants who did not respond were called at least twice before their contact information was deleted.

4.3.4 Analyses

Descriptive analyses were used to analyze the baseline questionnaire and the daily survey. Geolocation data were mapped to symptom categories and their intensity. Feedback results were displayed graphically. All statistical analyses were performed with the statistical software R version 4.0.4, R Foundation for statistical computing, Vienna, Austria [15].

4.4 Results

Sixty-four participants were recruited for the ITIT pilot study, of whom 38 (60%) completed the baseline questionnaire and 32 (50%) completed at least one daily symptom questionnaire, and 18 (28%) completed the feedback questionnaire.

4.4.1 Demographics

The majority (20/38, 53%) of the participants were traveling for leisure or tourism, with only 2 traveling for business. and 3 for visiting friends and relatives (VFR) (Table 4.2). Five participants were attending the Shanghai Olympics, and 8 were traveling for their medical studies. Overall, 45% were male, and the average age was 35 years old. 87% of participants did not smoke, and only one had a chronic disease (high blood pressure). The trips were between 2 and 68 days long, with a mean of 28 days, and the most highly visited region was Sub-Saharan Africa (58%) (Table 4.1).

Of the 38 participants who filled out the demographic questionnaire, 32 filled out at least one daily survey, and when accounting for each day of travel, the overall survey response rate was 31%, ranging from 0 to 95% (Table 4.2).

A total of 1070 daily surveys were completed by the participants, and 43 symptoms were reported, ranging in intensity from mild to very severe (Figure 4.2). The most commonly reported symptoms were gastrointestinal (9 travellers), notably diarrhea (7 travellers) and stomach pain (8 travellers). No travellers reported any skin conditions or rashes. Several travellers reported multiple symptoms, notably a traveller to Senegal who had seven symptoms including a very severe sore throat and severe runny nose. For most travellers, their symptoms did not have a large impact on their daily activities, but 4 participants could not perform their daily activities due to their symptoms.

Table 4.1: Demographic table of ITIT pilot participants (N = 38).

	Leisure/Tourism (N=20)	Business/Corporate Travel (N=2)	VFR[a] (N=3)	Mass Gathering Events (N=5)	Other (N=8)	Overall (N=38)
N	20	2	3	5	8	38
Sex						
Male	9 (45.0%)	0 (0%)	1 (33.3%)	3(60%)	4(50%)	17(44,7%)
Female	11 (55.0%)	2 (100%)	2 (66.7%)	2(40%)	4(50%)	21(55,3%)
Age (years)						
Mean (SD)[b]	37.0 (13.8)	31.0 (9.90)	36.7 (20.3)	44.(11,5)	25.(1,30)	35.(13,1)
Median [Min, Max]	32.0 [23.0, 72.0]	31.0 [24.0, 38.0]	27.0 [23.0, 60.0]	40[34,63]	26[23,27]	30[23,72]
Travel Duration (days)						
Mean (SD)[b]	18.6 (14.5)	33.0 (31.1)	14.7 (10.4)	21.(6,98)	58.(5,30)	27.(20,6)
Median [Min, Max]	14.0 [5.00, 60.0]	33.0 [11.0, 55.0]	18.0 [3.00, 23.0]	22[11,30]	59[50,68]	21[3,68]
Smoking						
Not Smoking	17 (85.0%)	2 (100%)	1(33.3%)	5(100%)	8(100%)	33(86,8%)
Daily	1 (5.0%)	0 (0%)	1(33.3%)	(00%)	(00%)	2(5,3%)
Weekly	2 (10.0%)	0 (0%)	1(33.3%)	(00%)	(00%)	3(7,9%)
Monthly	0 (0%)	0 (0%)	(00%)	(00%)	(00%)	(00%)
Former Smoker	0 (0%)	0 (0%)	(00%)	(00%)	(00%)	(00%)
Chronic Disease						
High BP[c]	1 (5.0%)	0 (0%)	3(100%)	5(100%)	8(100%)	(02%,6)
None	19 (95.0%)	2 (100%)	(00%)	(00%)	(00%)	(00%)
Region						
Eastern Asia	1 (5.0%)	0 (0%)	0 (0%)	5 (100%)	1 (12.5%)	7 (18.4%)
Latin America and the Caribbean	2 (10.0%)	0 (0%)	1 (33.3%)	0 (0%)	1 (12.5%)	4 (10.5%)
Southern Europe	5 (25.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (13.2%)
Sub-Saharan Africa	12 (60.0%)	2 (100%)	0 (0%)	0 (0%)	6 (75.0%)	20 (52.6%)
Northern America	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)	1 (2.6%)
Nothern Europe	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)	1 (2.6%)

[a] VFR: Visiting friends and relatives
[b] SD: Standard Deviation
[c] BP: Blood pressure.

Table 4.2: Follow-up time and response rates of ITIT pilot participants.

Questionnaire	N = 38[a]
Over all follow-up time (days)	
17	3 (7.9%)
714	7 (18%)
1431	8 (21%)
>31	14 (37%)
No questionnaire completed	6 (16%)
Number of missed surveys (n)	
Mean (SD)	20 (16)
Range	2, 56
Survey Response rate (%)	
Mean (SD)	0.31 (0.28)
Range	0.00, 0.95

[a] n (%)

Figure 4.3 shows a map of all daily questionnaires, and all reported symptoms by symptom group and intensity. Here again the spread of participants can be visualized, and the range and intensity of symptoms. The most symptoms were reported by participants traveling the African continent.

4.4.2 Feedback form

The responses of the feedback questionnaire can be seen in Figure 4.4. The majority of participants found the app easy to find, install and use and felt comfortable using mobile applications, and found it easy to answer the daily surveys. However, some found it difficult to answer the surveys, due to not receiving notifications every day of the trip. Some participants received no notifications, and others received them before and after the trip. This was discussed with the app developer and the issue resolved in the future app versions. Over 60% of participants found all app functionalities useful, with 68% finding the specific country information useful, and 63% finding the DONS and travel health topics useful. 79% of participants would recommend the app to others. Specific feedback on questionnaires and pop-up notifications was also collected and relayed to the developer. Several participants reached over the phone disclosed that they had forgotten to download the app at all.

4.5 Discussion

Using the ITIT app, a total of 38 participants resulted in over 1000 data points outlining illness symptoms encountered by travellers globally. This method of data collection is fast, real-time, less labour intensive than traditional methods, and has the potential to give more accurate data, without recall bias.

Participant	Demographics	Travel Location, Duration (days)	Nausea	Vomiting	Stomach Pain	Diarrheoa	Constipation	Cough	Sore throat	Stuffed or runny nose	Out of breath - resting	Out of breath - running	Fever	Dizziness	Ear ache	Headache	Pain behind the eyes	Muscle pain	Aching limbs	Other	Pain in the joints	Swelling of the joints	Impact on Activities	Day Overall
1	26 f	Cameroon (55)				1																	1	3
						2																	1	3
						1																	0	3
						1																	0	3
						1																	0	3
			3	2		3																	2	2
2	26 m	Korea (62)											2			2				1			1	1
													2	1		1	1			1			1	1
3	24 m	Cameroon (58)	1		3	3										2		2					4	1
			1		2	2										1							4	1
					1	2																	0	3
						2																	1	2
4	26 f	Bolivia (63)																					1	2
									1	2		1											0	3
																							1	2
																							0	3
								1	1	4	1	2		1		1				1			1	2
								1		3		1											1	3
			2		1	3		1		2		1											2	2
										1													1	3
									1	1		1											0	2
5	25 m	Cameroon (61)	2		1	3																	2	2
			1		1	2																	1	3
					1	2																	0	3
						1																	1	3
6	28 f	Spain (10)														2							1	4
																				1			1	3
7	28 m	South Africa (41)	3	1	4	4					3	1											4	2
					1	2																	0	3
8	23 f	Senegal (57)						2	4	3		1		1		1		1					1	2
9	25 f	Cameroon (50)			1	1																	0	2
10	30 f	South Africa (34)														3							2	2
																							2	2
					3								1			3		3	2				4	1
11	27 m	Cameroon (60)			1	2																	2	2
12	38 m	China (11)																			4	2	1	3
13	38 f	Burkina Faso (5)																					0	3
14	26 f	South Africa (41)	1																				1	4
					2																		0	4

Figure 4.2: Symptoms reported by ITIT pilot participants, coloured by symptom intensity and grouped by traveller.

59% of recruited participants downloaded the app and filled out the demographic questionnaire, but of these, 84% then filled out at least one daily symptom survey. These results were relayed back to the development team, and some changes were made to the app to increase user retention and use, including ensuring that the participants get pop-up notifications on their phone during their trip that lead directly to the survey screen, and a reminder pop-up if the first is ignored. Most participants, when contacted for feedback, stated that they had simply forgotten to download the app between the time of their travel clinic visit and their trip, or forgotten to fill the survey during their trip. Therefore, when training and onboarding new centres for the ITIT project, there is also now emphasis on getting participants to download and fill the demographic questionnaire directly at the clinic, to reduce chances of travellers forgetting to download the app at a later date. Once the demographic questionnaire is filled out, the pop-ups will remind travellers of the app, which is essential for travellers who visit clinics far in advance of their

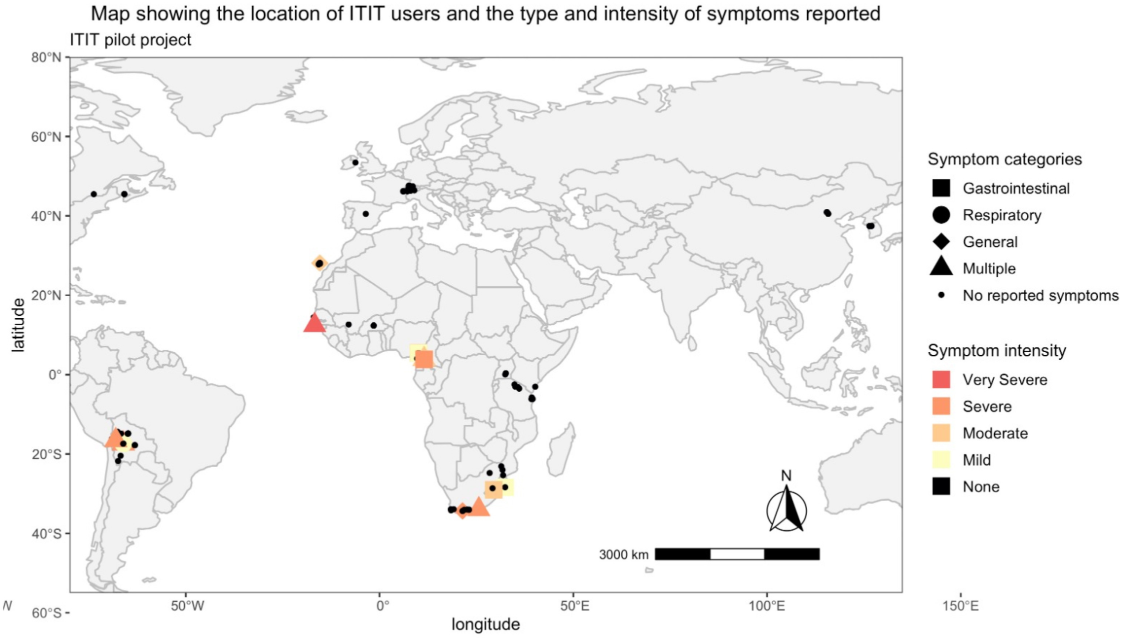

Figure 4.3: Map of daily surveys filled out by ITIT pilot participants with location, symptom category and intensity (n = 43).

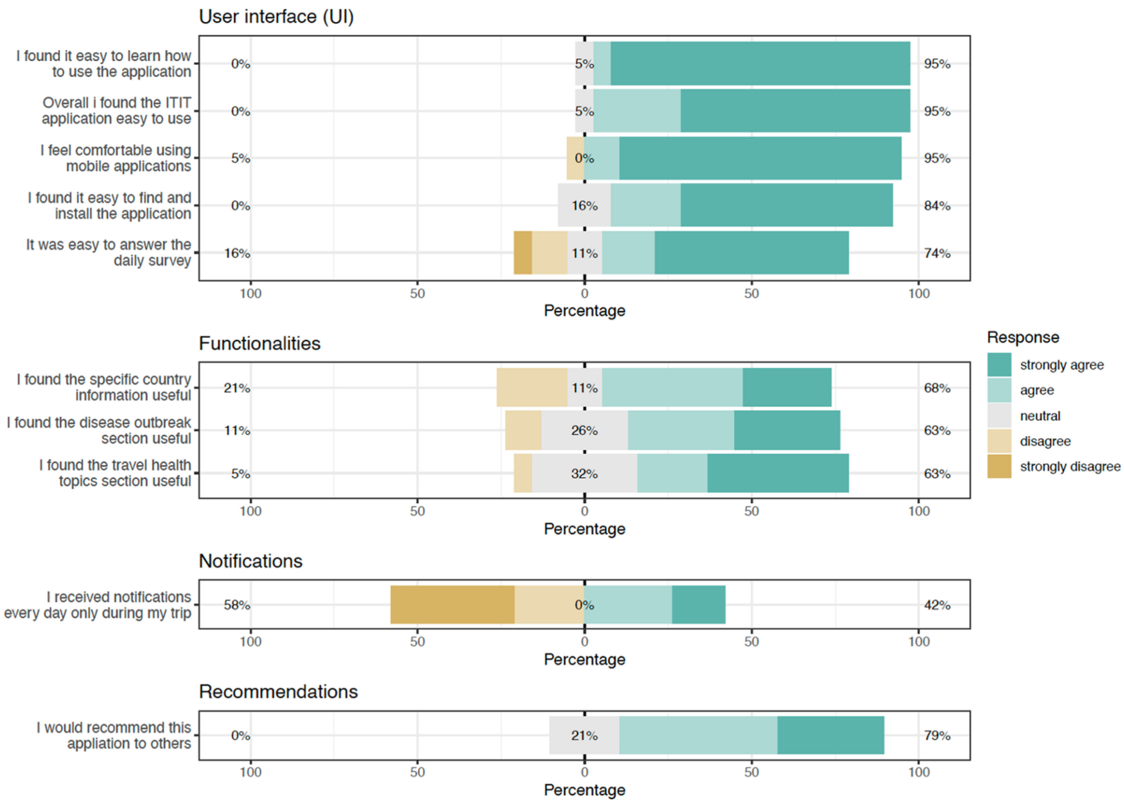

Figure 4.4: Pilot participant responses to the ITIT app feedback form (n = 18).

travel dates. In addition, clear recruitment materials were created to gather interest and to simplify the recruitment process. Other additions to the app are planned, including a personalised 'my trip' screen, where participants will be able to see their entered data, in order to provide feedback, and be a valuable tool for travellers who develop symptoms, to record when, where and which symptoms occurred.

