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# Surveillance of global, travel-related illness using a novel app: a multivariable, cross-sectional study

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

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For the ITIT Global Network

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#### Abstract

#### **Introduction :**

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.

#### Methods :

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 >18 years of age travelled internationally, and provided electronic 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 administered. Logistic mixed models examined factors relating to symptom presence, and a random forest model examined symptom impact.

#### **Results:**

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.

#### **Conclusion:**

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.

#### **Trial Registration**

This study was registered in the "ClinicalTrials.gov" database (identifier NCT04672577) (1)

Keywords: Travel, malaria, dengue, Travel-Related Illness, Mobile Applications

#### **Key Messages**

#### WHAT IS ALREADY KNOWN ON THIS TOPIC?

- Previous research showed that a majority of travellers are willing to fill out symptom surveys in real time and have their associated location tracked.
- Key ethical considerations for digital health surveillance are privacy and data protection.

### WHAT THIS STUDY ADDS?

- This study shows the utility of the Illness Tracking in Travellers (ITIT) App 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.
- Symptoms were reported on 35% of itineraries and it was possible to profile travellers and their illnesses during and after travel and to determine the impact of their illnesses.
- These data from large populations of diverse travellers, can be sent in raw and anonymised form to a protected central database and linked with geolocation and environmental data to provide a granular representation of global illness in travellers.

# HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY?

- Large numbers of 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.
- This tool will complement, augment and digitize current infectious disease surveillance systems and constitute an evidence base for travel medicine guidelines

#### 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 (2,3). 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 (3,4). 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 (5). 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 (6). Surveillance networks that collate clinician verified data on travellers' illness such as EuroTravNet (2) or GeoSentinel (7) are limited by a lack of denominator data and also capture only a small portion of travel-related 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' selfreports 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 real-time 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 travel-related illnesses. Research has shown that a majority of travellers are also willing to fill out symptom surveys and have their associated location tracked (8). 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 (9). 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, user-friendly 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 (10). 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.

#### Methods

This study was approved by the Swiss Ethics Committee (BASEC number 2020–02292) and registered in the "ClinicalTrials.gov" database (identifier NCT04672577) (1).

Patient and Public Involvement

The public was involved in this study as pilot participants, giving feedback for the ITIT app, suggesting improvements and modifications, and demonstrating study feasibility.(10) A feedback button on the app allows for participants to give input throughout their participation.

Recruitment

Participants were recruited from April 1<sup>st</sup> 2022 to July 15<sup>th</sup> 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 (sixpoint Likert scale: none', 'mild', 'moderate', 'bad', 'very bad' and 'medical visit') and the impact of these symptoms on the participant's day on a seven-point Likert scale ranging from no impact on activities to hospitalisation. Finally, after the trip is completed, participants are sent a followup 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.

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 Zürich, 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.

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 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.

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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.

#### **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 1).

Table 1. Sociodemographic characteristics of ITIT participants (n = 609).

Characteristic	<b>Overall</b> , N = 609 <sup>1</sup>	Leisure/tourist travellers, N = 401 <sup>1</sup>	Visiting friends and relatives (VFR), N = 99 <sup>1</sup>	Business/corporate travellers, N = 80 <sup>1</sup>	<b>Other</b> , N = 29 <sup>2</sup>
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%)

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21	
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39	
40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	

Characteristic	<b>Overall</b> , N = 609 <sup>1</sup>	Leisure/tourist travellers, N = 401 <sup>1</sup>	Visiting friends and relatives (VFR), N = 99 <sup>1</sup>	Business/corporate travellers, N = 80 <sup>1</sup>	<b>Other</b> , N = 29 <sup>2</sup>
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 <sup>3</sup>					
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 <sup>4</sup>					
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%)

¹n (%)

<sup>2</sup>Includes specific groups of travelers who do not fit into the previously defined categories. These travelers attended mass gathering events such as the Hajj, Olympics, or World Cup, or were involved in research, education, humanitarian work, or other activities

<sup>3</sup>Includes participants who completed the baseline questionnaire but did not complete any subsequent surveys.

<sup>4</sup>Includes participants who completed at least one survey.

Overall, there were 2905 daily symptom surveys with associated location data filled out by participants. Figure 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 (section 5)*. 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,

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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 (Table 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 stelf-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 amoebic dysentery. One survey reported hospitalisation.

		Overall (N=3739)ª		Africa (N=699)ª		Americas (N=870) <sup>a</sup>		Asia (N=1006)ª		Europe (N=1109)ª		Oceania (N=55)ª		Female (N=2175)ª		Male (N=1564)ª
Symptoms	n <sup>b</sup>	IR°	n <sup>b</sup>	IR°	n <sup>b</sup>	IR°	n <sup>b</sup>	IR°	n <sup>b</sup>	IR°	n <sup>b</sup>	IRc	n <sup>b</sup>	IR°	n <sup>b</sup>	IR
Gastrointestin al	248	66,33	42	60,09	63	72,41	125	124,25	17	15,33	1	18,18	170	78,16	78	49,8
Nausea	104	27,81	21	30,04	21	24,14	59	58,65	3	2,71	0	0,00	81	37,24	23	14,7
Vomiting	20	5,35	2	2,86	7	8,05	11	10,93	0	0,00	0	0,00	11	5,06	9	5,7
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
Constipatio n	43	11,50	2	2,86	4	4,60	30	29,82	7	6,31	0	0,00	31	14,25	12	7,6
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	25,7 5	2 0	22,9 9	5 2	51,6 9	6 6	59,5 1	2	36,3 6	95	43,6 8	63	40,2 8
Sore Throat	114	30,49	5	7,15	1 2	13,7 9	3 7	36,7 8	6 0	54,1 0	0	0,00	81	37,2 4	33	21,
Runny Nose	164	43,86	2 0	28,6 1	2 4	27,5 9	5 7	56,6 6	6 1	55,0 0	2	36,3 6	99	45,5 2	65	41,

Table 2. Absolute number and incidence rate of symptoms reported by travellers using the ITIT app, stratified by sex and location of travel (n=3739).

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		Overall (N=3739)ª		Africa (N=699)ª		Americas (N=870)ª		Asia (N=1006)ª		Europe (N=1109) <sup>a</sup>		Oceania (N=55)ª		Female (N=2175)ª		Male (N=1564) <sup>a</sup>
Symptoms	n⁵	IR°	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR℃	n <sup>b</sup>	IR⁰	n <sup>b</sup>	IR℃	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR⁰
Out of Breath (Resting)	43	11,5 0	2	2,86	5	5,75	3	2,98	3 3	29,7 6	0	0,00	2 9	13,3 3	1 4	8,95
Out of Breath (Running)	78	20,8 6	6	8,58	1 3	14,9 4	1 5	14,9 1	4 4	39,6 8	0	0,00	5 6	25,7 5	2 2	14,0 7
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	10,1 6	4	5,72	3	3,45	2 4	23,8 6	6	5,41	1	18,1 8	3 3	15,1 7	5	3,20
Itchy Insect Bite	64	17,1 2	4	5,72	1 4	16,0 9	3 2	31,8 1	1 3	11,7 2	1	18,1 8	5 4	24,8 3	1 0	6,39
ltchy (Other)	18	4,81	1	1,43	1	1,15	9	8,95	6	5,41	1	18,1 8	1 5	6,90	3	1,92
Sunburn	30	8,02	1	1,43	7	8,05	1 9	18,8 9	3	2,71	0	0,00	2 3	10,5 7	7	4,48
Itchy Red	17	4,55	0	0,00	3	3,45	8	7,95	6	5,41	0	0,00	1	6,90	2	1,28
Eyes General	158	42,26	21	30,04	35	40,23	63	62,62	39	35,17	0	0,00	5 115	52,87	43	27,49
		42,20			1	40,23	1	16,9	1	16,2			3	15,1	43	
Fever	49	1	4	5,72	0	9	7	0	8	3	0	0,00	3	7	6	10,2 3
Dizziness	63	16,8 5	4	5,72	1 0	11,4 9	3 0	29,8 2	1 9	17,1 3	0	0,00	4 4	20,2 3	1 9	12,1 5
Ear Ache	30	8,02	3	4,29	1 0	11,4 9	7	6,96	1 0	9,02	0	0,00	2 5	11,4 9	5	3,20
Headache	114	30,4 9	1 3	18,6 0	2 8	32,1 8	4 3	42,7 4	3 0	27,0 5	0	0,00	8 4	38,6 2	3 0	19,1 8
Pain in Eyes	36	9,63	6	8,58	5	5,75	1 4	13,9 2	1 1	9,92	0	0,00	1 9	8,74	1 7	10,8 7
Muscle Pain	47	12,5 7	5	7,15	1 1	12,6 4	1 6	15,9 0	1 5	13,5 3	0	0,00	2 6	11,9 5	2 1	13,4 3
Aching Limbs	53	14,1	5	7,15	1	12,6 4	2 3	22,8 6	1 4	12,6 2	0	0,00	3 1	14,2 5	2 2	14,0 7
Body												0.00				
(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 Joint	33	8,83	1 0	14,3 1	2	2,30	1 6	15,9 0	5	4,51	0	0,00	2 3	10,5 7	1 0	6,39
Swelling in Joint	10	2,67	4	5,72	1	1,15	2	1,99	3	2,71	0	0,00	8	3,68	2	1,28
	I															
<sup>a</sup> Absolute Numb	er of Surve	eys Complete	d													
<sup>b</sup> Absolute Numb	er of Repo	rted Symptor	ns													
° Incidence Rate	per 1000 (	Completed Su	irveys													
When ex modellin business	ng, u	nivaria	ate ar	nalysis	shov	wed th	at du	ration	of t	ravel,	age,	locati	on of	f trave	1 to	Asia,

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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 (see Table 3).

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  $\mu$ g/m<sup>3</sup>) 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 1-4).

Table 3: Univariate and multivariate analyses of variables influencing symptom expression using complete case analysis and imputed full sample analysis

			С	omplete c	ase analysis	5			Imputed full sample analysis <sup>3</sup>				
	Univariate a	nalysis			Multivariat	e model <sup>2</sup>			Multivaria	e model <sup>2</sup>			
Predictors <sup>1</sup>	Odds Ratios	Lower Cl	Upper Cl	p	Odds Ratios	Lower Cl	Upper Cl	p	Odds Ratios	Lower Cl	Upper Cl	р	
Survey Day	3.72	2.65	5.22	<0.001	3.10	2.13	4.51	<0.001	1.26	1.01	1.57	0.04	
Age	0.44	0.33	0.59	<0.001									
Gender: Female	Reference												
Gender: Male	0.63	0.36	1.09	0.100									
Continent: Europe	Reference												
Continent: Africa	0.80	0.36	1.80	0.592									
Continent: Americas	1.78	0.84	3.76	0.134									
Continent: Asia	3.90	1.95	7.82	<0.001									
Continent: Oceania	0.56	0.04	6.99	0.650									
Travel Purpose: Leisure/Tourist Travellers	Reference												
Travel Purpose: Visiting Friends and Relatives (VFR)	0.86	0.41	1.80	0.689									
Travel Purpose: Business/Corporate Travellers	0.41	0.18	0.92	0.030									
Travel Purpose: Other	0.52	0.11	2.56	0.423									
Smoking Status: Never Smoked	Reference												
Smoking Status: Current Smoker	2.13	0.83	5.45	0.115									

					-	case analysis					uted full sar		
		Univariate a	analysis			Multivariat	e model <sup>2</sup>			Multivariat	te model <sup>2</sup>		
Predicte	ors <sup>1</sup>	Odds Ratios	Lower Cl	Upper Cl	р	Odds Ratios	Lower Cl	Upper Cl	р	Odds Ratios	Lower Cl	Upper Cl	р
Smokin Smoker	g Status: Former	0.78	0.28	2.15	0.633								
Chronic None	Health Conditions:	Reference											
Chronic Yes	Health Conditions:	0.70	0.29	1.72	0.441								
Clouds	(%)	0.97	0.84	1.12	0.669								
Humidit	y (%)	1.25	1.07	1.46	0.005	1.16	0.99	1.37	0.069	1.76	1.53	2.02	<0.001
Pressu	re (hPa)	1.06	0.93	1.20	0.372								
Temper	rature (°C)	0.97	0.81	1.15	0.690								
UV Inde	ex (UVI)	0.97	0.85	1.10	0.633								
Visibility	/ (m)	0.97	0.86	1.09	0.579								
Wind S	peed (m/s)	0.90	0.78	1.03	0.139	0.91	0.78	1.05	0.179	0.98	0.84	1.14	0.8
Air Qua CO (μg	lity Components - /m³)	1.02	0.91	1.14	0.691								
Air Qua NH3 (μ	lity Components - g/m³)	1.10	0.98	1.24	0.105								
Air Qua NO (μg	lity Components - /m³)	0.98	0.87	1.11	0.733								
Air Qua NO2 (μ	lity Components - g/m³)	1.03	0.90	1.16	0.692								
Air Qua O3 (μg	lity Components - 'm³)	0.94	0.81	1.10	0.444								
Air Qua PM10 (	lity Components - μg/m³)	1.08	0.95	1.23	0.229								
Air Qua SO2 (μ	lity Components - g/m³)	1.02	0.93	1.12	0.732								
Season	: Summer	Reference				Reference	•			Reference	)		
Season	: Autumn	1.33	0.73	2.41	0.347	1.27	0.66	2.45	0.468	0.93	0.49	1.75	0.8
Season	: Spring	1.25	0.75	2.10	0.390	1.63	0.92	2.88	0.096	1.26	0.73	2.18	0.4
Season	: Winter	1.85	1.09	3.14	0.023	2.79	1.51	5.13	0.001	1.51	0.85	2.69	0.2

<sup>1</sup>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.

<sup>2</sup>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.

<sup>3</sup>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 2).

#### 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 (10). 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 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)10/26/2023 8:45:00 AM. 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 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 1-4) 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 self-treatments 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 location-associated 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 self-reported 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.

### 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.

### **CRediT** author statement

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.

# **Declaration of interests**

All authors have completed the ICMJE uniform disclosure form

at <u>http://www.icmje.org/disclosure-of-interest/</u> and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

### **Transparency declaration**

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

### Data Availability

Restrictions apply to the availability of the data that support the findings of this study, and so are not publicly available. Some data can be made available from the authors upon reasonable request and with permission of Prof. Patricia Schlagenhauf.

#### **Role of the Funder**

This study was funded by the Swiss National Science Foundation, Switzerland (grant number 320030\_192653). The funder played no role in study design, data collection, analysis and interpretation of data, or the writing of this manuscript.

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#### **Figures:**

Figure 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.

Figure 2: 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. 

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# Appendix

Appendix (section 1): Univariate and Multivariate Analyses of Variables Influencing Gastrointestinal Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis gastro\_any\_table\_3.docx

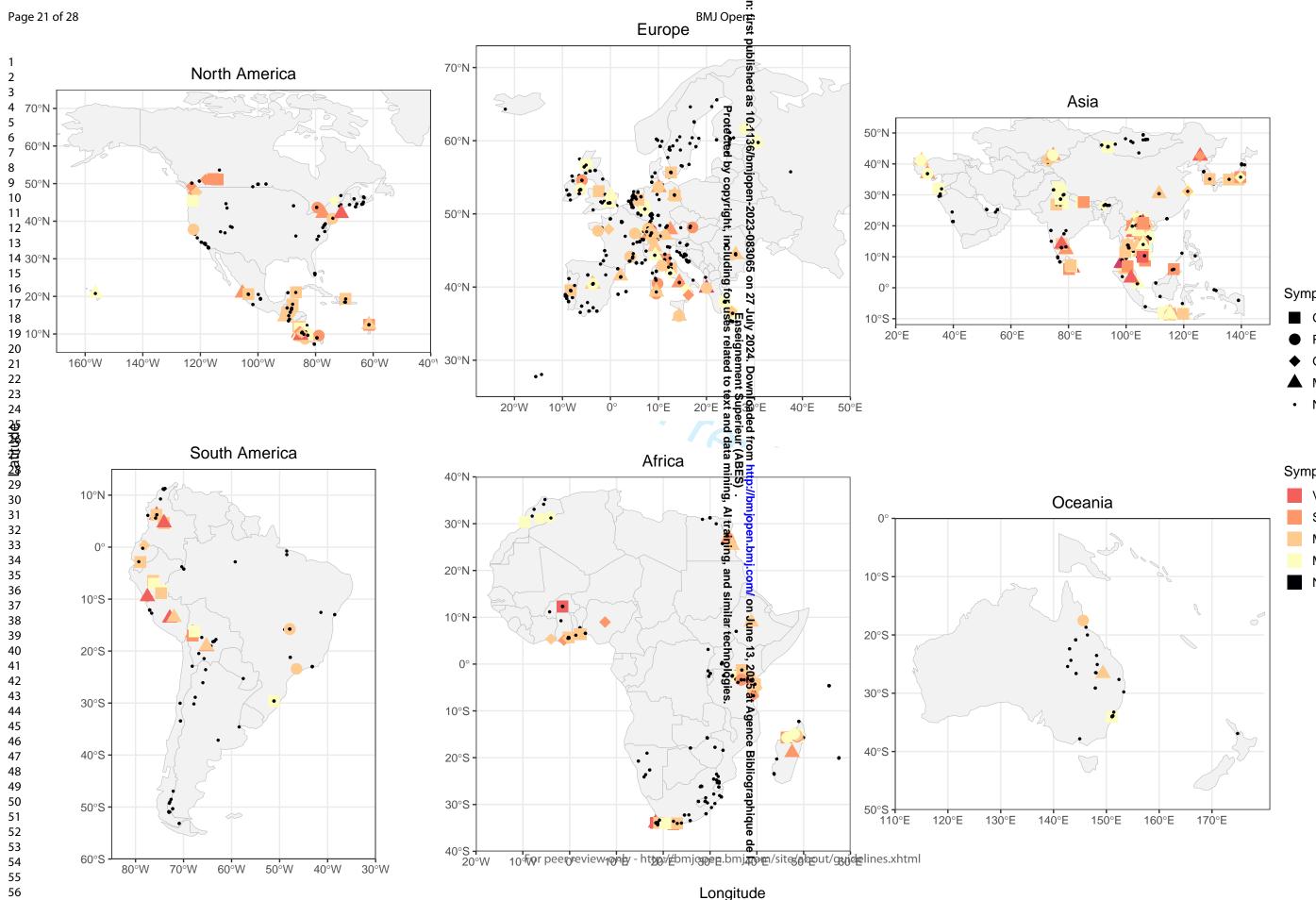
Appendix (section 2): Univariate and Multivariate Analyses of Variables Influencing Respiratory Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis respi\_any\_table\_3.docx