Overall, the app was successfully able to collect illness symptom data and the linked location and climate information in real-time. A variety of locations around the world were included in the initial pilot participants, and a range of symptoms and symptom intensities were seen. The wealth of information, including participant demographics, dates of symptoms, and climate information can lead to interesting analyses when more data points are collected in the larger ITIT study. This is promising for the larger study, and more data points will also allow for more sophisticated statistical analyses and visualisations and infectious disease predictions. Some proposed future work includes making profiles of expected symptoms by type of traveller and travel demographics through CART analysis and making maps showing hotspots of illness symptoms over time. Eventually the app could be used for real-time outbreak detection to supplement existing surveillance programs.

A limitation of this study is that there was no follow-up of participants, to see if anyone had developed symptoms after the last day of the trip, or to see if those participants with symptoms had any official diagnosis from a health practitioner, however, a follow-up, electronic questionnaire exploring these questions will be included in the larger ITIT project. This questionnaire will be sent to all participants post travel, and will include questions on persisting symptoms, diagnoses, and any treatment obtained. In addition, the small number of data points were not conducive for most statistical tests, so this pilot was primarily descriptive, again, an issue that will be resolved in the larger study. A further limitation is the fact that the recruitment of participants has the potential to be biased, as only travellers who visit a travel centre for pre-travel advice were asked to participate, and only travellers who have and can operate a mobile phone and download the app and who consent to having their location recorded would take part. This results in, on average, younger, more tech-savvy people with a higher socio-economic status that allows for travel clinic visits and international travel in the ITIT population. However, as compared to most infection surveillance in health care systems, this method will still cast a wider net. The goal of the larger ITIT project is to reach 10,000 participants, a number much larger than typical travel health studies, and from more diverse areas, as recruitment will not only be done through travel clinics, but also through universities, online through social media, and through the news, reaching a much broader population than only those who attend pre-travel consultations. The completely digital eConsent form also ensures that recruitment is less labour intensive, and that participants who have no in-person contact with the study team can also easily take part in the study across the globe.

The ITIT project shows great promise in not only the number and variety of participants, but also the amount of real-time data that will be gathered, infection symptom data linked to real-time GPS and climate data, as well as information on travel type and traveller demographics. This, as well as the WHO vetted travel health information and timely disease outbreak news makes ITIT a trustworthy, valuable tool for travellers and travel health research alike. Using the ITIT app and shortening information flows to create a loop of travellers being data consumers and providers will enable many new use cases in illness monitoring such as early warnings and more accurate risk and symptom map data. And through being distributed as a mobile app we aim to reach an unprecedented number of participants for studies, with all the benefits of more data, coverage, and significance.

4.6 Conclusions

These results show great promise for the launch of the main ITIT project, and for app-based infection surveillance r. The data produced in the study are rich and will be even more valuable when there are more data points from the larger project. With some modifications to the app based on feedback from pilot participants, and what was seen in the data, the ITIT app has the potential to revolutionise modern illness surveillance.

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5
Study IV

Surveillance of global, travel-related illness using a novel app: a multivariable, crosssectional, digital health study

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Contents

5.1 Abstract

Background: Current traveller health surveillance is top-down. Mobile-based surveillance could capture infection symptoms in real-time. We aimed to evaluate the spectrum of illness in travellers using a mobile app-based system.

Method: This study (ClinicalTrials.gov NCT04672577) used an application called Infection Tracking in Travellers (ITIT) that records travel-related illness symptoms with associated geolocation and weather data. The free ITIT app is available in 14 languages. Participants were recruited globally from December 2021. Participants were over 18 years of age, travelled internationally, and provided electronic informed consent. Incentives included provision of travel health information imported from the WHO website. Symptoms were recorded with daily pop-up questionnaires and symptom severity was assessed using a Likert scale. Two post-travel questionnaires were also administered. Logistic mixed models examined factors relating to symptom presence, and a random forest model examined symptom impact.

Findings: 609 participants were recruited until July 2023. Participants had an average age of 37 years (18-79), and an average travel duration of 26 days (2-281). Most participants were travelling for leisure/tourism (401; 66%), followed by "visiting friends and relatives" (VFR) (99; 16%) and business travel (80; 13%).

Every UN global subregion was visited by at least one traveller. Of 470 registered trips, symptoms were reported on 163 trips (35%). Gastrointestinal symptoms were reported on 87 trips (19%), and respiratory symptoms on 81 trips (17%). The most important factors in predicting presence of symptoms were duration of travel, travelling in winter, and high humidity. Diarrhoea, headache, and nausea were symptoms with most impact on daily activities. Post-travel questionnaires showed that 12% of surveyed participants experienced symptoms with several episodes of self-treatment. Two diagnoses were recorded: Lyme Disease and amoebic dysentery.

Interpretation: The digital tool ITIT successfully captures the spectrum of travel-related illness. This detailed epidemiology is crucial for outbreak detection and for the formulation of travel medicine guidelines.

Funding: The funding for this study came from the Swiss National Science Foundation (grant number 320030_192653).

5.2 Research in context

5.2.1 Evidence before this study

We searched PubMed for articles published in English in the time frame January 1st 2020 and September 30th 2023 using the key words "app*", "traveller" (or traveler), and "illness" or "infection". We found five studies that described the use of a mobile application to monitor illness symptoms in travellers. The number of participants in these studies ranged from 37 to 1000. Previous research showed that a majority of travellers are willing to fill out symptom surveys in real time and have their associated location tracked. A systematic review of traveller apps showed that ethical issues including data privacy and protection were important factors. The novel mobile application, ITIT (Illness Tracking in Travellers) collects real time symptom and location data from travellers and has been evaluated in a pilot study (n=37) and was found to be an effective method of obtaining granular, bottom-up illness information from travellers.

5.2.2 Added value of this study

This study confirmed the utility of the ITIT App as a tool for travellers to provide "bottom-up" travel-related, illness surveillance data in real time in a large, global, cross-sectional setting. More than 600 travellers filled out over 3700 daily symptom surveys, travelling to every continent, and displaying a wide range of illness symptom and intensities. These data, combined with geolocation data, and associated climate and air quality information, could then be used to examine the epidemiology of travel related illnesses, and what external factors are associated with illness symptoms. In addition, post -travel surveys examined longer sequelae of infection, and linked diagnoses or use of medication to symptoms.

5.2.3 Implications of all the available evidence

Travellers, using a novel application such as ITIT, can collate data and serve as sentinels for travel-related illnesses and for the identification of infection clusters and possible alerts. These data from large populations of diverse travellers, can be sent in raw and anonymised form to a central database in near real-time and linked with geolocation and environmental data to provide a granular representation of global illness in travellers. The ITIT app shows that it is possible to digitise and speed up the process of travel-related disease surveillance, supporting and improving current global health surveillance.

5.3 Introduction

International travel is an integral part of life, whether for tourism, migration, business, or visiting friends and family, living in a different country. International mobility also exposes travellers to a range of health risks. Depending on the destination, traveller characteristics and purpose of travel, travel is associated with a broad spectrum of illnesses, including gastrointestinal complaints, respiratory infections, and vector-borne diseases such as malaria and dengue [1, 2]. In addition, travellers can introduce pathogens to new regions and initiate disease outbreaks on return to their home countries particularly in vulnerable regions with conducive transmission conditions [2, 3]. Travellers' mobility and exposure to infections in different global regions make them valuable sources of data on disease transmission patterns and key sentinels for monitoring and detecting potential outbreaks [4]. Therefore, early detection and reporting of travel-related illnesses are crucial to implementing effective public health measures and safeguarding both travellers and the communities they interact with. In addition, recommendations for the protection of travellers' health need to be evidence-based and up-to-date with respect to infectious disease epidemiology.

Historically, 'top-down' reporting has been the go-to method of tracking travel-related illnesses. These systems rely on healthcare professionals, laboratories and official health authorities to report mandatory infections or cases of interest regionally and nationally. However, there are several significant drawbacks to this approach. First, there is often a time lag in data reporting, as information must be logged, recorded, and sent to relevant health agencies before it is available. Secondly, the data collected may lack crucial details that travellers themselves can provide and be inconsistent in reporting quality. Lastly, it relies on travellers attending medical facilities and seeking care, and such systems consequently do not capture less severe or asymptomatic cases, resulting in an incomplete picture of the actual disease burden [Leder et al. [5]). Surveillance networks that collate clinician verified data on travellers' illness such as EuroTravNet [Schlagenhauf et al. [1]) or GeoSentinel [6] are limited by a lack of denominator data and also capture only a small portion of travelrelated illness with a focus on severe illness.

'Bottom-up' symptom reporting by travellers themselves therefore offers a revolutionary solution to these challenges, and an invaluable tool to supplement existing surveillance systems. There are several advantages of a real-time bottom-up reporting system. Firstly, it ensures the timely detection of illness clusters, allowing for prompt investigation and intervention. This can facilitate rapid interventions, preventing localised outbreaks from spreading globally. Public health authorities can implement containment measures, quarantine protocols, and vaccination campaigns promptly, curbing the progression of diseases. Secondly, travellers' self-reports can provide valuable insights into environmental exposures, regional risk factors, and potential disease hotspots, aiding in targeted preventive strategies to protect vulnerable populations. Lastly, the system fosters a sense of shared responsibility among travellers in safeguarding public health. The widespread adoption of smartphones and digital platforms presents an unprecedented opportunity to implement a bottom-up, self-reported, illness tracking system. By encouraging travellers to report their symptoms and health conditions in realtime through user-friendly mobile applications, a vast amount of data can be collected in real-time, more accurately representing the true prevalence and distribution of travelrelated illnesses. Research has shown that a majority of travellers are also willing to fill out symptom surveys and have their associated location tracked [7]. However, with the advent of this quickly accessible data, it is more important than ever to consider the ethical implications and ensure privacy, and security for participants [8]. Another issue in participatory studies is the retention and motivation of participants. We obtained travel health information from WHO in a format uploadable to the app as an incentive to take part in the study.

Using the ITIT Travelhealth app, travellers report daily symptoms through a short, userfriendly questionnaire, and this information is then linked to location data as well as climate and air quality information. The app also collects demographic information and follows up with travellers after their trip to gain information on any persisting symptoms, self-treatments or confirmed medical diagnoses. More detailed information about the app can be seen in the pilot study, which looked at ease of use and feasibility of using the app, with promising results [9]. This study evaluates data collected through the ITIT app from the first 609 recruited participants, and examines the epidemiological patterns of reported symptoms by traveller demographics and location.

5.4 Methods

This study was approved by the Swiss Ethics Committee (BASEC number 2020–02292) and registered in the "ClinicalTrials.gov" database (identifier NCT04672577) [10].

5.4.1 Recruitment

Participants were recruited from April 1st 2022 to July 15th 2023 through travel clinics and partners of the ITIT global network, as well as through university-wide emails, conference promotions, public promotional material, and word-of-mouth. The ITIT app is free of charge and available on the Apple App store and Google Play store, and information regarding the study, including a completely electronic informed consent form is found on the app. When participants download the app, they click through the informed consent, sign it electronically and then complete a preliminary demographic questionnaire. This questionnaire collects information about the traveller (> 18 years old) and their trip, including the date and duration of their trip (minimum travel duration of two days). This information is then used to prompt pop-up reminders for the participants to complete the daily survey on each day of their trip. The daily survey collects information about the symptom type (gastrointestinal, respiratory, dermatological and general) and intensity of symptoms (six-point Likert scale: none‘, ’mild‘, ’moderate‘, ’bad‘, ’very bad‘ and ’medical visit‘) and the impact of these symptoms on the participant’s day on a sevenpoint Likert scale ranging from no impact on activities to hospitalisation. Finally, after the trip is completed, participants are sent a follow-up questionnaire seven and twenty eight days post travel. This questionnaire retrieves information about symptoms that may have occurred after the trip, and also about any diagnoses or medications used for self-treatment. As an incentive to take part in the project, the travellers are also provided with travel health information published by the World Health Organisation, freely available on the app. This information includes general travel-health information, specific vaccination information and disease outbreak news known as DONs (Daily Outbreak News) via API from WHO and updated in real-time.

5.4.2 Data storage and weather data

All the self-reported symptom and demographic information is linked to location and climate data and stored on secure servers in Zurich, Switzerland. The climate information is fed via the weather API from OpenWeatherMap and includes data on temperature, weather, humidity, and air quality. This linked data was tied to the daily surveys, and tagged with anonymized participant and trip IDs, as participants were able to take part in the study for multiple trips.