Appendix (section 3): Univariate and Multivariate Analyses of Variables Influencing Dermatological Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis skin\_any\_table\_3.docx

Appendix (section 4): Univariate and Multivariate Analyses of Variables Influencing General Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis body\_any\_table\_3.docx

*Appendix (section 5): Traveler Profile and Symptom Intensity Among Travelers Who Had a Medical Visit During Their Trip* <u>table\_4.docx</u>



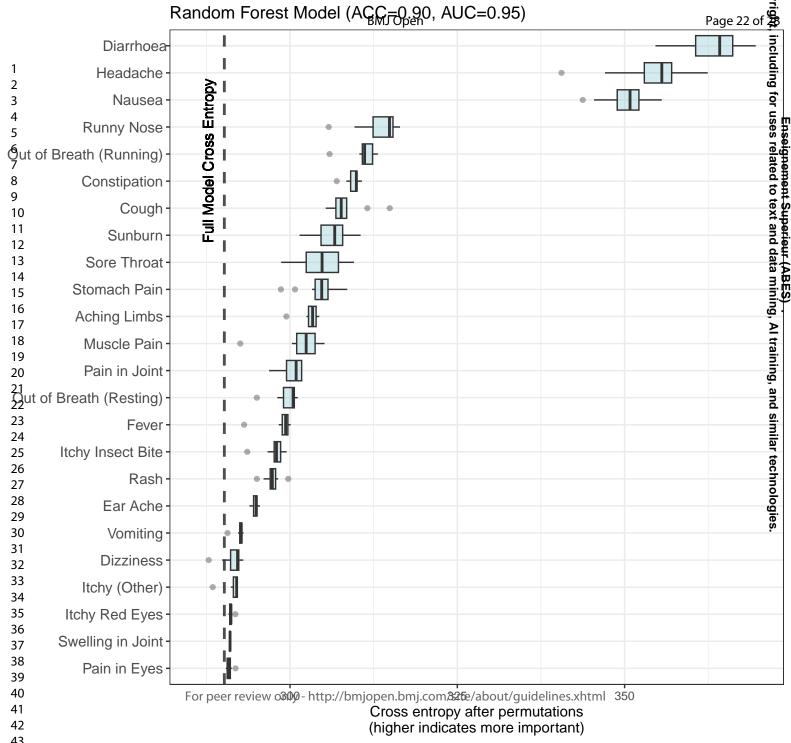


#### Symptom categories

- Gastrointestinal
- Respiratory
- General
- Multiple
- No reported symptoms

#### Symptom intensity

- Very Severe
- Severe
- Moderate
- Mild
- None



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Appendix (section 1): Univariate and Multivariate Analyses of Variables Influencing Gastrointestinal Symptom Expression Using Complete	Case Analysis and Imputed
Full Sample Analysis	

	Univariate ana	lvsis			Multivariate m	odel <sup>2</sup>		Multivariate model <sup>2</sup>				
Predictors <sup>1</sup>	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	п	Odds Ratios	Lower CI	Upper CI	р
Survey Day	3.03	2.09	4.38	<0.001	3.06	1.99	4.71	<0.001	1.36	1.03	1.79	0.028
Age	0.69	0.47	1.01	0.053	0.00	1,77		0.001	1.00	1.00	1.17	0.020
Gender: Female	Reference											
Gender: Male	0.59	0.28	1.24	0.164								
Continent: Europe	Reference											
Continent: Africa	4.10	1.49	11.31	0.006								
Continent: Americas	5.02	1.88	13.41	0.001								
Continent: Asia	13.25	5.33	32.95	<0.001								
Continent: Oceania	1.37	0.05	41.32	0.856								
Fravel Purpose: Leisure/Tourist Travellers	Reference	0.05	11.52	0.020								
Fravel Purpose: Visiting Friends and	0.40	0.14	1.16	0.091								
Relatives (VFR)	0.40	0.14	1.10	0.071								
Fravel Purpose: Business/Corporate Fravellers	0.50	0.18	1.44	0.201								
Fravel Purpose: Other	0.99	0.14	6.78	0.990								
moking Status: Never Smoked	Reference											
moking Status: Current Smoker	1.78	0.51	6.24	0.366								
moking Status: Former Smoker	1.83	0.53	6.36	0.340								
Chronic Health Conditions: None	Reference											
Chronic Health Conditions: Yes	0.84	0.25	2.77	0.770								
Clouds (%)	1.06	0.89	1.26	0.536								
Iumidity (%)	1.19	0.97	1.46	0.101	1.12	0.91	1.39	0.279	1.65	1.38	1.96	<0.00
Pressure (hPa)	1.25	0.92	1.69	0.150								
Cemperature (°C)	1.17	0.93	1.46	0.170								
JV Index (UVI)	1.05	0.90	1.22	0.546								
Visibility (m)	0.99	0.85	1.15	0.850								
Vind Speed (m/s)	0.93	0.78	1.11	0.412								
Air Quality Components - CO (µg/m <sup>3</sup> )	1.06	0.93	1.20	0.401								
Air Quality Components - NH3 (µg/m <sup>3</sup> )	1.18	1.04	1.34	0.011	1.17	1.03	1.34	0.016	1.25	1.10	1.43	<0.00
Air Quality Components - NO ( $\mu g/m^3$ )	0.94	0.79	1.12	0.498		BMJ						
Air Quality Components - NO2 (µg/m <sup>3</sup> )	1.13	0.97	1.31	0.112		Oper						
Air Quality Components - O3 (µg/m <sup>3</sup> )	0.88	0.72	1.06	0.175		n: first						
Air Quality Components - PM10 (µg/m <sup>3</sup> )	1.16	1.01	1.35	0.042		BMJ Open: first published as 10.1136/b						
Air Quality Components - SO2 (µg/m <sup>3</sup> )	1.02	0.87	1.20	0.818		ished						
eason: Summer	Reference				Reference	as 10 Pro			Reference			
eason: Autumn	2.86	1.33	6.13	0.007	2.57	5 10.1136/1	5.72	0.021	2.06	0.88	4.83	0.10
Season: Spring	1.92	0.99	3.72	0.053	1.86	d b9).9 ∭ o	3.78	0.088	1.68	0.80	3.50	0.2
Season: Winter	2.15	1.06	4.36	0.035	3.13	bmjopen-2023- by copyright,	6.74	0.004	2.10	0.95	4.65	0.069