5.4.3 Statistical analysis

Demographic questionnaires were linked to the daily questionnaires using the trip ID column. Descriptive statistics were compiled based on the demographic information, including an analysis of average age, proportion of travellers with chronic diseases or smoking status, and average trip duration. Using the linked location data, a map of daily surveys was created showing the presence and intensity of symptoms. The absolute number of all reported symptoms was calculated both individually and in symptom groups (gastrointestinal, respiratory, dermatological and general) and then stratified by travel region and sex. The incidence rate of these reported symptoms was calculated by dividing the number of reported symptoms by the total number of completed surveys and then multiplying by 1000 to obtain the rate per 1000 surveys. This information was visualised in a heat map table. Logistic mixed models were used to account for the clustering of participants by trip and to understand which variables influence the expression of symptoms overall and in the four subcategories of symptoms. Univariate analysis was conducted

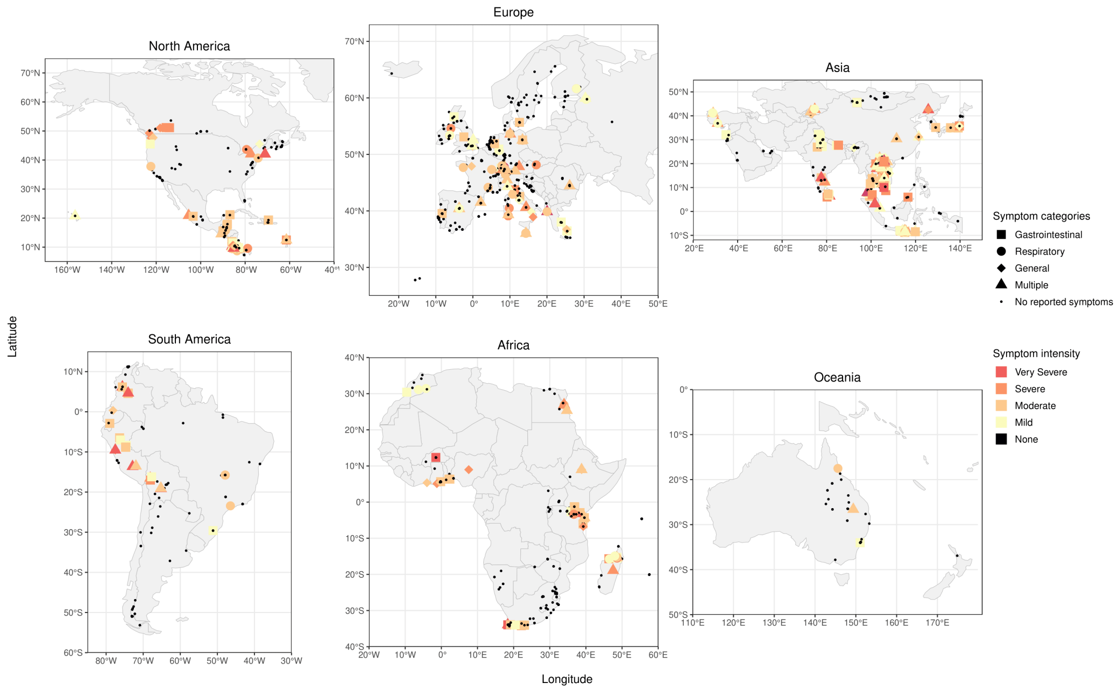

Figure 5.1: Map of daily surveys with available GPS location completed by ITIT participants, including symptom category and intensity (n=2905). Note: The delimitation of continents is based on the Natural Earth Data v4.1.0 (March 2018). Points located in international waters are associated with the nearest continent.

first, followed by multivariate analysis based on the optimal model. The optimal model was determined by a combination of 'order' and 'backward' elimination, using the Akaike Information Criterion (AIC) as the selection criterion. In the 'order' method, the terms are ordered according to their contribution to the model to ensure that the model converges before performing 'backward elimination'. Due to the large amount of missing survey data, Multivariate Imputation by Chained Equations (MICE) with 15 imputations was applied to the optimal models using linear mixed models for numerical data, two-stage logistic models for binary data and replication of the most likely value within a class for factors with more than two stages. These methods were chosen to account for the clustering of participants within their respective trip. Several classification models were evaluated to predict the impact of symptoms on daily activities, including random forest, penalised logistic regression, XGBoost, decision tree (CART), and k-nearest neighbours (k-NN). The models were carefully evaluated and tuned for optimal performance. The Random Forest model was selected as the best performing model based on AUC score. A significance level of 0.05 was used for all statistical tests. All analyses and data processing were done using the statistical software R, version 4.2.3. Role of the funding source The funding for this study came from the Swiss National Science Foundation (grant number 320030_192653). The funding source had no influence on the study design, data collection, data analyses, data interpretation, or the writing and submission of the paper for publication.

Table 5.1: Sociodemographic characteristics of ITIT participants (n = 609).

Characteristic	Overall, N = 609[a]	Leisure/tourist travellers, N = 401[a]	Visiting friends and relatives (VFR), N = 991[a]	Business/corporate travellers, N = 801[a]	Other, N = 292[b]
Age [years]					
Mean (SD)	37 (14)	37 (15)	35 (13)	41 (13)	35 (15)
Minimum-Maximum	18-79	18-79	19-69	19-71	19-65
Gender					
Female	337 (55%)	221 (55%)	58 (59%)	40 (50%)	18 (62%)
Male	271 (45%)	179 (45%)	41 (41%)	40 (50%)	11 (38%)
Unknown	1	1	0	0	0
United Nations continent name					
Africa	103 (17%)	69 (17%)	9 (9.1%)	17 (21%)	8 (28%)
Americas	115 (19%)	82 (21%)	19 (19%)	11 (14%)	3 (10%)
Asia	145 (24%)	110 (28%)	15 (15%)	12 (15%)	8 (28%)
Europe	233 (38%)	131 (33%)	56 (57%)	37 (46%)	9 (31%)
Oceania	11 (1.8%)	7 (1.8%)	0 (0%)	3 (3.8%)	1 (3.4%)
Unknown	2	2	0	0	0
Smoking status					
Current smoker	61 (10%)	49 (12%)	5 (5.1%)	5 (6.3%)	2 (6.9%)
Former smoker	46 (7.6%)	33 (8.3%)	4 (4.0%)	7 (8.8%)	2 (6.9%)
Never smoked	501 (82%)	318 (80%)	90 (91%)	68 (85%)	25 (86%)
Unknown	1	1	0	0	0
Comorbidities	58 (9.5%)	36 (9.0%)	7 (7.1%)	11 (14%)	4 (14%)
Duration of travel [days]					
Mean (SD)	26 (32)	28 (32)	20 (19)	19 (26)	56 (67)
Minimum-Maximum	2-281	2-281	3-120	2-112	3-180
Overall response rate[c]					
Mean (SD)	0.31 (0.35)	0.31 (0.35)	0.34 (0.35)	0.35 (0.37)	0.18 (0.32)
Minimum-Maximum	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00	0.00-1.00
Active travellers response rate[d]					
Mean (SD)	0.46 (0.34)	0.46 (0.34)	0.46 (0.33)	0.51 (0.34)	0.36 (0.37)
Minimum-Maximum	0.00-1.00	0.00-1.00	0.03-1.00	0.03-1.00	0.01-1.00
Number of trips during study period					
No active participation	205 (34%)	137 (34%)	27 (27%)	27 (34%)	14 (48%)
Questionnaires filled for 1 trip	353 (58%)	235 (59%)	61 (62%)	43 (54%)	14 (48%)
Questionnaires filled for 2 or more trips	51 (8.4%)	29 (7.2%)	11 (11%)	10 (13%)	1 (3.4%)

[a] n (%)
[b] Includes specific groups of travelers who do not fit into the previously defined categories.
[c] Includes participants who completed the baseline questionnaire but did not complete any subsequent surveys.
[d] Includes participants who completed at least one survey.

5.5 Results

In total, 609 travellers participated in the study. Of these, 401 (66%) were tourists, and 99 (16%) were visiting friends and relatives. The mean age was 37 years old, and 337 (55%) were female. A total of 501 (82%) of participants had never smoked, and only 58 (9.5%) had any comorbidities. The mean travel duration was 26 days (2 to 281), and the most common travel destination was Europe with 233 travellers (38%), followed by Asia with 145 (24%), the Americas with 115 (24%), Africa with 103 (17%), and Oceania with 11 (1.8%). Overall, 66% (n = 404) of travellers who downloaded the app and filled out the demographic survey also filled out at least one daily survey. The response rate for these 'active travellers' was 46% (Table 5.1).

Overall, there were 2905 daily symptom surveys with associated location data filled out by participants. Figure 5.1 shows the distribution of all the daily questionnaires, as well as if a symptom was reported, and if so, which symptom category it belonged to, and the symptom intensity. Almost the full range of symptom intensities and categories was seen with four surveys reporting symptoms prompting medical attention (see travellers' details in Appendix E. Some initial symptom clusters can be visually identified, including groups of symptoms around southeast Asia, and central America, as well southern Europe.

In total there were 3739 surveys filled, when including surveys with no associated location data; of these, 512 reported some symptoms (14%). On evaluation of the symptom types reported, stratified by region of travel and sex, gastrointestinal symptoms are most frequently reported, with an incidence rate of 66.33 per 1000 completed surveys, and dermatological symptoms the least, at 25.41 per 1000 completed surveys. In addition, when looking at individual symptoms, diarrhoea is most often reported with 52.69 reports per 1000 surveys. In travellers visiting Asia, this rate increases to 90.46 per 1000 completed surveys. Women reported overall more symptoms than male participants (IR of 154 vs. 115 per 1000) and reported more symptoms in all categories. Respiratory symptoms, mainly cough and a runny nose, were reported most frequently in Europe, and were overall the second-most reported group of symptoms. No participants reported other body aches, and only 10 (0.03%) surveys reported swollen joints (Figure 5.2). Of the 470 recorded active trips, travellers reported experiencing symptoms on at least one day during their travels on 163 trips, representing 35% of the total recorded active trips. The breakdown of symptoms reported is as follows: 87 (19%) trips reported at least one gastrointestinal symptom; 81 (17%) reported at least one respiratory symptom, 35 trips (7.4%) reported at least one dermatological symptom; and 77 trips (16%) reported at least one general symptom. A total of 74 post-travel surveys were completed from 72 distinct travellers. Of these, 9 (12%) of the surveys reported travellers experiencing symptoms since their return. Furthermore, 24 (32%) of surveys reported self-treatment. These self-treatments included over-the-counter medications such as loperamide and paracetamol, antibiotics such as streptomycin, and other treatments including vitamins, mosquito bite balms and natural oils. Among those travellers reporting symptoms post travel, 2 (22%) sought medical attention and the same percentage received a medical diagnosis. One participant travelling to Italy and Australia reported a co-infection with Lyme Disease and

	Overall (N=3739)[a]		Africa (N=699)[a]		Americas (N=870)[a]		Asia (N=1006)[a]		Europe (N=1109)[a]		Oceania (N=55)[a]		Female (N=2175)[a]		Male (N=1564)[a]	
Symptoms	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]
Any Symptom	512	136.94	71	101.57	107	122.99	209	207.75	122	110.01	3	54.55	335	154.02	177	113.17
Gastrointestinal	248	66.33	42	60.09	63	72.41	125	124.25	17	15.33	1	18.18	170	78.16	78	49.87
Nausea	104	27.81	21	30.04	21	24.14	59	58.65	3	2.71	0	0.00	81	37.24	23	14.71
Vomiting	20	5.35	2	2.86	7	8.05	11	10.93	0	0.00	0	0.00	11	5.06	9	5.75
Stomach Pain	143	38.25	25	35.77	41	47.13	71	70.58	5	4.51	1	18.18	95	43.68	48	30.69
Diarrhoea	197	52.69	36	51.50	57	65.52	91	90.46	13	11.72	0	0.00	127	58.39	70	44.76
Constipation	43	11.50	2	2.86	4	4.60	30	29.82	7	6.31	0	0.00	31	14.25	12	7.67
Respiratory	218	58.30	24	34.33	30	34.48	70	69.58	92	82.96	2	36.36	141	64.83	77	49.23
Cough	158	42.26	18	25.75	20	22.99	52	51.69	66	59.51	2	36.36	95	43.68	63	40.28
Sore Throat	114	30.49	5	7.15	12	13.79	37	36.78	60	54.10	0	0.00	81	37.24	33	21.10
Runny Nose	164	43.86	20	28.61	24	27.59	57	56.66	61	55.00	2	36.36	99	45.52	65	41.56
Out of Breath (Resting)	43	11.50	2	2.86	5	5.75	3	2.98	33	29.76	0	0.00	29	13.33	14	8.95
Out of Breath (Running)	78	20.86	6	8.58	13	14.94	15	14.91	44	39.68	0	0.00	56	25.75	22	14.07
Dermatologic	95	25.41	5	7.15	18	20.69	55	54.67	16	14.43	1	18.18	82	37.70	13	8.31
Rash	38	10.16	4	5.72	3	3.45	24	23.86	6	5.41	1	18.18	33	15.17	5	3.20
Itchy Insect Bite	64	17.12	4	5.72	14	16.09	32	31.81	13	11.72	1	18.18	54	24.83	10	6.39
Itchy (Other)	18	4.81	1	1.43	1	1.15	9	8.95	6	5.41	1	18.18	15	6.90	3	1.92
Sunburn	30	8.02	1	1.43	7	8.05	19	18.89	3	2.71	0	0.00	23	10.57	7	4.48
Itchy Red Eyes	17	4.55	0	0.00	3	3.45	8	7.95	6	5.41	0	0.00	15	6.90	2	1.28
General	158	42.26	21	30.04	35	40.23	63	62.62	39	35.17	0	0.00	115	52.87	43	27.49
Fever	49	13.11	4	5.72	10	11.49	17	16.90	18	16.23	0	0.00	33	15.17	16	10.23
Dizziness	63	16.85	4	5.72	10	11.49	30	29.82	19	17.13	0	0.00	44	20.23	19	12.15
Ear Ache	30	8.02	3	4.29	10	11.49	7	6.96	10	9.02	0	0.00	25	11.49	5	3.20
Headache	114	30.49	13	18.60	28	32.18	43	42.74	30	27.05	0	0.00	84	38.62	30	19.18
Pain in Eyes	36	9.63	6	8.58	5	5.75	14	13.92	11	9.92	0	0.00	19	8.74	17	10.87
Muscle Pain	47	12.57	5	7.15	11	12.64	16	15.90	15	13.53	0	0.00	26	11.95	21	13.43
Aching Limbs	53	14.17	5	7.15	11	12.64	23	22.86	14	12.62	0	0.00	31	14.25	22	14.07
Body (Other)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pain in Joints	33	8.83	10	14.31	2	2.30	16	15.90	5	4.51	0	0.00	23	10.57	10	6.39
Swelling in Joints	10	2.67	4	5.72	1	1.15	2	1.99	3	2.71	0	0.00	8	3.68	2	1.28

[a] Absolute Number of Surveys Completed
[b] Absolute Number of Reported Symptoms
[c] Incidence Rate per 1000 Completed Surveys

Figure 5.2: Absolute number and incidence rate of symptoms reported by travellers using the ITIT app, stratified by sex and location of travel (n=3739).

amoebic dysentery. One survey reported a diagnosis (common cold) without having any symptoms or consultation. No traveller reported hospitalisation.