<sup>2</sup>The optimal model was determined using a combination of 'order' and 'backward' elimination, with the Akaike Inderright Criterion (AIC) as the selection criteria. The 'order' method orders terms by <sup>1</sup> be grinnal model was determined using a combination of 'vde' and 'vade' wand' elimination, with the Adaka le Marginging Octaticion (ALC) as the selection criteria. The 'order' method orders terms by the contribution to the model, ensating that the model converges before performing backward elimination.
<sup>1</sup> builtwaria lumpatation by Chained Equacions (MCE) with 15 importations were used with linear mixed models. The conder is a constrained of the model is for binary data, and replication of the mosel target within a class for factors with more than two levels. These methods were chosen to account for cluster of the user of the model. **Protection of the model is a constrained of the model is for binary data, and replication of the model is a constrained of the model is a constrained of the model.
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<b>Protection of the model is a constrained of the model. Protection of the model is a constrained of the model. Protection of the model is a constrained of the model. Protection of the model is a constrained of the mode** their contribution to the model, ensuring that the model converges before performing backward elimination. for 

Appendix (section 2): Univariate and Multivariate Analyses of Variables Influencing Respiratory Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis

			(	Complete c	ase analysis				In	nputed full sam	ple analysis	3
	Univariate ana	lysis			Multivaria	ate model <sup>2</sup>			Multivaria	ate model <sup>2</sup>		
Predictors <sup>1</sup>	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р
Survey Day	10.95	5.05	23.74	<0.001	9.99	3.80	26.29	<0.001	1.09	0.79	1.50	0.5
Age	0.45	0.22	0.92	0.029								
Gender: Female	Reference											
Gender: Male	0.57	0.15	2.15	0.410								
Continent: Europe	Reference											
Continent: Africa	0.16	0.02	1.71	0.131								
Continent: Americas	0.56	0.10	3.22	0.513								
Continent: Asia	0.94	0.20	4.56	0.943								
Continent: Oceania	0.52	0.00	249.52	0.835								
Travel Purpose: Leisure/Tourist Travellers	Reference											
Travel Purpose: Visiting Friends and Relatives (VFR)	1.31	0.25	6.73	0.748								
Travel Purpose: Business/Corporate Travellers	0.41	0.05	3.60	0.425								
Travel Purpose: Other	0.41	0.00	48.58	0.712								
Smoking Status: Never Smoked	Reference											
Smoking Status: Current Smoker	1.42	0.15	13.16	0.757								
Smoking Status: Former Smoker	0.64	0.06	7.23	0.717								
Chronic Health Conditions: None	Reference											
Chronic Health Conditions: Yes	0.87	0.10	7.59	0.902								
Clouds (%)	0.92	0.72	1.18	0.509								
Humidity (%)	1.79	1.31	2.45	<0.001	1.50	1.05	2.14	0.026	1.10	0.98	1.24	0.1
Pressure (hPa)	2.11	1.30	3.43	0.002	1.91	1.11	3.29	0.019	1.12	0.81	1.54	0.4
Temperature (°C)	0.66	0.47	0.92	0.015	0.78	0.50	1.21	0.266	0.97	0.84	1.13	0.7
UV Index (UVI)	0.73	0.51	1.04	0.082								
Visibility (m)	0.89	0.72	1.09	0.256								
Wind Speed (m/s)	0.84	0.65	1.10	0.203								
Air Quality Components - CO ( $\mu g/m^3$ )	1.15	0.97	1.35	0.099								
Air Quality Components - NH3 (µg/m <sup>3</sup> )	1.16	0.96	1.41	0.117		BMJ						
Air Quality Components - NO ( $\mu g/m^3$ )	1.09	0.95	1.25	0.225		Oper						
Air Quality Components - NO2 (µg/m <sup>3</sup> )	1.07	0.88	1.30	0.496		1: first						
Air Quality Components - O3 (µg/m <sup>3</sup> )	0.91	0.68	1.21	0.510		t publ						
Air Quality Components - PM10 ( $\mu g/m^3$ )	1.20	0.98	1.47	0.077		BMJ Open: first published as 10.1136/bm Protected by						
Air Quality Components - SO2 (µg/m <sup>3</sup> )	1.06	0.94	1.19	0.346		as 10 Prc						
Season: Summer	Reference					s 10.1136/bmjopen-2023-0830 Protected by copyright, inclu						
Season: Autumn	0.41	0.09	1.90	0.253		√bmjc d by c						
Season: Spring	1.18	0.39	3.58	0.776		jopen-2023-0830 / copyright, inclu						
Season: Winter	0.56	0.16	1.97	0.364		<u>2</u> 023- ight,						

<sup>1</sup>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.

<sup>2</sup>The optimal model was determined using a combination of 'order' and 'backward' elimination, with the Akaike In a combination (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.

<sup>3</sup>Multivariate Imputation by Chained Equations (MICE) with 15 imputations were used with linear mixed 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 rip\_id in the data.

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Appendix (section 3): Univariate and Multivariate Analyses of Variables Influencing Dermatological Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis

			(	Complete c	ase analysis				Imp	uted full sam	ple analysis	3
	Univariate ana	lysis			Multivariate r	nodel <sup>2</sup>			Multivariate n	nodel <sup>2</sup>		
Predictors <sup>1</sup>	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р
Survey Day	3.82	2.19	6.66	<0.001	3.36	1.63	6.92	0.001	1.69	1.05	2.70	0.02
Age	0.57	0.23	1.39	0.215								
Gender: Female	Reference											
Gender: Male	0.43	0.08	2.40	0.337								
Continent: Europe	Reference											
Continent: Africa	0.43	0.02	9.03	0.585								
Continent: Americas	1.34	0.15	12.29	0.799								
Continent: Asia	4.18	0.64	27.37	0.135								
Continent: Oceania	3.23	0.01	1009.68	0.689								
Travel Purpose: Leisure/Tourist Travellers	Reference											
Travel Purpose: Visiting Friends and Relatives (VFR)	0.23	0.01	4.72	0.342								
Travel Purpose: Business/Corporate Travellers	0.11	0.00	6.89	0.296								
Travel Purpose: Other	0.75	0.01	57.62	0.896								
Smoking Status: Never Smoked	Reference											
Smoking Status: Current Smoker	1.82	0.14	24.20	0.649								
Smoking Status: Former Smoker	0.56	0.02	13.41	0.722								
Chronic Health Conditions: None	Reference											
Chronic Health Conditions: Yes	0.20	0.00	15.67	0.466								
Clouds (%)	0.93	0.69	1.24	0.606								
Humidity (%)	1.21	0.83	1.76	0.315								
Pressure (hPa)	0.96	0.60	1.54	0.873								
Temperature (°C)	1.85	1.20	2.85	0.005	1.90	1.19	3.03	0.007	1.68	1.04	2.69	0.032
UV Index (UVI)	1.01	0.74	1.40	0.936								
Visibility (m)	1.02	0.78	1.34	0.887								
Wind Speed (m/s)	1.11	0.84	1.47	0.446								
Air Quality Components - CO (µg/m <sup>3</sup> )	1.03	0.87	1.23	0.703								
Air Quality Components - NH3 (µg/m <sup>3</sup> )	0.97	0.80	1.18	0.796		BA						
Air Quality Components - NO (µg/m <sup>3</sup> )	0.96	0.74	1.25	0.764		VD Ob						
Air Quality Components - NO2 ( $\mu g/m^3$ )	1.06	0.86	1.30	0.576		en: fii						
Air Quality Components - O3 (µg/m <sup>3</sup> )	1.19	0.87	1.63	0.266		BMJ Open: first published as 10.1136/gr						
Air Quality Components - PM10 (µg/m <sup>3</sup> )	1.06	0.87	1.29	0.574		blishe						
Air Quality Components - SO2 (µg/m <sup>3</sup> )	1.03	0.91	1.17	0.638		∌d as ∍						
Season: Summer	Reference				Reference	s 10.1136/gr			Reference			
Season: Autumn	0.01	0.00	0.43	0.019	0.01	36/99 1990	0.97	0.048	0.05	0.00	0.91	0.04
Season: Spring	0.38	0.10	1.48	0.163	0.78	mjogen-2023-0: 0/223-0:	3.84	0.761	0.56	0.15	2.06	0.4
Season: Winter	0.30	0.07	1.31	0.110	1.55	n-2027 Vrigh	8.76	0.620	0.51	0.12	2.21	0.4

<sup>1</sup>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.

<sup>2</sup>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.

<sup>1</sup>The optimal model was determined using a combination of vorder' and 'backward' elimination, with the Akakar elimination (briterion (ALC) as the selection criteria. The 'order' method orders terms by their combination of the model, surgery selected elimination, with the Akakar elimination (briterion to the model, ensuing that the model converges before performing backward elimination) and the provided of the model of the model or the model of the model of the model is for binary data, and replication of the model with a class for factors with more than two levels. These methods were chosen to account for class in the data.

Appendix (section 4): Univariate and Multivariate Analyses of Variables Influencing General Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis

	Complete case analysis					Imputed full sample analysis <sup>3</sup>						
	Univariate analysis			Multivariate model <sup>2</sup>				Multivariate model <sup>2</sup>				
Predictors <sup>1</sup>	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р
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 (°C)	0.89	0.66	1.22	0.473	0.75	0.54	1.04	0.086	0.96	0.83	1.11	0.
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.
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 (µg/m <sup>3</sup> )	1.10	0.96	1.26	0.173								
Air Quality Components - NH3 (µg/m <sup>3</sup> )	1.10	0.93	1.30	0.270								
Air Quality Components - NO ( $\mu$ g/m <sup>3</sup> )	1.03	0.91	1.16	0.677		BMJ						
Air Quality Components - NO2 (µg/m <sup>3</sup> )	1.05	0.89	1.25	0.565		Open:						
Air Quality Components - O3 (µg/m <sup>3</sup> )	1.09	0.85	1.40	0.507		BMJ Open: first published						
Air Quality Components - PM10 (µg/m <sup>3</sup> )	1.12	0.94	1.32	0.196	1.08	<b>pu9</b> 1	1.29	0.385	1.05	0.96	1.14	0.
Air Quality Components - SO2 ( $\mu g/m^3$ )	1.02	0.93	1.12	0.719		shed						
Season: Summer	Reference				Pro	as 10.1136/bm						
Season: Autumn	0.59	0.17	2.01	0.399	tecter	.1136/						
Season: Spring	0.89	0.38	2.05	0.782	Protected by copyright,	'bmjoj						
Season: Winter	1.34	0.52	3.45	0.538	оруг	jopen-2023-						

<sup>1</sup>Generalized Linear Mixed-Effects Models (GLMMs) were used to analyze our data, with trip\_id included as a random of fect to account for variations between trips.

<sup>1</sup> the optimal model was determined using a combination of 'order' and 'backward' climination. with the Akaike Inform The optimal model is using a combination of 'order' and 'backward' climination.
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<sup>1</sup> the optimal model wa <sup>2</sup>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

	Traveller 1	Traveller 2	Traveller 3	Traveller 4
Traveller Profile				
Age	36	56	24	41
Gender	Female	Male	Male	Male
Destination	Thailand	Argentina	Thailand	Albania
Travel Purpose	Leisure/tourist travellers	Leisure/tourist travellers	Leisure/tourist travellers	Leisure/tourist traveller
Smoking Status	Not smoking	Former smoker	Not smoking	Former smoker
Health Chronic	None	Heart disease	None	High blood pressure
Day(s) into Travel	42	1	1	4
Symptoms Intensity				
Nausea	medical visit	none	medical visit	none
Vomiting	none	none	medical visit	none
Stomach Pain	none	none	medical visit	none
Diarrhea	none	none	medical visit	none
Cough	none	medical visit	none	moderate
Sore Throat	none	moderate	none	very bad
Runny Nose	none	moderate	none	medical visit
Out of Breath (Resting)	none	mild	none	bad
Out of Breath (Running)	none	moderate	none	bad
Rash	mild	none	none	none
Dizziness	moderate	none	medical visit	none
Headache	mild	none	medical visit	bad
Eye Pain	none	none	medical visit	mild
Muscle Pain	none	none	medical visit	very bad
Aching Limbs	none	none	Enedical visit	none

#### Appendi

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STROBE Statement-Checklist of items that should be included in reports of cross-sectional studie	es
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	Item No	Recommendation	Don
Title and abstract	1	( <i>a</i> ) Indicate the study's design with a commonly used term in the title or the abstract	Х
		(b) Provide in the abstract an informative and balanced summary of what	x
		was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being	х
		reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	х
Methods			
Study design	4	Present key elements of study design early in the paper	x
Setting	5	Describe the setting, locations, and relevant dates, including periods of	х
		recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of	х
		participants	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders,	х
		and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	x
measurement		assessment (measurement). Describe comparability of assessment methods if	
		there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	х
Study size	10	Explain how the study size was arrived at	х
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If	х
		applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for	х
		confounding	
		(b) Describe any methods used to examine subgroups and interactions	X
		(c) Explain how missing data were addressed	Х
		( <i>d</i> ) If applicable, describe analytical methods taking account of sampling	na
		strategy	
		( <u>e</u> ) Describe any sensitivity analyses	na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers	х
		potentially eligible, examined for eligibility, confirmed eligible, included in	
		the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Х
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical,	х
		social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of	х
		interest	
Outcome data	15*	Report numbers of outcome events or summary measures	Х
Main results	16	( <i>a</i> ) Give unadjusted estimates and, if applicable, confounder-adjusted	х
		estimates and their precision (eg, 95% confidence interval). Make clear	

		(b) Report category boundaries when continuous variables were categorized	x
		(c) If relevant, consider translating estimates of relative risk into absolute	na
		risk for a meaningful time period	
Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and	Х
		sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	х
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias	х
		or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	х
		limitations, multiplicity of analyses, results from similar studies, and other	
		relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	X
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study	х
		and, if applicable, for the original study on which the present article is based	

\*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

# Surveillance of global, travel-related illness using a novel app: a multivariable, cross-sectional study

Journal:	BMJ Open		
Manuscript ID	bmjopen-2023-083065.R1		
Article Type:	Original research		
Date Submitted by the Author:	16-Apr-2024		
Complete List of Authors:	Lovey, Thibault; University of Zurich Institute of Epidemiology Biostatistics and Prevention Hedrich, Nadja; University of Zurich Institute of Epidemiology Biostatistics and Prevention, Epidemiology Grobusch, Martin; Amsterdam UMC Locatie AMC, Center for Tropical Medicine and Travel Medicine, Department of Infectious Diseases Bernhard, Julian; Charité Universitätsmedizin Berlin, Charité Center for Global Health, Institute of International Health Schagenhauf, Patricia; University of Zurich Institute of Epidemiology Biostatistics and Prevention, Public and Global Health		
<b>Primary Subject Heading</b> :	Infectious diseases		
Secondary Subject Heading:	Epidemiology, Global health, Public health		
Keywords:	Malaria, Epidemiology < TROPICAL MEDICINE, Public health < INFECTIOUS DISEASES		

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	1	Surveillance of global, travel-related illness using a novel app: a multivariable, cross-
4 E	2	sectional study
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#### Abstract

#### **Introduction :**

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. 

#### **Methods** :

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 April 2022 to July 2023. Participants >18 years of age travelled internationally, and provided electronic 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 administered. Logistic mixed models examined factors relating to symptom presence, and a random forest model examined symptom impact. 

#### **Results:**

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%). All continents were 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. 

#### **Conclusion:**

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.

Keywords: Travel, malaria, dengue, Travel-Related Illness, Mobile Applications

#### **Trial Registration** This study was registered in the "ClinicalTrials.gov" database (identifier NCT04672577) (1)

1 2		
2 3 4	88	Strengths and limitations of this study
5 6	89	• Provides real-time surveillance data on travel-related illnesses through a "bottom-up"
7	90	approach.
8 9	91	• Links geolocation and environmental data with symptom reports for precise
9 10	92	epidemiological profiling and illness cluster identification.
11	93	• Non-commercial, public health surveillance of travellers' health
12	94	<ul> <li>To date, focuses mainly on European travellers which may influence the</li> </ul>
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### 100 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(5). Surveillance networks that collate clinician verified data on travellers' illness such as EuroTravNet (1)or GeoSentinel (6)are limited by a lack of denominator data and also capture only a small portion of travel-related 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, guarantine 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 real-time 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 travel-related 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 

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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. 

**Methods** 

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

Patient and Public Involvement

The public was involved in this study as pilot participants, giving feedback for the ITIT app, suggesting improvements and modifications, and demonstrating study feasibility(9). A feedback button on the app allows for participants to give input throughout their participation. 

Recruitment 

Participants were recruited from April 1st 2022 to July 15th 2023 through a convenience sampling approach in travel clinics in Switzerland, Berlin, Amsterdam 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 seven-point Likert scale ranging from no impact on activities to hospitalisation. The daily survey can be filled out in less than a minute. 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 

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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 the WHO and updated in real-time. 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 Zürich, 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. 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
  - 197 of average age, proportion of travellers with chronic diseases or smoking status, and average trip
     198 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 analyze participants' daily surveys, taking into account the clustering of data by individual trips. These models assessed the influence of various factors on the likelihood of symptom expression, both overall and within four symptom subcategories(11). Univariate analysis was conducted 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.