When examining which factors influence the presence of reported symptoms using logistic mixed modelling, univariate analysis showed that duration of travel, age, location of travel to Asia, business travel, humidity, and travelling in winter were significant at the 5% level. The optimised multivariate model using complete case analysis however, only kept duration of travel, humidity, wind speed, and season at destination, and of these, only duration of travel and winter travel are significant (OR 3.10, $p < 0.001$ and OR 2.79, p 0.001, respectively). When looking at the MICE multivariate model, the same explanatory variables are kept in the model as the previously discussed mode, but in this case only duration of travel (OR 1.26, $p = 0.043$) and humidity (OR: 1.76, $p < 0.001$) were significant (Table 5.2).

When examining symptom categories separately, the multivariate models using MICE showed different factors as being associated with symptom presence. Duration of travel, higher humidity and atmospheric ammonia (NH3 g/mş) were associated with gastrointestinal symptom presence, whereas for respiratory symptoms and general symptoms, no factor was significantly associated with symptom presence in the imputed model. Duration of travel, higher temperatures and travelling in summer versus autumn were associated with higher incidence of dermatological symptoms (Appendix A-D).

Table 5.2: Univariate and multivariate analyses of variables influencing symptom expression using complete case analysis and imputed full sample analysis

	Complete case analysis								Imputed full sample analysis[c]			
	Univariate analysis				Multivariate model[b]				Multivariate model[b]			
Predictors[a]	Odds Ratios	Lower CI	Upper CI	p	Odds Ratios	Lower CI	Upper CI	p	Odds Ratios	Lower CI	Upper CI	p
Survey Day	3.46	2.08	5.76	<0.001	2.51	1.39	4.52	0.002	1.16	0.80	1.68	0.4
Age	0.37	0.23	0.60	<0.001								
Gender: Female	Reference											
Gender: Male	0.71	0.26	1.92	0.499								
Continent: Europe	Reference											
Continent: Africa	0.73	0.09	6.16	0.775								
Continent: Americas	1.97	0.35	11.06	0.442								
Continent: Asia	3.10	0.64	14.95	0.158								
Continent: Oceania	0.00	0.00		0.996								
Travel Purpose: Leisure/Tourist Travellers	Reference											
Travel Purpose: Visiting Friends and Relatives (VFR)	1.53	0.44	5.31	0.506								
Travel Purpose: Business/Corporate Travellers	0.59	0.13	2.63	0.492								
Travel Purpose: Other	1.44	0.11	18.72	0.782								
Smoking Status: Never Smoked	Reference											
Smoking Status: Current Smoker	3.15	0.67	14.87	0.146								
Smoking Status: Former Smoker	0.56	0.09	3.64	0.545								
Chronic Health Conditions: None	Reference											
Chronic Health Conditions: Yes	0.59	0.11	3.20	0.543								
Clouds (%)	1.07	0.85	1.35	0.573								
Humidity (%)	1.03	0.79	1.34	0.823								
Pressure (hPa)	1.00	0.85	1.16	0.956								
Temperature (řC)	0.89	0.66	1.22	0.473	0.75	0.54	1.04	0.086	0.96	0.83	1.11	0.6
UV Index (UVI)	1.17	0.95	1.43	0.144	1.23	0.99	1.52	0.058	1.03	0.91	1.16	0.7
Visibility (m)	1.01	0.81	1.27	0.898								
Wind Speed (m/s)	0.94	0.74	1.20	0.619								
Air Quality Components - CO (ţg/mş)	1.10	0.96	1.26	0.173								
Air Quality Components - NH3 (ţg/mş)	1.10	0.93	1.30	0.270								
Air Quality Components - NO (ţg/mş)	1.03	0.91	1.16	0.677								
Air Quality Components - NO2 (ţg/mş)	1.05	0.89	1.25	0.565								
Air Quality Components - O3 (ţg/mş)	1.09	0.85	1.40	0.507								
Air Quality Components - PM10 (ţg/mş)	1.12	0.94	1.32	0.196	1.08	0.91	1.29	0.385	1.05	0.96	1.14	0.3
Air Quality Components - SO2 (ţg/mş)	1.02	0.93	1.12	0.719								
Season: Summer	Reference											
Season: Autumn	0.59	0.17	2.01	0.399								
Season: Spring	0.89	0.38	2.05	0.782								
Season: Winter	1.34	0.52	3.45	0.538								

[a] Generalized Linear Mixed-Effects Models (GLMMs) were used to analyze our data, with trip_id included as a random effect to account for variations between trips.
[b] The optimal model was determined using a combination of order and backward elimination, with the Akaike Information Criterion (AIC) as the selection criteria. The order method orders terms by their contribution to the model, ensuring that the model converges before performing backward elimination.
[c] Multivariate Imputation by Chained Equations (MICE) with 15 imputations were used with linear mixed models for numerical data, two-level logistic models for binary data, and replication of the most likely value within a class for factors with more than two levels. These methods were chosen to account for clustering of trip_id in the data.

The random forest model, which predicts the impact of symptoms on daily activities with an accuracy (ACC) of 90% and an area under the curve (AUC) of 0.95, indicates that diarrhoea, headache, and nausea are the three most important symptoms for predicting the impact on a participant's daily activities. These symptoms have an average cross entropy of 362.9, 354.5, and 350.3, respectively, representing a raise of 72.7, 64.3, and 60.1 from the full model cross entropy of 290.2. Other symptoms such as having a runny nose and being out of breath also have an impact, but to a lesser extent (Figure 5.3).

5.6 Discussion

The ITIT project is a non-commercial, public health endeavour that enables travellers to provide "bottom-up" travel-related, illness surveillance data in real time. In the first year of recruitment, over 600 travellers filled out over 3700 daily symptom surveys, travelling to every continent, and displaying a wide range of symptom types and intensities. This study confirmed the feasibility of using ITIT for larger numbers of participants, reaffirming the conclusions of the pilot ITIT study [9]. Travel across any international border qualified for participation and also allowed for the surveillance of travellers' health in Europe, a continent with the largest numbers of visitors worldwide but an area, which is often not on the surveillance radar. In addition, the epidemiological profile of travellers' illness and initial hotspots of symptoms could be seen using the linked demographic and location information. A milestone with the ITIT app is the incentive for users to have access to information published by WHO on malaria risk and yellow fever/other vaccination requirements at the destination and also access via API to the WHO publication 'daily outbreak news'.

Due to the method of recruitment, primarily through EuroTravNet partners and pre-travel clinics, which see tourists more often than other traveller types, it was unsurprising that more than half of participants were tourists. Other studies also saw tourists comprising more than 50% of their study population [11]. A wide range of ages, and a relatively even split across the sexes was observed in the participant population, although due to recruitment methods and study type, there was a bias that travellers who were more health conscious, and willing to take part in citizen science were included in the dataset. The response rate of 46% for active travellers in this study was lower compared to a similar app-based travel health study (Table 5.1). However, the number of participants and the total number of responses were significantly higher. In addition, the recruitment process was paperless and allowed for more flexibility and a broader range of recruitment with both passive (the travellers download the app themselves outside medical centres) and active (through medical professional) recruitment methods. [12]. We also sought to increase participation of travellers attending mass gathering events such as the pilgrims to the Hajj in Saudi Arabia and visitors to sporting events such as the Winter Olympics in Beijing.

The full range of symptoms surveyed was reported, except for 'other body aches', which were not reported by any participant. Symptoms were reported by 35% of travellers, which is higher than previously reported estimates, with a study showing

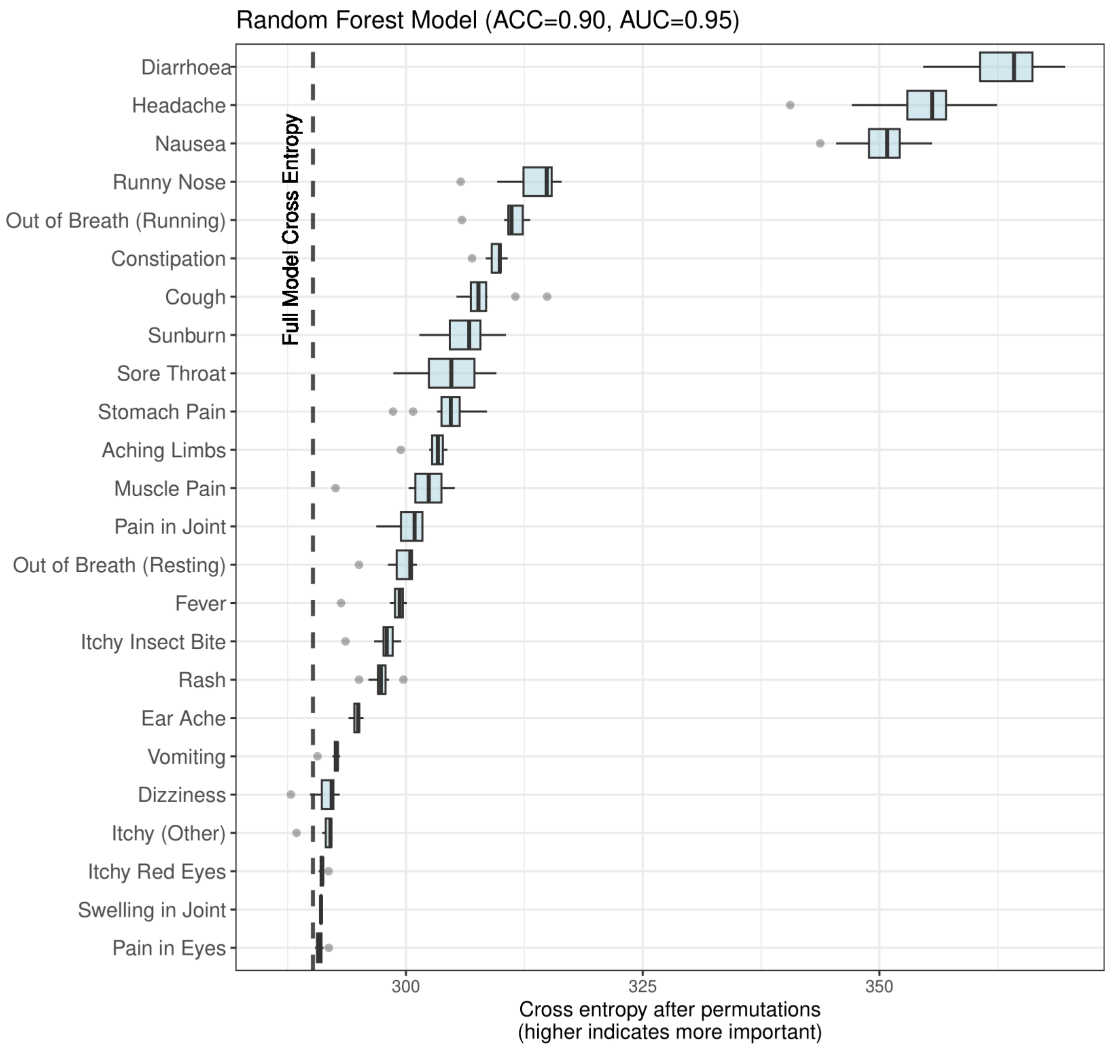

Figure 5.3: Impact of symptoms on daily activities disturbances as measured by mean cross entropy raise after 10 permutations using a Random Forest model. Note: The vertical line in the figure represents the cross entropy of the full model. Each row displays the new cross entropy of the model when the variable of interest is removed, shown as a boxplot with the mean cross entropy after ten permutations. The larger the increase in cross entropy when the variable is removed, the more important that variable is to the model.

15% of travellers to developing countries becoming ill [13]. This is expected, as less severe symptoms will be caught by bottom-up, traveller-reported methods than most other studies which receive data from 'top down' official health systems. A majority of gastrointestinal and respiratory symptoms was also seen as expected [14], with gastrointestinal issues being most common in travellers to Asia, where the risk of food-borne pathogens can be high. More participants would be needed to more clearly differentiate epidemiological patterns of symptoms by region, as Oceania did not have many travellers. Differences in illness symptoms for male and female travellers were also seen and have been reported in previous analyses of travel infection data [15]. Some differences, such as the higher proportion of diarrhoea in females supports previous literature [12]; however, the higher proportion of fever in women is in contrast to what has previously been observed, with males usually reporting more febrile illnesses [15]. However, this difference may also be partially accounted for by differences in self-reporting habits between the sexes, although more research is needed here.

Multivariate modelling showed that the most important variables when looking at risk of symptoms overall are duration of travel, and either humidity or travelling during winter, with all three variables being associated with an increased risk of symptom presence. Humidity, atmospheric pressure and air pollutants were found to have a significant impact on some symptoms (Appendix A-D) and larger numbers of travellers are needed to further elucidate these associations. Increased duration of travel increases the probability of symptom reporting [16]. Winter travel, including winter travel in Europe, can be associated with increased respiratory illness due to cold temperatures and influenza seasons, and humidity was observed to be associated with increased respiratory illness prevalence [17]. For travel consultations, this could mean that different illnesses and preventative measures should be emphasised depending on the season at the destination. The impact of symptoms on the travellers' day overall, using self-reported impact ratings showed that diarrhoea, headache, and nausea were the three most important symptoms. This should guide recommendations for the most likely selftreatments needed during travel suggesting that medications such as paracetamol to treat headaches, loperamide for diarrhoea, and domperidone for nausea could be recommended in pre-travel consultations.

Our study had some limitations; the recruitment for the study was mainly done through the EuroTravNet partners, which led to a majority of European travellers being recruited and destinations favoured by Europeans being over-represented. As a result, the incidence rate for less frequently visited destinations, such as Oceania, may be underestimated. Missing data points could potentially have decreased the quality of the data. This issue can also be observed in the analysis of under-represented symptom groups in our study, such as dermatological and general symptoms, where the estimation could be impacted. The intensive nature of the study selected for travellers who were perhaps more careful about their health. Ongoing recruitment will focus recruiting larger numbers and a broader range of travellers including VFRs and mass gathering travellers. The updated app will monitor persisting illness post-travel. The ITIT project has some major advantages compared to other travel health apps. These include, having the WHO publications uploaded to the app, recruiting at many global locations outside Europe - recently extended to South Africa, Malaysia and Japan. Another advantage is the fact that the app is available in fourteen languages and will be available for all categories of travellers independently of travel clinics. Compared to traditional surveillance systems, we suggest that ITIT captures a more accurate, granular picture of symptoms experienced by the traveller, with a future potential for outbreak detection due to the real-time and locationassociated nature of the data when large numbers of travellers use the app.

Digital innovations in the health field, and travel health specifically, have already shown promise in the COVID-19 pandemic, whether through passive wearable technologies, or self-reported test results and symptoms [18–20]. In a similar manner, ITIT, using selfreported symptom surveillance in travellers has the potential to innovate the field of travel medicine, and supplement existing disease surveillance methods, giving real-time outbreak detection data, far before they would be registered by traditional means.

5.7 Conclusion

In conclusion, this era of global travel necessitates an evolution in the way travellers prepare for their trip and how we monitor and report travel-related illnesses and identify clusters of infections and possible alerts. Travellers can play an invaluable role as sentinels for outbreak detection and disease surveillance if large numbers are contributing data to a centralised system. By embracing real-time, bottom-up symptom reporting, we can support existing programmes and improve global health surveillance.

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5.9 Supporting Informations

5.9.1 Appendix A

Univariate and Multivariate Analyses of Variables Influencing Gastrointestinal Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis Available at: https://doi.org/10.2139/ssrn.4603329

5.9.2 Appendix B

Univariate and Multivariate Analyses of Variables Influencing Respiratory Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis Available at: https://doi.org/10.2139/ssrn.4603329

5.9.3 Appendix C

Univariate and Multivariate Analyses of Variables Influencing Dermatological Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis Available at: https://doi.org/10.2139/ssrn.4603329

5.9.4 Appendix D

Univariate and Multivariate Analyses of Variables Influencing General Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis Available at: https://doi.org/10.2139/ssrn.4603329

5.9.5 Appendix E

Traveler Profile and Symptom Intensity Among Travelers Who Had a Medical Visit During Their Trip Available at: https://doi.org/10.2139/ssrn.4603329

6
Study V

Illness tracking in SARS-CoV-2 tested persons using a smartphone app: a non-interventional, prospective, cohort study

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Contents

6.1 Abstract

There are few data on the range and severity of symptoms of SARS-CoV-2 infection or the impact on life quality in infected, previously healthy, young adults such as Swiss Armed Forces personnel. It is also unclear if an app can be used to remotely monitor symptoms in persons who test positive. Using a smartphone app called ITITP (Illness Tracking in Tested Persons) and weekly pop-up questionnaires, we aimed to evaluate the spectrum, duration, and impact of symptoms reported after a positive SARS-CoV-2 test according to sex, age, location, and comorbidities, and to compare these to responses from persons who tested negative. We followed up 502 participants (57% active participation), including 68 (13.5%) positive tested persons. Hospitalisation was reported by 6% of the positive tested participants. We found that positives reported significantly more symptoms that are typical of COVID-19 compared to negatives. These symptoms with odds ratio (OR $>$ 1) were having difficulty breathing (OR 3.35; 95% CI: 1.16, 9.65; $p = 0.03$), having a reduced sense of taste (OR 5.45; 95% CI: 1.22, 24.34; $p = 0.03$) and a reduced sense of smell (OR 18.24; 95% CI: 4.23, 78.69; $p < 0.001$). Using a random forest model, we showed that tiredness was the single symptom that was rated as having a significant impact on daily activities, whereas the other symptoms, although frequent, had less impact. The study showed that the use of an app was feasible to remotely monitor symptoms in persons infected with SARS-CoV-2 and could be adapted for other settings and new pandemic phases such as the current Omicron wave.

6.2 Introduction

The COVID-19 pandemic, caused by the coronavirus SARS-CoV-2 continues and the epidemiological situation is increasingly complex with new waves of infection and the emergence of highly transmissible virus variants [1]. Vaccines [2], wearing masks [3], social distancing [4], hand hygiene and community mitigation measures [5] are recommended to reduce the impact of the pandemic. There are few data on the range and severity of symptoms or the impact of the infection on life quality in young adults. Data on the persistence of protective immunity after recovery from SARS-CoV-2 infection are scarce [6, 7]. Will young people who were infected with an ancestral variant of SARS-CoV-2 produce antibodies that can cross neutralize the emerging and highly transmissible variants such as Omicron, or will they become reinfected with newer variants? Several studies have reported data on patients with severe disease [8] but few articles are evaluating young persons who test positive and who have mild illness or who are asymptomatic. Such data are most important for young population groups as they constitute the workforce of many economies and most likely to engage in social activities and larger events [9]. The Swiss Armed Forces have several bases throughout Switzerland where young recruits and military personnel spend weeks to months as part of their training and military service. During the early period of the pandemic, RT-PCR testing for SARS-CoV-2 was mandatory. We aimed to follow up on those army recruits and personnel with a confirmed positive test for SARS-CoV-2 and compare them to those who tested negative. Our goals were to evaluate the spectrum, duration, severity, and impact of symptoms reported after a positive SARS-CoV-2 test according to sex, age, and location, and compare these to responses from those who tested negative. Furthermore, we aimed to evaluate the feasibility of using an app to identify clusters of symptoms and emerging symptoms such as ageusia (loss of taste functions), anosmia (loss of smell functions) that could be predictive of SARS-CoV-2 infection. We wanted to evaluate symptom duration and impact on daily life activities. A secondary objective was to analyse the geolocation changes of positive cases.

6.3 Methods

To follow up on the spectrum of symptoms, their evolution and resolution we designed a study using a repurposed app for a weekly survey of tested persons (positives, and negatives as a control group) in the army setting. The study app was called ITITP (Illness Tracking in Tested Persons). The University of Zürich Travel Clinic, Epidemiology, Biostatistics, and Prevention Institute (EBPI), and the ETH Wearable Computing Lab partnered in 2014 to develop and field test a smartphone app called "Tourist" for use in travel medicine. Further expertise in using mobile apps to track infection has been gained in a recent project called ITIT (Infection Tracking in Travelers), which received funding in March 2020 from the Swiss National Foundation [10]. We used the knowledge and experience gained in these projects to follow up on army recruits and personnel who tested positive or negative for SARS-CoV-2 before enrolment either with RT-PCR nasopharyngeal tests or serological tests. After approval by the ethical commission of the Republic and Canton of Ticino, Comitato Etico Cantonale (BASEC Number.2020-01146 CE 3637), we recruited participants at Swiss Armed Forces bases in Airolo and Monte Ceneri, Canton Ticino, Switzerland. Inclusion criteria were completion of consent form, being willing and able to participate and to complete the weekly electronic pop-up questionnaires (push notification on smart phone). Tested persons (regardless of whether positive or negative) could participate. After signing an informed consent form, they downloaded the smartphone app using a provided QR code and completed a simple baseline questionnaire simple baseline questions (age, sex, body height, body weight, date of positive test, hospitalised y/n, co-morbidities (such as asthma, high blood pressure), and smoking habits. The pop-up weekly questionnaires were available in English, German, French, and Italian and queried illness symptoms (Appendix A). All illness symptoms reported were self-rated by the participants using a Likert scale ranging from 1 (none) to 5 (severe). Anyone reporting illness symptoms was asked two additional questions on the impact of illness on their activities and on their general mood (Appendix B). The surveys were anonymous, and the participants could elect to delete their data using a feature on the app.

In addition to the active data received via the weekly survey questionnaires, the app collected passive data only if this was agreed by the participant. Allowing access to passive data was included in the digital consent and was an opt-in or out option. Weekly surveys were geotagged and timestamped when they were filled out and uploaded to the server along with the user ID of the mobile device, which enabled the mapping of locations where the participant completed the survey. The survey upload locations were mapped over time and by whether or not the participant had tested positive or negative.

Data were analysed using R statistical Software Version 4.0.4, R Foundation for statistical computing, Vienna, Austria [11]. Symptom data were evaluated in a random forest model to predict impact on daily activities, and we used the Gini Index to display the impact of the reported symptoms.

6.4 Results

The recruitment started in May 2020 and ended in October 2021.

6.4.1 Socio-demographic characteristics and health determinants.

Of the 502 military personnel who participated in the ITITP project, 14% (68/502) had a positive PCR or a positive SARS-CoV-2 serology test at the time of enrolment. The age of participants ranged from 18 to 60 years, with a mean age of 21 (3.63) years, 12% (58/502) of the participants were female, 27% (122/459) were not in their optimal BMI range: 4.1% (19/459) were classified as underweight and 22.9% (103/459) as overweight, with 6% (19/459) being obese. 35% (178/502)

Table 6.1: Socio-demographic characteristics and health determinants of the SARS-CoV-2 negative and SARS-CoV-2 positive groups

Characteristic	Overall N = 502[a]	SARS-Cov-2 positive (PCR/Serology) N = 68[a]	SARS-CoV-2 negative (PCR/Serology) N = 434[a]
Age [years][b]	21.55 (3.63)	21.06 (1.55)	21.63 (3.86)
Gender			
Female	58 (12%)	7 (10%)	51(12%)
Male	444 (88%)	61 (90%)	383(88%)
BMI [kg/m2]			
Normal weight	337 (73%)	53 (80%)	284(72%)
Obese	26 (5.7%)	4 (6.1%)	22(5.6%)
Overweight	77 (17%)	9 (14%)	68(17%)
Underweight	19 (4.1%)	0 (0%)	19(4.8%)
Smoker			
Never	310 (62%)	37 (54%)	273(63%)
Current	88 (18%)	10 (15%)	78(18%)
Occasional	90 (18%)	17 (25%)	73(17%)
Former	14 (2.8%)	4 (5.9%)	10(2.3%)
Daily medication	34 (6.8%)	4 (5.9%)	30(6.9%)
Comorbidity	45 (9.0%)	5(7.4%)	40(9.2%)

[a] n (%)
[b] Mean (SD) Minimum-Maximum

were current smokers, of which 18% (88/502) were daily smokers and 18% (90/502) were occasional smokers. Daily medication use was reported by 7% (34/502) of the soldiers. Comorbidities were reported by 9% (45/502) of participants, distributed as follows: 62% (28/45) asthma, 13% (6/45) hypertension, 7% (3/45) diabetes, 7% (3/45) cancer, 11% (5/45) other diseases (Table 6.1). Tests for homogeneity between the sociodemographic characteristics and health determinants of our two groups of interest (those who tested positive and those who tested negative) showed no significant differences (Table 6.1).

6.4.2 Completion of weekly questionnaires and retention in the study

Of the 502 initial participants, 288 (57%) actively participated in the study by completing at least one questionnaire. A total of 2393 questionnaires were completed, representing an average of five (SD 11) questionnaires per participant. Completion of questionnaires was similar between the sexes (females: eight, SD sixteen; males four, SD ten) (Table 6.2).

Of the 288 participants who completed at least one weekly questionnaire, 49% (140/288) participated for less than one month, 23% (65/288) between one and three months, 14% (39/288) from three to six months, and 14% (39/288) longer than six months (Table 6.2).

Table 6.2: Comparison of follow-up time and participation in the weekly questionnaire between the SARS-CoV-2 positive and negative groups

Questionnaire (descriptive analysis)	Overall N = 502[a]	SARS-Cov-2 positive (PCR/Serology) N = 68[a]	SARS-CoV-2 negative (PCR/Serology) N = 434[a]	P-value[b]
Overall follow-up time [week]				0.6
< 1 month	142 (29%)	21 (31%)	121(28%)	
13 months	63 (13%)	12 (18%)	51(12%)	
36 months	37 (7.5%)	5 (7.5%)	32(7.5%)	
6+ months	39 (7.9%)	4 (6.0%)	35(8.2%)	
No follow-up	214 (43%)	25 (37%)	189(44%)	
Number of missed surveys [n]				0.6
Mean (SD)	3 (5)	3 (5)	3(6)	
Median (IQR)	0 (0,3)	1 (0,3)	0(0,3)	
Range	0, 36	0,18	0,36	
Survey response rate [%]				0.3
Mean (SD)	85 (22)	82 (22)	85(22)	
Median (IQR)	100 (75,100)	86 (70,100)	100(75,100)	
Range	17, 100	29, 100	17,100	

[a] n (%); Mean (SD), Median (IQR), Range.
[b] Pearson's Chi-squared test; Wilcoxon rank sum test.

The time between positive PCR or antigen test and response to the first questionnaire (start of follow-up) ranged from zero days to approximately one year with a median of 54 days.

We counted a total of 793 missing questionnaires over the entire observation period, which corresponds to 24% (793/3184) of the missing weekly surveys in our dataset. With a median of eleven weeks for the distribution of total missing weeks, most questionnaires were missed before the third month of follow-up. This corresponds to an average of three (SD five) missing weeks per participant with a maximum of 35 missing questionnaires and a minimum of zero. We can therefore report a survey response rate that varies individually from 17% to 100% and an average of 83% (22) (Table 6.2).