225 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.

13 229

# 15 230 **Results** 16

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 1). 

239	Table 1. Sociodemographic characteristics of ITIT participants ( $n = 60$	)9).
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Characteristic	<b>Overall</b> , N = 609 <sup>1</sup>	Leisure/tourist travellers, N = 401 <sup>1</sup>	Visiting friends and relatives (VFR), N = 991	Business/corporate travellers, N = 80 <sup>1</sup>	Other, N 29 <sup>2</sup>
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

Characteristic	<b>Overall</b> , N = 609 <sup>1</sup>	Leisure/tourist travellers, N = 401 <sup>1</sup>	Visiting friends and relatives (VFR), N = 99 <sup>1</sup>	Business/corporate travellers, N = 80 <sup>1</sup>	<b>Other</b> , N = 29 <sup>2</sup>
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 <sup>3</sup>					
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 <sup>4</sup>					
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%)

¹n (%)

<sup>2</sup>Includes specific groups of travelers who do not fit into the previously defined categories. These travelers attended mass gathering events such as the Hajj, Olympics, or World Cup, or were involved in research, education, humanitarian work, or other activities

<sup>3</sup>Includes participants who completed the baseline questionnaire but did not complete any subsequent surveys.

<sup>4</sup>Includes participants who completed at least one survey.

Overall, there were 2905 daily symptom surveys with associated location data filled out by participants. Figure 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 (section 1)*. 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 (Table 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 amoebic dysentery. One survey reported a diagnosis (common cold) without having any symptoms or consultation. No traveller reported hospitalisation. 

- -	279	Table 2. Absolute number and incidence rate of symptoms reported by travellers using the ITIT
) :	280	app, stratified by sex and location of travel (n=3739).

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		Overall (N=3739) <sup>a</sup>		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 <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘
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

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2 3																	
4			Overall (N=3739)ª		Africa (N=699) <sup>a</sup>		Americas (N=870)ª		Asia (N=1006)ª		Europe (N=1109)ª		Oceania (N=55)ª		Female (N=2175)ª		Male (N=1564) <sup>a</sup>
5 6	Symptoms	n <sup>b</sup>	IR∘	n <sup>b</sup>	IRc	n <sup>b</sup>	IR∘	n <sup>b</sup>	IRc	n <sup>b</sup>	IR°	n <sup>b</sup>	IR∘	n <sup>b</sup>	IRc	n <sup>b</sup>	IRc
7 8 9	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
10 11 12	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
13	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
14	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
15 16 17	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
18	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
19	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
20 21 22	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
22	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
24	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
25 26	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
27	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
28 29	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
30	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
31	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
32 33	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
34 35	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
36 37	Pain in Joint	33	8,83	10	14,31	2	2,30	16	15,90	5	4,51	0	0,00	23	10,57	10	6,39
37 38 39	Swelling in Joint	10	2,67	4	5,72	1	1,15	2	1,99	3	2,71	0	0,00	8	3,68	2	1,28
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<sup>a</sup> Absolute Number of Surveys Completed

<sup>b</sup> Absolute Number of Reported Symptoms

° Incidence Rate per 1000 Completed Surveys

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 (see Table 3).

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291 292 When examining symptom categories separately, the multivariate models using MICE showed 293 different factors as being associated with symptom presence. Duration of travel, higher humidity 294 and atmospheric ammonia (NH3 µg/m<sup>3</sup>) were associated with gastrointestinal symptom presence, 295 whereas for respiratory symptoms and general symptoms, no factor was significantly associated 296 with symptom presence in the imputed model. Duration of travel, higher temperatures and 297 travelling in summer versus autumn were associated with higher incidence of dermatological 298 symptoms (Appendix 2-5). 299

Table 3: Univariate and multivariate analyses of variables influencing symptom expression using
 complete case analysis and imputed full sample analysis

			C		Imputed full sample analysis <sup>3</sup>							
	Univariate a	nalysis			Multivariate	e model <sup>2</sup>			Multivaria	te model <sup>2</sup>		
Predictors <sup>1</sup>	Odds Ratios	Lower Cl	Upper Cl	p	Odds Ratios	Lower Cl	Upper Cl	p	Odds Ratios	Lower Cl	Upper Cl	p
Survey Day	3.72	2.65	5.22	<0.001	3.10	2.13	4.51	<0.001	1.26	1.01	1.57	0.04
Age	0.44	0.33	0.59	<0.001								
Gender: Female	Reference											
Gender: Male	0.63	0.36	1.09	0.100								
Continent: Europe	Reference											
Continent: Africa	0.80	0.36	1.80	0.592								
Continent: Americas	1.78	0.84	3.76	0.134								
Continent: Asia	3.90	1.95	7.82	<0.001								
Continent: Oceania	0.56	0.04	6.99	0.650								
Travel Purpose: Leisure/Tourist Travellers	Reference											
Travel Purpose: Visiting Friends and Relatives (VFR)	0.86	0.41	1.80	0.689								
Travel Purpose: Business/Corporate Travellers	0.41	0.18	0.92	0.030								
Travel Purpose: Other	0.52	0.11	2.56	0.423								
Smoking Status: Never Smoked	Reference											
Smoking Status: Current Smoker	2.13	0.83	5.45	0.115								
Smoking Status: Former Smoker	0.78	0.28	2.15	0.633								
Chronic Health Conditions: None	Reference											
Chronic Health Conditions: Yes	0.70	0.29	1.72	0.441								

			С	omplete o	case analysis	;			Imputed full sample analysis <sup>3</sup>					
	Univariate	analysis			Multivariat	e model <sup>2</sup>		Multivariate	Multivariate model <sup>2</sup>					
Predictors <sup>1</sup>	Odds Ratios	Lower Cl	Upper Cl	p	Odds Ratios	Lower Cl	Upper Cl	p	Odds Ratios	Lower Cl	Upper Cl	р		
Clouds (%)	0.97	0.84	1.12	0.669										
Humidity (%)	1.25	1.07	1.46	0.005	1.16	0.99	1.37	0.069	1.76	1.53	2.02	<0.0		
Pressure (hPa)	1.06	0.93	1.20	0.372										
Temperature (°C)	0.97	0.81	1.15	0.690										
UV Index (UVI)	0.97	0.85	1.10	0.633										
Visibility (m)	0.97	0.86	1.09	0.579										
Wind Speed (m/s)	0.90	0.78	1.03	0.139	0.91	0.78	1.05	0.179	0.98	0.84	1.14	0.8		
Air Quality Components - CO (μg/m³)	1.02	0.91	1.14	0.691										
Air Quality Components - NH3 (µg/m³)	1.10	0.98	1.24	0.105										
Air Quality Components - NO (µg/m³)	0.98	0.87	1.11	0.733										
Air Quality Components - NO2 (µg/m³)	1.03	0.90	1.16	0.692										
Air Quality Components - O3 (µg/m³)	0.94	0.81	1.10	0.444										
Air Quality Components - PM10 (µg/m³)	1.08	0.95	1.23	0.229										
Air Quality Components - SO2 (µg/m³)	1.02	0.93	1.12	0.732										
Season: Summer	Reference	)			Reference	•			Reference					
Season: Autumn	1.33	0.73	2.41	0.347	1.27	0.66	2.45	0.468	0.93	0.49	1.75	0.8		
Season: Spring	1.25	0.75	2.10	0.390	1.63	0.92	2.88	0.096	1.26	0.73	2.18	0.4		
Season: Winter	1.85	1.09	3.14	0.023	2.79	1.51	5.13	0.001	1.51	0.85	2.69	0.2		

<sup>1</sup>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.

<sup>2</sup>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.

<sup>3</sup>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.

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308 350.3, respectively, representing a raise of 72.7, 64.3, and 60.1 from the full model cross entropy
309 of 290.2. Other symptoms such as having a runny nose and being out of breath also have an impact,
310 but to a lesser extent (Figure 2).