Table 6.3: Comparison of maximum symptom intensity between the positive and negative SARS-CoV-2 groups

Symptom	N	Overall N = 502[1]	SARS-Cov-2 positive (PCR/Serology) N = 68[1]	SARS-CoV-2 negative (PCR/Serology) N = 434[1]	P-value[23]
Cough	288				ns

Table 6.3: Comparison of maximum symptom intensity between the positive and negative SARS-CoV-2 groups *(continued)*

Symptom	N	Overall N = 502[1]	SARS-Cov-2 positive (PCR/Serology) N = 68[1]	SARS-CoV-2 negative (PCR/Serology) N = 434[1]	P-value[23]
None		185 (64%)	27(63%)	158(64%)	
Mild		53 (18%)	9(21%)	44(18%)	
Moderate		29 (10%)	6(14%)	23(9.4%)	
Moderate-severe		15 (5.2%)	1(2.3%)	14(5.7%)	
Severe		6 (2.1%)	0(0%)	6(2.4%)	
Runny nose	288				
None		143 (50%)	20(47%)	123(50%)	
Mild		64 (22%)	10(23%)	54(22%)	
Moderate		42 (15%)	7(16%)	35(14%)	
Moderatesevere		24 (8.3%)	4(9.3%)	20(8.2%)	
Severe		15 (5.2%)	2(4.7%)	13(5.3%)	
Sore throat	288				ns
None		202 (70%)	29(67%)	173(71%)	
Mild		42 (15%)	9(21%)	33(13%)	
Moderate		24 (8.3%)	2(4.7%)	22(9.0%)	
Moderatesevere		13 (4.5%)	2(4.7%)	11(4.5%)	
Severe		7 (2.4%)	1(2.3%)	6(2.4%)	
Headache	288				0.078
None		157 (55%)	16(37%)	141(58%)	
Mild		68 (24%)	15(35%)	53(22%)	
Moderate		37 (13%)	6(14%)	31(13%)	
Moderatesevere		15 (5.2%)	4(9.3%)	11((4.5))	
Severe		11 (3.8%)	2(4.7%)	9((3.7))	
Difficulty breathing	288				ns
None		238 (83%)	31(72%)	207((84))	
Mild		31 (11%)	9(21%)	22((9))	
Moderate		13 (4.5%)	2(4.7%)	11((4))	
Moderatesevere		1(0.3%)	0 (0%)	1 (0.4%)	
Severe		5(1.7%)	1 (2.3%)	4 (1.6%)	
Out of breath	288				0.053
None		212(74%)	25 (58%)	187 (76%)	
Mild		46(16%)	11 (26%)	35 (14%)	
Moderate		19(6.6%)	6 (14%)	13 (5.3%)	
Moderatesevere		8(2.8%)	1 (2.3%)	7 (2.9%)	
Severe		3(1.0%)	0 (0%)	3 (1.2%)	
Reduced sense of smell	288				0.006
None		254(88%)	32 (74%)	222 (91%)	
Mild		14(4.9%)	3 (7.0%)	11 (4.5%)	
Moderate		9(3.1%)	5 (12%)	4 (1.6%)	
Moderatesevere		8(2.8%)	2 (4.7%)	6 (2.4%)	
Severe		3(1.0%)	1 (2.3%)	2 (0.8%)	

Table 6.3: Comparison of maximum symptom intensity between the positive and negative SARS-CoV-2 groups *(continued)*

Symptom	N	Overall N = 502[1]	SARS-Cov-2 positive (PCR/Serology) N = 68[1]	SARS-CoV-2 negative (PCR/Serology) N = 434[1]	P-value[23]
Reduced sense of taste	288				0.031
None		259(90%)	35 (81%)	224 (91%)	
Mild		15(5.2%)	3 (7.0%)	12 (4.9%)	
Moderate		8(2.8%)	4 (9.3%)	4 (1.6%)	
Moderatesevere		4(1.4%)	0 (0%)	4 (1.6%)	
Severe		2(0.7%)	1 (2.3%)	1 (0.4%)	
Tiredness	288				ns
None		177(61%)	25 (58%)	152 (62%)	
Mild		50(17%)	9 (21%)	41 (17%)	
Moderate		28(9.7%)	5 (12%)	23 (9.4%)	
Moderate-severe		20(6.9%)	4 (9.3%)	16 (6.5%)	
Severe		13(4.5%)	0 (0%)	13 (5.3%)	
Memory loss	288				ns
None		219(76%)	34 (79%)	185 (76%)	
Mild		42(15%)	6 (14%)	36 (15%)	
Moderate		20(6.9%)	1 (2.3%)	19 (7.8%)	
Moderatesevere		5(1.7%)	2 (4.7%)	3 (1.2%)	
Severe		2(0.7%)	0 (0%)	2 (0.8%)	
Diarrhoea	288				ns
None		220(76%)	35 (81%)	185 (76%)	
Mild		35(12%)	5 (12%)	30 (12%)	
Moderate		24(8.3%)	2 (4.7%)	22 (9.0%)	
Moderatesevere		4(1.4%)	1 (2.3%)	3 (1.2%)	
Severe		5(1.7%)	0 (0%)	5 (2.0%)	
Skin symptoms	288				ns
None		251(87%)	39 (91%)	212 (87%)	
Mild		21(7.3%)	1 (2.3%)	20 (8.2%)	
Moderate		11(3.8%)	2 (4.7%)	9 (3.7%)	
Moderatesevere		2(0.7%)	0 (0%)	2 (0.8%)	
Severe		3(1.0%)	1 (2.3%)	2 (0.8%)	
Night sweating	288				ns
None		210(73%)	33 (77%)	177 (72%)	
Mild		38(13%)	4 (9.3%)	34 (14%)	
Moderate		23(8.0%)	3 (7.0%)	20 (8.2%)	
Moderatesevere		8(2.8%)	2 (4.7%)	6 (2.4%)	
Severe		9(3.1%)	1 (2.3%)	8 (3.3%)	
Fever	271				ns
None		214(79%)	35 (85%)	179 (78%)	
Above 37.5		54(20%)	6 (15%)	48 (21%)	
Above 39		3(1.1%)	0 (0%)	3 (1.3%)	

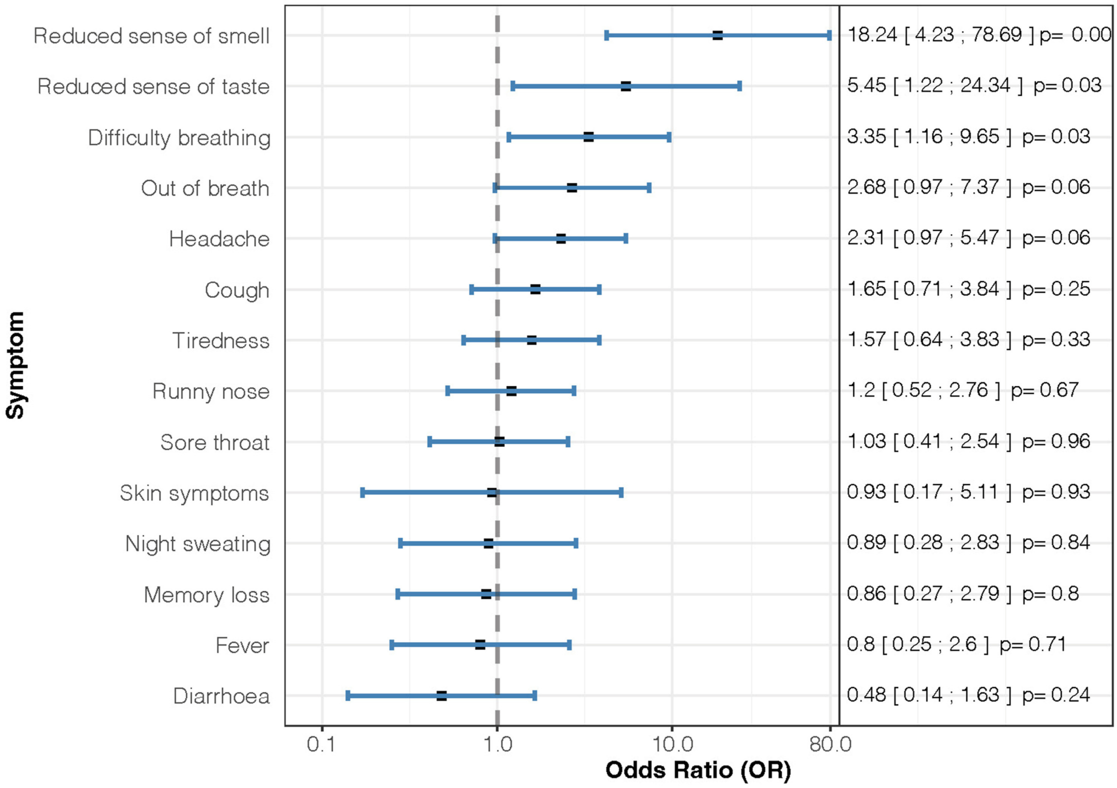

Figure 6.1: Odds ratio of symptom occurrence in SARS-CoV-2 positive versus SARS-CoV-2 negative person. Odds ratio less than one (symptoms typical of a negative person). Odds ratio greater than one (symptoms typical of a positive person).

6.4.3 Reported symptoms

Having a runny nose was the most common symptom, reported by 50% (145/288) of the participants who completed questionnaires during period of the study, followed by headache 46% (131/288), and tiredness 39% (111/288). Other reported symptoms were a decreased sense of taste 10% (29/288) and a decreased sense of smell 11.8% (34/288) (Table 6.3).

Considering the highest score on the Likert scale from not at all to severe, we found a significant difference between the two groups for decreased sense of smell ($p = 0.006$) and decreased sense of taste ($p = 0.031$). Headache ($p = 0.078$) and shortness of breath ($p = 0.053$) tested just above the significance threshold of alpha 0.05. (Table 6.3). Controlling for duration of follow-up and participant individuality, our generalized mixed-effects linear models predict that a participant without infection will express the following symptoms significantly less frequently and with less intensity when baseline demographics remain constant (sex, age, smoking, BMI, medications, comorbidities): reduced sense of smell (OR 18.24; 95% CI: 4.23, 78.69; $p = 0.00$), reduced sense of taste (OR 5.45; 95% CI: 1.22, 24.34; $p = 0.03$) and difficulty breathing (OR 3.35; 95% CI: 1.16,9.65; $p = 0.03$). Out of breath (OR 2.68; 95% CI: 0.97, 7.37; $p = 0.06$) and headache (OR 2.31; 95% CI: 0.97,5.47; $p = 0.06$) also appeared to occur less frequently, but not significantly, in healthy participants (Figure 6.1).

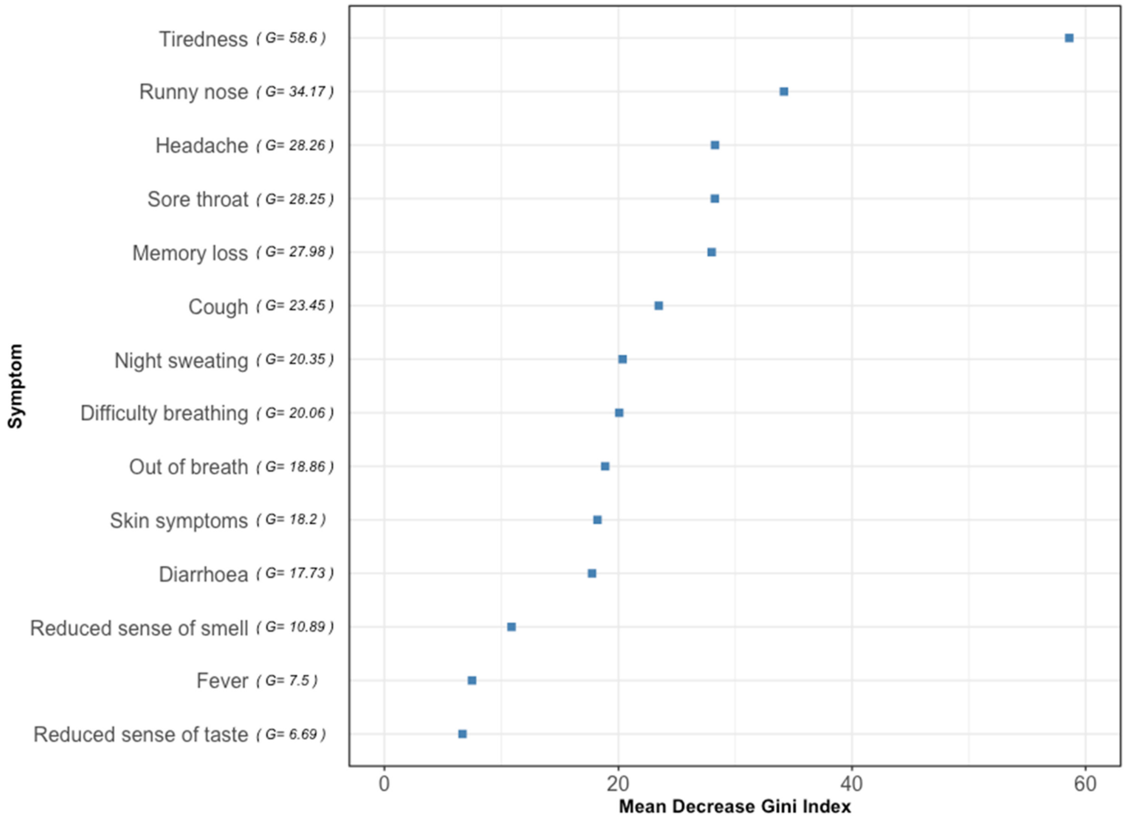

Figure 6.2: Impact of symptoms on daily activities. The mean decrease in Gini coefficient is a measure of how each variable contributes to the homogeneity of the random forest's nodes and leaves. The greater the mean decrease accuracy or mean decrease Gini score, the greater the importance of the variable in the model and the greater the impact on daily activities

6.4.4 Impact of symptoms on daily activities

Using a random forest method, the four different levels of impact (none, mild, moderate, and severe) were classified based on the different symptoms that participants experienced during the week. We found that the highest value for the average Gini Index reduction, and thus the most important variable for our model, is tiredness (57.19), followed by runny nose (34.52). In contrast, some symptoms such as decreased sense of smell and taste (10.34, 7.04) or fever (7.31) do not seem to affect daily activities (Figure 6.2). Symptoms persisted for periods ranging from of mean of 1.38 (SD 1.19) weeks for diarrhoea to longer duration symptoms such as persistent loss of smell (mean 6 .45, SD 11.44) (Figure 6.3).

Four participants (6%, 4/68) reported a severe Covid with hospitalization among the 68 participants who reported a positive PCR result or anti-SRAS-CoV-2 antibody status at enrolment. Nevertheless, no differences were found in their sociodemographic characteristics or health factors compared with the participant with mild COVID-19 illness.

During the study, no reinfections were reported, but one patient reported a first infection after three months of study participation between the second and

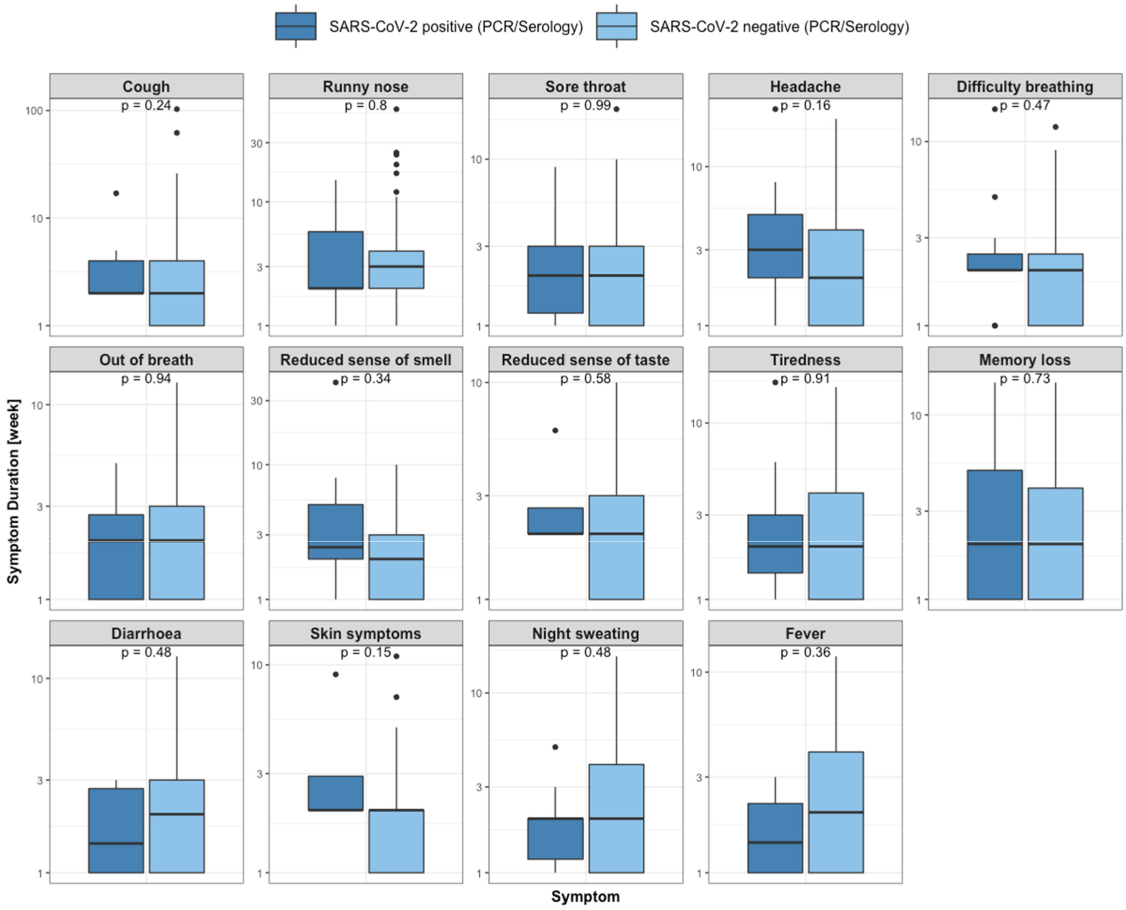

Figure 6.3: Time in weeks to resolution of symptoms reported by SARS-CoV-2 positive and negative participants.

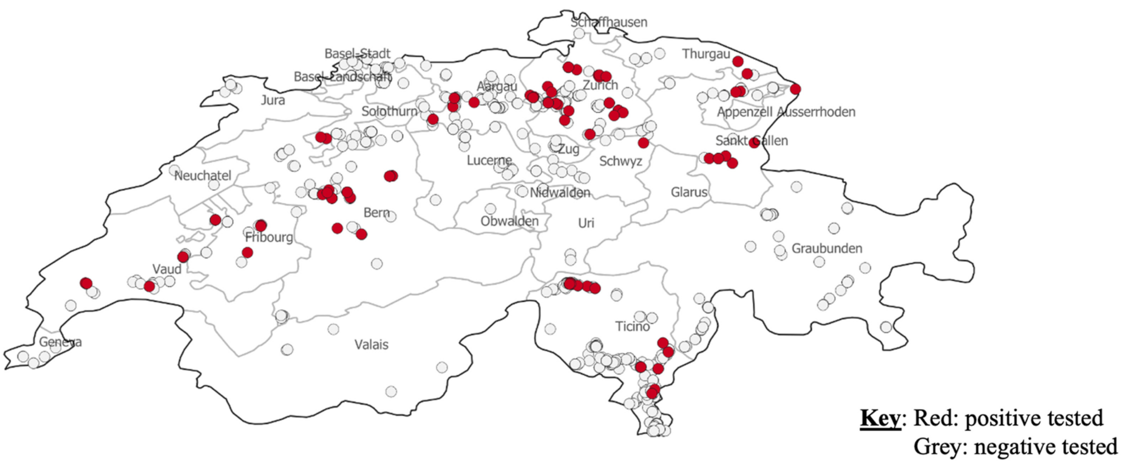

Figure 6.4: Geolocation of ITITP participants when completing weekly pop-up questionnaires.

third waves (12/02/2021). He presented all classic symptoms with high fever (> 39řC), significant impact on his daily activities, described his day as very poor, but did not report hospitalization.

Geolocation data did not yield major differences between positives and negatives. Positives in general did not seem to move far with the exception of the one positive that went to Northern Italy (Figure 6.4).

6.5 Discussion

Our study showed that use of an app was feasible to remotely monitor symptoms in persons infected with SARS-CoV-2. It was possible to show the range, duration and severity of symptoms experienced, and the impact on daily activities. We showed that those who tested positive for SARS-CoV-2 reported significantly more symptoms that are typical of COVID-19 compared to those who tested negative. These were having difficulty breathing, having a reduced sense of taste (ageusia) and a reduced sense of smell (anosmia). These results correlate with other studies that describe these typical symptoms in younger populations with COVID-19 [12]. With regard to impact on daily activities, tiredness was the single symptom that was rated as a major problem. In contrast, the other symptoms above, although frequent, were not considered to have such a major impact. The finding is corroborated by other articles that describe tiredness, fatigue, and exhaustion in SARS-CoV-2 infected persons [12]. In contrast, a metanalysis describing symptoms of a total of 24,410 adults (mean age 49 years) showed that the cardinal symptoms of COVID-19 are fever and a new persistent cough [13]. In our study, 6% (4/68) of those who tested positive were hospitalized (mean: 22 (SD 0) years, male: 3, female: 1). Another study of young adults aged 18-24 living in the United States recorded a 2.7% hospitalization rate with 0.8% admitted to the ICU [14]. This study shows that symptoms persisted for periods of mean of 1.38 (SD 1.19) weeks for diarrhoea to longer duration symptoms such as persistent loss of smell mean (6.45 weeks, SD 11.44). This is corroborated by a telephone survey of symptomatic adults (under 35 years old) with mild COVID-19 where 35% did not return to their usual state of health two to three weeks after testing [15].

Several apps focusing on different aspects such as health monitoring, contact tracing, pulse oximeter, thermometer, prevalence, and research apps, emerged during the pandemic [16]. The app, with the largest amount of data and patients recruited, used for symptom tracking is probably the Zoe COVID study app [17, 18] which evaluated age- and sex-based discrepancies in early symptoms and also found different sets of relevant features between health-care workers and non-health-care workers. Another app with a similar aim is the CoroNotes app by the University of Tübingen [19] which focuses on the well-being of the users: “Users answer questions on whether they feel well, or whether they are experiencing symptoms like headaches, aching limbs, or a fever, for instance.” Another app, COVID Control App was developed by John Hopkins University for patients to submit their daily body temperature [20]. To the best of our knowledge, ours is the only COVID app study that focuses on a homogenous group of young, previously healthy persons and that combines geolocation with self-reported symptoms over a period of one year. The knowledge gained here could be applied in the future in similar settings to allow for remote monitoring of positive cases in outbreak situations such as in schools, hospitals, companies, or in sport clubs or music groups. The remote surveillance, as pioneered here with the ITITP app, could be further developed so that positive cases could be monitored from their homes but when pre-defined clusters or severe symptoms are reported, an alert could be created that promotes medical intervention.

6.6 Strengths and limitations

Strength of our study was the strong and collaborative response to the call for participants at the Swiss Armed Forces bases in the Canton Ticino. Furthermore, our study population was homogenous, young and familiar with smartphone and app technology, and found the app easy to download and use. Participation in the study was completely voluntary. Retention and the enthusiasm to continue to complete the weekly questionnaires declined over the year of follow-up and this was a limitation.

6.7 Conclusions

Remote monitoring of symptoms in those who test positive for SARS-CoV-2 is feasible. Efforts and incentives are needed to increase retention of volunteers over time. Remote surveillance as in the ITITP study could be further developed for different settings such as schools, sporting clubs, and other organisations, and may be particularly applicable to monitor symptom spectrums in new phases of the pandemic or with the emergence of variants of concern with vaccine escape, such as Omicron.

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6.9 Supporting Informations

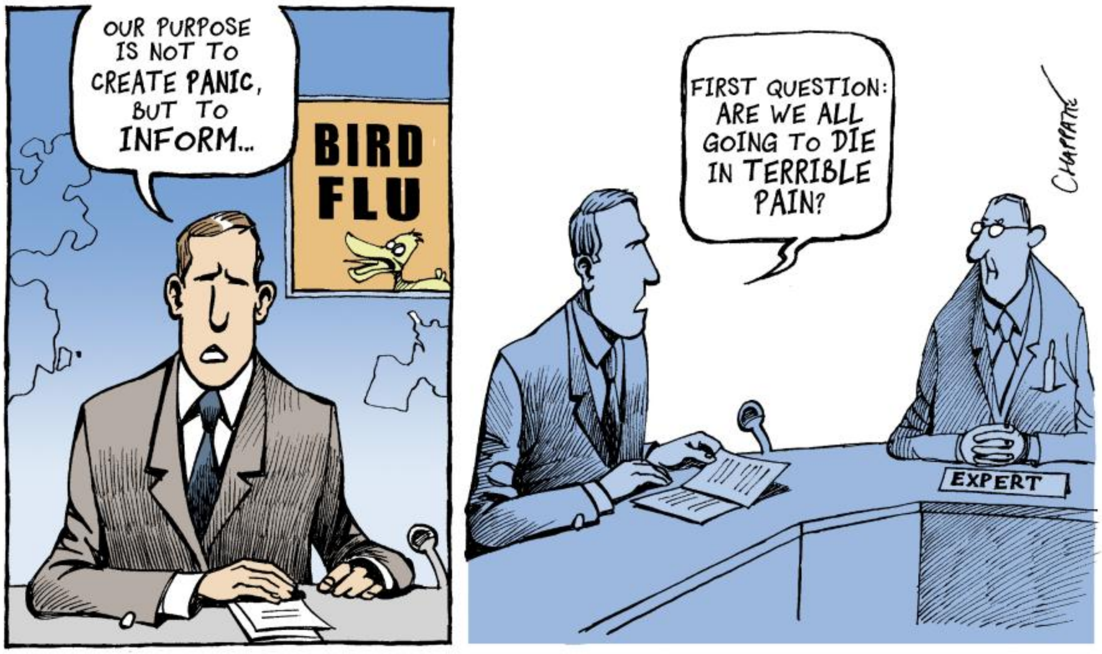
6.9.1 Appendix A

List of questions on the weekly pop-up questionnaire, each rated on a Likert severity scale of 1- 4 (1: mild, 2: moderate, 3: moderate-severe, 4: severe). Available at: https://ars.els-cdn.com/content/image/1-s2.0-S2052297522000191-mmc1.docx

6.9.2 Appendix B

Drop-down list of questions on the impact of illness symptoms on weekly activities and general mood. Available at: https://ars.els-cdn.com/content/image/1-s2.0-S2052297522000191-mmc1.docx

7
Discussion



Contents

7.1 Ethical Lesson

Privacy and data protection are of utmost importance in the development of mobile applications for traveller health. Study I highlights the ethical issues surrounding these topics, including the lack of comprehensive ethical standards and data regulation at the international level. Currently, the General Data Protection Regulation (GDPR) in Europe serves as the only established standard for the sharing and storage of personal data on an international level.

Data quality is another challenge frequently underscored in the literature. The accuracy and representativeness of self-reported user data can pose problems. While real-time self-reporting can minimise recall errors and enhance data quality, it presents a challenge for researchers to verify the accuracy and completeness of the information provided. Developers could utilise GPS and phone-collected metadata to counter potential errors and biases. However, it is also crucial to ensure the inclusion of minorities and other population subgroups in the development and utilisation of health apps to prevent selection bias.

Informed consent is another critical aspect of travel medicine app development that has received scant attention in the context of travel medicine apps despite its prominence in mHealth literature. To foster trust, researchers should engage users by transparently communicating the objectives of the app, addressing data confidentiality concerns, and obtaining informed consent prior to data collection and usage. Moreover, developers should prioritise user satisfaction by offering an intuitive, accessible app compatible with multiple platforms.

In light of the ethical concerns related to privacy, data protection, data quality, and informed consent in mobile applications development for travel medicine, the ITIT app has been designed to address these issues. The app complies with relevant data protection regulations and ensures data quality by utilising GPS and metadata collected directly from the phone. Furthermore, it engages users by offering electronic informed consent and transparently communicating its objectives and data confidentiality concerns. By prioritising these crucial considerations, the ITIT app aims to establish trust with its users and provide a secure, reliable platform for travel medicine.

7.2 ITIT pilot

Study II, the ITIT pilot project, demonstrates the potential of the ITIT application to collect detailed data and link location data and weather information in real-time. The app has been well-received, with 79% of users expressing their willingness to recommend it to other travellers. The integration of WHO published travel health information and disease outbreak news makes the ITIT app a valuable and reliable tool for both travel health researchers and travellers.

The pilot project provided several valuable insights. Firstly, given that participants may experience delayed symptoms, follow-up surveys will be conducted at one week and one month post-travel in the larger ITIT study. This approach will capture any lingering or new symptoms and provide information on medical consultations, self-treatments and diagnoses. Secondly, improvements are needed in the notifications to ensure that participants receive daily pop-up notifications on their smartphone that redirect them directly to the daily questionnaire. To encourage participants recruitment, travel centre staff have been trained to assist with app installation and initial questionnaire completion.