### 313 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'. 

With regard to possible participation bias, the target population for the ITIT project is all travellers who cross an international border and travel for 2 days or longer. Travellers do not form a homogenous group but rather encompass many types of travellers who are categorised by their purpose of travel - these include: tourists, visiting friends and relatives (VFR), migrants, business travellers, visitors to mass events/other. This paper includes all these traveller types with tourists (66%), VFR (16%) and business travellers (13%) and a small number of mass gathering visitors. The proportions of these traveller types within the ITIT cohort corresponds with other papers on travel-related illness (1,12) (tourists 51%, VFR 14%, business 11%) and (5) (tourists 63%, VFR 16.3% and business 14%). To avoid sex bias, this study evaluates data on approximately equal numbers of men and women, wide range of ages and there are also short- and long-term travellers. In ITIT we aimed to include short haul travel including travel to bordering countries in Europe. This is important as travel anywhere can be associated with infection dissemination. Our travellers were recruited mainly from travel clinics who see all the types of travellers listed above so our participants do reflect the traveling public in general. We agree with the reviewer that there may be a slight bias to recruiting persons who travel to areas or regions where pre-travel advice is indicated but we countered this with promoting the project to students and older alumni.One possible bias may be 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 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 travel medicine professionals) 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 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(16); 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 2-5) and larger numbers of travellers are needed to further elucidate these associations. Increased duration of travel increases the probability of symptom reporting (17). 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 (18). For travel consultations, this could mean that different illnesses and preventative measures should be emphasised depending on the season at the destination. Consistent with previous studies and observed in our results, older travellers exhibit fewer symptoms, likely due to their better adherence with travel health recommendations and prevention strategies (19). 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 self-treatments 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 fortravellers who were perhaps more careful about their health or more likely to report symptoms. Ongoing recruitment will focus on recruiting larger numbers and a broader range of travellers and the creation of large datasets with possible Artificial Intelligence applications.. The updated app will monitor persisting illness post-travel. The ITIT project has some major advantages compared to

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400 other travel health apps. These include, having the WHO publications uploaded to the app,
401 recruiting at many global locations outside Europe - recently extended to South Africa, Malaysia
402 and Japan. Another advantage is the fact that the app is available in fourteen languages and will
403 be available for all categories of travellers independently of travel clinics. Compared to traditional
404 surveillance systems, we suggest that ITIT captures a more accurate, granular picture of symptoms
405 experienced by the traveller, with a future potential for outbreak detection due to the real-time and
406 location-associated nature of the data when large numbers of travellers use the app.
407

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 (20-22). In a similar manner, ITIT, using self-reported 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. 

# <sup>20</sup><sub>21</sub> 414 **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. 

### <sup>31</sup> 421 CRediT author statement

32 <sup>421</sup> 33 422

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. 

### 43 429 **Declaration of interests**

46 431 All authors have completed the ICMJE uniform disclosure form

432 at <u>http://www.icmje.org/disclosure-of-interest/</u> and declare: no support from any organisation for
433 the submitted work; no financial relationships with any organisations that might have an interest
434 in the submitted work in the previous three years; no other relationships or activities that could
435 appear to have influenced the submitted work.

437 Transparency declaration

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3 4	439	The lead author affirms that this manuscript is an honest, accurate, and transparent account of the
5	440	study being reported; that no important aspects of the study have been omitted; and that any
6	441	discrepancies from the study as planned have been explained.
7	442	
8	443	Data Availability
9	444	
10	445	Restrictions apply to the availability of the data that support the findings of this study, and so are
11 12	446	not publicly available. Some data can be made available from the authors upon reasonable request
12 13	447	and with permission of Prof. Patricia Schlagenhauf.
14	448	
15	449	Ethics approval
16	450	
17	451	This study was approved by the Swiss Ethics Committee (BASEC number 2020–02292)
18	452	
19	453	Role of the Funder
20 21	454	
22	455	This study was funded by the Swiss National Science Foundation, Switzerland (grant number
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54 55	483	Hanna K. de Jong: Center for Tropical Medicine and Travel Medicine, Department of Infectious
56	484	Diseases, Amsterdam UMC, location University of Amsterdam, Amsterdam, Netherlands
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19		
20	498	Figures:
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22	499	
23	500	Figure 1. Map of daily surveys with available GPS location completed by ITIT participants,
24 25	501	including symptom category and intensity (n=2905)
23 26	502	Note: The delimitation of continents is based on the Natural Earth Data v4.1.0 (March 2018).
27	503	Points located in international waters are associated with the nearest continent.
28	504	
29	505	Figure 2: Impact of symptoms on daily activities disturbances as measured by mean cross entropy
30	506	raise after 10 permutations using a Random Forest model.
31	507	Note: The vertical line in the figure represents the cross entropy of the full model. Each row
32 33	508	displays the new cross entropy of the model when the variable of interest is removed, shown as a
34	509	boxplot with the mean cross entropy after ten permutations. The larger the increase in cross entropy
35	510	when the variable is removed, the more important that variable is to the model.
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Appendix 

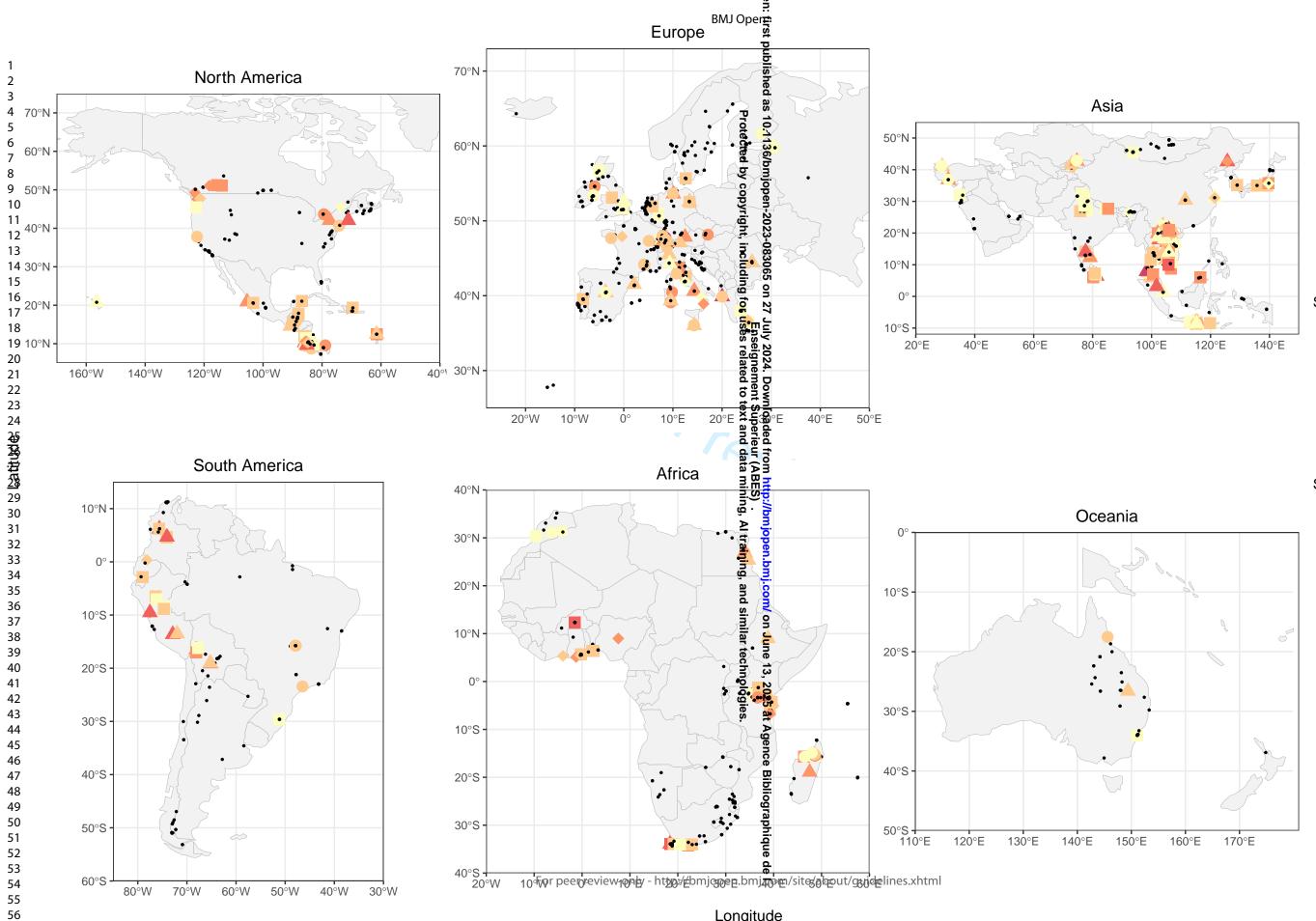
Appendix (section 1): Traveler Profile and Symptom Intensity Among Travelers Who Had a *Medical Visit During Their Trip* table 4.docx 