Future enhancements to the ITIT app include adding a "My Trip" feature, which will allow participants to view a map summary of their trip, with their daily reports displayed graphically. This feature could prove valuable for physicians as well, enabling them to better understand their patients' symptom expression and allowing for the evaluation of incubation periods in differential diagnoses.

7.3 Symptoms suggestive of RTIs

Respiratory symptoms, second only to gastrointestinal symptoms, are a common health issue encountered by travellers [1]. Over the past two decades, our meta-analysis of literature Study II revealed a prevalence of 37% [27%; 48%] for symptoms suggestive of RTIs among travellers. To further investigate this issue, we utilised real-time data collected using the ITIT application. In our Study IV, 17% of trips (81 out of 470) recorded with the ITIT application reported at least one respiratory symptom. The incidence of these symptoms was found to be 58.3 per 1000 daily surveys completed, coming second only to gastrointestinal symptoms with an incidence of 66.3 per 1000 daily surveys.

Interestingly, different traveller groups appear to be affected differently. For instance, travellers attending mass gathering events had a prevalence of respiratory symptoms that was 1.7 times higher than the overall prevalence in our Study II. High proportions of respiratory symptoms have been described in events such as Hajj (Saudi Arabia), Grand Magal of Touba (Senegal), Bb Fard (Pakistan), Rock Werchter (Belgium), Sziget Festival (Hungary), among others. On the other hand, respiratory cases among airplane and cruise ship passengers were lower than average with 8% and 15% respectively.

Geographical location also seems to influence symptom expression. The Americas, particularly the Latin America and Caribbean subregion, had the highest absolute number of respiratory symptoms among travellers. However, more reports of respiratory symptoms were seen in Europe and Asia. It's important to note that our recruitment occurs mainly among European travellers and therefore the actual distribution probably reflects more the risk for European travellers.

Cough was the most frequently reported respiratory symptom among travellers, with 11,206 cases. Similarly, cough and runny nose had the highest incidence rates, at 42 and 43 per 1000 daily surveys, respectively. Fever, often associated with respiratory symptoms, was also commonly reported, confirming that respiratory infections are a major cause of fever in returning travellers [2–4]. Moreover, common symptom syndromes such as Influenza-like Illness (ILI) were prevalent in areas with increased transmission risk like mass gathering events and cruises.

While literature suggests that women are more susceptible to respiratory symptoms than men [5], Study II and Study IV found no significant difference in symptom incidence between genders. Age seemed to reduce the expression of respiratory symptoms in a univariate analysis but had no effect in the full analysis. Due to a large number of missing values for sex and age in Study II, we couldn't draw definitive conclusions about their impact on symptom expression in mobile populations. Further research is needed to better understand these factors' influence.

Meteorological data such as temperature, humidity, and pressure were found to affect respiratory symptom expression in travellers. This could significantly impact travellers as global warming and extreme temperatures become more prevalent worldwide. Although respiratory infections can disrupt travellers' daily activities, they do so less than gastrointestinal symptoms like diarrhoea and nausea, as observed in Study IV. However, respiratory infections should not be underestimated; in Study II, half of the patients requiring a medical visit suffered from these infections.

7.4 Respiratory tract infections (RTIs)

Our Study II on respiratory tract infections (RTIs) in travellers over the past two decades revealed a prevalence rate of 10% [8%; 14%]. This suggests that at least one in ten travellers is likely to experience respiratory infections during their journey. However, this figure may underestimate the actual burden as only 8–55% of travellers seek medical attention when they fall ill during their trip [6]. Consequently, milder respiratory infections are often underreported.

Our Study II also highlighted variations in RTI risks among travellers. For instance, attendees of mass gatherings were found to have a 1.8 times higher prevalence of confirmed RTIs compared to the baseline prevalence. Moreover, 60% of reported respiratory infections with known acquisition areas were traced back to mass gathering events, underscoring the significant transmission risk associated with such events [7].

Asia, particularly Southern Asia, accounted for the highest number of confirmed respiratory infections, making up 14% of all cases. This is particularly alarming given Asia's status as the second most visited continent after Europe, with a total of 360 million international tourist arrivals in 2019 [8].

Our Study II found that over the past 22 years, viruses were identified as the causative agents in 94% of RTIs in travellers. Given that viruses are typically responsible for URTIs, it is not surprising that medically diagnosed infections were predominantly URTIs (49%), compared to LRTIs (29%) [9]. Pharyngitis accounted for 51% of URTIs, a finding that aligns with existing literature [10]. In terms of LRTIs, pneumonia and tuberculosis were most frequently reported among travellers, accounting for 43% and 41% of all LRTIs respectively. Interestingly, one study found that refugees and asylum seekers accounted for over 70% of tuberculosis cases [11, 12], highlighting tuberculosis as a major health concern among this population.

While Influenza is often cited as the most common virus among travellers with an estimated prevalence of 2.8%, there has been a significant increase in SARS-CoV-2 infections among this group over the past two years. In Study II, Coronaviridae accounted for 54% of all detected viruses, with SARS-CoV-2 making up 95% of those cases. However, Orthomyxoviridae were detected in 35% of virus cases, with H1N1 (A/H1N1) constituting 22% of these cases. Bacteria, although less commonly found in travellers, were mostly gram-negative bacteria such as *Haemophilus influenzae*. For fungi, *Candida albicans* has been the most frequently reported over the last 20 years.

7.5 Travellers as sentinella

The scientific community's interest in documenting respiratory infections or symptoms in travellers has seen a significant increase over the past two decades. This upward trend can be partially attributed to advancements in diagnostic methods, the discovery of new respiratory pathogens, and a growing interest in RTIs within the scientific community as well as the ever present pandemic threat of RTIs. Moreover, the four respiratory virus outbreaks this century have underscored the importance of travellers in understanding these outbreaks, as they are directly affected by these new infections.

Maps generated from reported cases among travellers in Study II show a significant overlap with official maps detailing the total case count, suggesting that travellers are directly impacted by global outbreaks and could potentially act as early detectors for new infections. For instance, among the nine cases of H5N1 reported in China during 2010-14, two were found in travellers, with one as early as November 2010 in a traveller returning from a poultry market in Shanghai [13].

However, there can be a delay between case reports and the actual detection of an outbreak, sometimes spanning years. This highlights the need for real-time surveillance. The ITIT system addresses this reporting delay by offering immediate, detailed data about participants, including location and weather conditions. This data allowed us to calculate the incidence of respiratory symptoms and predict key factors that influence the expression of those symptoms in our cohort in Study IV.

Expanding the project would enable real-time surveillance of traveller symptoms, potentially detecting outbreaks ahead of other systems. One can envision filtering a certain symptom type and detecting cases in the vicinity, or using a threshold that could send automatic alerts to users and authorities in case of overshoot.

Broadening the project's audience would allow us to create outbreak detection based on reports of symptoms. Study V exemplifies the use of an application to characterise the symptoms of a new infection. The data collected by the ITITp application accurately predicted COVID-19 symptoms. Covid-positive participants were found to have three main symptoms: a decreased sense of smell (with an odds ratio of 18.24 and a 95% confidence interval of 4.23 to 78.69), a decreased sense of taste (odds ratio 5.45, 95% CI: 1.22 to 24.34) and difficulty breathing (odds ratio 3.35, 95% CI: 1.16 to 9.65). These symptoms have also been recognised as key indicators of COVID-19 in other scientific literature.

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8
Conclusion

This thesis highlights the critical importance of ethical considerations, data quality, and informed consent in the development of mobile applications for travel medicine. The ITIT app, meticulously designed with these principles at its core, has demonstrated its ability to gather real-time data and augment these data with location and climate information to produce large datasets. Its positive reception from users further validates its utility for both mobile populations and travel health researchers.

Respiratory symptoms are a frequent concern among travellers, with an estimated prevalence of 37% [27%; 48%]. This prevalence is corroborated by the data collected by the ITIT application. However, the incidence of these symptoms is not uniform but varies among different traveller groups and locations. It is influenced by factors such as humidity and pressure, underscoring the complex interplay between environmental conditions and health.

The prevalence of respiratory tract infections (RTIs) in travellers was estimated to be 10% [8%; 14%], suggesting that at least one in every ten travellers will encounter RTIs during their journey. The risk of contracting RTIs significantly varies among travellers, with those attending mass gatherings being at a higher risk. Asia recorded the highest absolute number of confirmed respiratory infections, accounting for 14% of cases.

Over the past two decades, there has been an increasing interest in reporting respiratory infections or symptoms in travellers. The SARS-CoV-2 pandemic has accentuated the important of real-time infection reporting and the experience from this pandemic shows that travellers are directly affected by new emerging infections and can act as sentinels. To minimise the delay between case reports and actual outbreak detection, real-time surveillance is crucial. The ITIT app addresses this delay by providing immediate detailed data about participants along with location and weather data elements.

Mobile applications like ITIT have the potential to revolutionize travel medicine by offering real-time surveillance of traveller symptoms. This innovative approach could potentially detect outbreaks ahead of other systems and provide valuable insights into the spread of infectious diseases. However, further research is needed to better understand the influence of various factors on symptom expression in mobile populations. In an increasingly digital world, these tools will undoubtedly play a crucial role in the future of travel medicine and disease surveillance.

Appendices

A

List of Publications

A.1 Publications included in this thesis

I. A. Ferretti et al. "Mobile Apps for Travel Medicine and Ethical Considerations: A Systematic Review". In: *Travel Medicine and Infectious Disease* 43 (Sept. 2021), p. 102143. DOI: 10.1016/j.tmaid.2021.102143

II. T. Lovey et al. "Travel-Related Respiratory Symptoms and Infections in Travellers (200022): A Systematic Review and Meta-Analysis". In: *Journal of Travel Medicine* (June 2023), taad081. DOI: 10.1093/jtm/taad081

III. N. Hedrich et al. "Infection Tracking in Travellers Using a Mobile App (ITIT): The Pilot Study". In: *Travel Medicine and Infectious Disease* 52 (Mar. 2023), p. 102526. DOI: 10.1016/j.tmaid.2022.102526

IV. T. Lovey et al. *Surveillance of Global, Travel-Related Illness Using a Novel App: A Multivariable, Cross-Sectional, Digital Health Study.* Preprint. SSRN, 2023. DOI: 10.2139/ssrn.4603329

V. T. Lovey et al. "Illness Tracking in SARS-CoV-2 Tested Persons Using a Smartphone App: A Non-Interventional, Prospective, Cohort Study". In: *New Microbes and New Infections* 46 (Mar. 2022), p. 100967. DOI: 10.1016/j.nmni.2022.100967

A.2 Other Publications

- J. W. Deuel et al. "Persistence, Prevalence, and Polymorphism of Sequelae after COVID-19 in Unvaccinated, Young Adults of the Swiss Armed Forces: A Longitudinal, Cohort Study (LoCoMo)". In: *The Lancet Infectious Diseases* 22.12 (Dec. 2022), pp. 1694–1702. DOI: 10.1016/S1473-3099(22)00449-2

- T. Lovey, P. O'Keeffe, and I. Petignat. "Basic Medical Training for Refugees via Collaborative Blended Learning: Quasi-Experimental Design". In: *Journal of Medical Internet Research* 23.3 (Mar. 2021), e22345. DOI: 10.2196/22345

- P. O'Keeffe and T. Lovey. "Meaningful Higher Education in Kakuma Refugee Camp: A Case Study of Why Context and Contextualization Matter". In: *PROSPECTS* 53.1-2 (May 2023), pp. 101–114. DOI: 10.1007/s11125-022-09610-z

- T. Lovey and P. Schlagenhauf. "Augmentation Des Températures et Menace Du Paludisme En Europe : Un Retour Indésirable ?" In: *Revue Médicale Suisse* 19.825 (2023), pp. 849–852. DOI: 10.53738/REVMED.2023.19.825.849

- J. A. Al-Tawfiq et al. "Infectious Disease Risks at the Rugby World Cup 2023 in France Beware of Aedes and Co!" In: *New Microbes and New Infections* 54 (Sept. 2023), p. 101178. DOI: 10.1016/j.nmni.2023.101178

- A. Buchs et al. "The Threat of Dengue in Europe". In: *New Microbes and New Infections* 49–50 (Nov. 2022), p. 101061. DOI: 10.1016/j.nmni.2022.101061

B

Author's Contributions

I. **Mobile apps for travel medicine and ethical considerations: A systematic review**
AF, NH and TL selected the articles, compiled the results, drafted the manuscript. All authors participated in the design of the project, the development of the final manuscript, and approved the submitted version.

II. **Travel-related respiratory symptoms and infections in travellers (200022): a systematic review and meta-analysis**
TL: Conceptualization Equal, Data curation Lead, Formal analysis Lead, Investigation Lead, Methodology Equal, Visualization Lead, Writingoriginal draft Lead. RH: Investigation Equal, Writing review & editing Supporting. PG: Validation Equal, Writingreview & editing Equal. PS: Conceptualization Equal, Investigation Equal, Methodology Equal, Supervision Lead, Validation Lead, Writingreview & editing Lead.

III. **Infection tracking in travellers using a mobile app (ITIT): The pilot study**
NH: Conceptualization Concept, Methodology, Data curation, Formal analysis, Writing original draft. TL: Conceptualization Concept, Methodology, Data curation, Formal analysis, Writing review & editing. EK: Data acquisition, Writing review & editing. GE: Data acquisition, Writing review & editing. UB: Methodology, Data curation, Writing review & editing. PS: Grant, and, Funding acquisition, Conceptualization Concept, Methodology, Supervision, Data curation, Writing review & editing.

IV. **Surveillance of global travel-related illness using a novel app: a multivariable, cross-sectional, digital health study**
TL: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualisation, Writing original draft. NH: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing original draft.

MPG: Investigation, Writing review & editing. JB: Investigation, Writing review & editing. PS: Project Initiation and grant writing, Funding acquisition, Conceptualisation, Methodology, Data curation, Supervision, Validation, Investigation, Writing original draft, review & editing.

V. **Illness tracking in SARS-CoV-2 tested persons using a smartphone app: a non-interventional, prospective, cohort study**
PS designed the study and wrote the protocol. MB, TL, FM, JD, PS were responsible for Data Collection. TL, JD did the analyses, PS, TL, MB, JD drafted the paper. NG, AS, ZS, AF and all authors contributed to the revisions and approved the final version.