Appendix (section 2): Univariate and Multivariate Analyses of Variables Influencing Gastrointestinal Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis gastro any table 3.docx 

Appendix (section 3): Univariate and Multivariate Analyses of Variables Influencing Respiratory Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis respi any table 3.docx 

Appendix (section 4): Univariate and Multivariate Analyses of Variables Influencing Dermatological Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis skin any table 3.docx 

### Appendix (section 5): Univariate and Multivariate Analyses of Variables Influencing General Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis body any table 3.docx



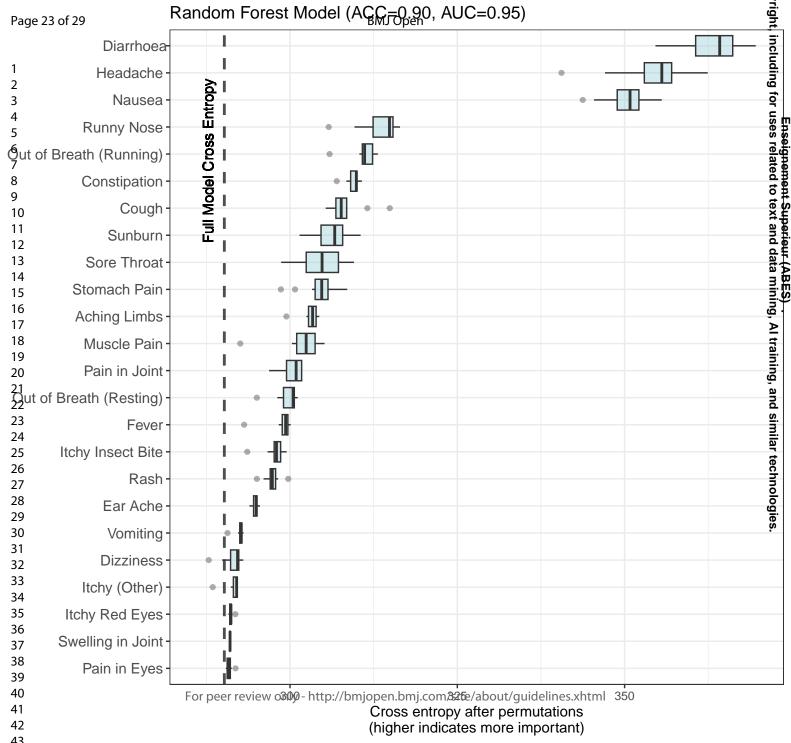
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### Symptom categories

- Gastrointestinal
- Respiratory
- General ٠
- Multiple
- No reported symptoms

### Symptom intensity

- Very Severe
- Severe
- Moderate
- Mild
- None



Appendix (section 1): Traveler Profile and Symptom Intensity Among Travelers Who Had a Medical Visit During Their Trip

	Traveller 1	Traveller 2	Traveller 3	Traveller 4
Traveller Profile				
Age	36	56	24	41
Gender	Female	Male	Male	Male
Destination	Thailand	Argentina	Thailand	Albania
Travel Purpose	Leisure/tourist travellers	Leisure/tourist travellers	Leisure/tourist travellers	Leisure/tourist travellers
Smoking Status	Not smoking	Former smoker	Not smoking	Former smoker
Health Chronic	None	Heart disease	None	High blood pressure
Day(s) into Travel	42	1	1	4
Symptoms Intensity				
Nausea	medical visit	none	medical visit	none
Vomiting	none	none	medical visit	none
Stomach Pain	none	none	medical visit	none
Diarrhea	none	none	medical visit	none
Cough	none	medical visit	none	moderate
Sore Throat	none	moderate	none	very bad
Runny Nose	none	moderate	none	medical visit
Out of Breath (Resting)	none	mild	none	bad
Out of Breath (Running)	none	moderate	none	bad
Rash	mild	none	none	none
Dizziness	moderate	none	medical visit	none
Headache	mild	none	medical visit	bad
Eye Pain	none	none	medical visit	mild
Muscle Pain	none	none	medical visit	very bad
Aching Limbs	none	none	Enedical visit	none

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### BMJ Open

Appendix (section 2): Univariate and Multivariate Analyses of Variables Influencing Gastrointestinal Symptom Exp	pression Using Complete Case Analysis and Imputed
Full Sample Analysis	

	T.T	1:-		compiete	case analysis	- 1-12			-	uted full sam	-pj	
	Univariate ana				Multivariate m				Multivariate n			
Predictors <sup>1</sup>	Odds Ratios	Lower CI	Upper CI		Odds Ratios	Lower CI	Upper CI		Odds Ratios	Lower CI		<i>p</i>
urvey Day	3.03	2.09	4.38	<0.001	3.06	1.99	4.71	<0.001	1.36	1.03	1.79	0.028
se l E l	0.69	0.47	1.01	0.053								
Gender: Female	Reference	0.00	1.04	0.164								
Gender: Male	0.59	0.28	1.24	0.164								
Continent: Europe	Reference			0.007								
Continent: Africa	4.10	1.49	11.31	0.006								
Continent: Americas	5.02	1.88	13.41	0.001								
Continent: Asia	13.25	5.33	32.95	<0.001								
ontinent: Oceania	1.37	0.05	41.32	0.856								
Travel Purpose: Leisure/Tourist Travellers	Reference											
ravel Purpose: Visiting Friends and elatives (VFR)	0.40	0.14	1.16	0.091								
Travel Purpose: Business/Corporate Travellers	0.50	0.18	1.44	0.201								
ravel Purpose: Other	0.99	0.14	6.78	0.990								
moking Status: Never Smoked	Reference											
moking Status: Current Smoker	1.78	0.51	6.24	0.366								
moking Status: Former Smoker	1.83	0.53	6.36	0.340								
hronic Health Conditions: None	Reference											
hronic Health Conditions: Yes	0.84	0.25	2.77	0.770								
Clouds (%)	1.06	0.89	1.26	0.536								
Iumidity (%)	1.19	0.97	1.46	0.101	1.12	0.91	1.39	0.279	1.65	1.38	1.96	<0.00
ressure (hPa)	1.25	0.92	1.69	0.150								
Semperature (°C)	1.17	0.93	1.46	0.170								
JV Index (UVI)	1.05	0.90	1.22	0.546								
visibility (m)	0.99	0.85	1.15	0.850								
Vind Speed (m/s)	0.93	0.78	1.11	0.412								
Air Quality Components - CO (µg/m <sup>3</sup> )	1.06	0.93	1.20	0.401								
ir Quality Components - NH3 (µg/m <sup>3</sup> )	1.18	1.04	1.34	0.011	1.17	1.03	1.34	0.016	1.25	1.10	1.43	<0.001
ir Quality Components - NO ( $\mu g/m^3$ )	0.94	0.79	1.12	0.498		BMJ						
ir Quality Components - NO2 ( $\mu$ g/m <sup>3</sup> )	1.13	0.97	1.31	0.112		Oper						
ir Quality Components - O3 (µg/m <sup>3</sup> )	0.88	0.72	1.06	0.175		n: firs						
ir Quality Components - PM10 (µg/m <sup>3</sup> )	1.16	1.01	1.35	0.042		t publ						
ir Quality Components - SO2 (µg/m <sup>3</sup> )	1.02	0.87	1.20	0.818		ished						
eason: Summer	Reference				Reference	las 10 Pro			Reference			
eason: Autumn	2.86	1.33	6.13	0.007	2.57	BMJ Open: first published as 10.1136/b	5.72	0.021	2.06	0.88	4.83	0.10
Season: Spring	1.92	0.99	3.72	0.053	1.86	ă <b>15</b> 9.9 19	3.78	0.088	1.68	0.80	3.50	0.2
Season: Winter	2.15	1.06	4.36	0.035	3.13	9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	6.74	0.004	2.10	0.95	4.65	0.069

<sup>2</sup>The optimal model was determined using a combination of 'order' and 'backward' elimination, with the Akaike Indernet in Criterion (AIC) as the selection criteria. The 'order' method orders terms by <sup>1</sup> be grinnal model was determined using a combination of 'vde' and 'backward elimination, with the Adaka Lefterminiation, with the Adaka Lefterminiation of the model, ensuing that the model converges before performing backward elimination.
<sup>1</sup> builtwards Inputation by Chained Equacions (MCE) with 15 imputations were used with linear mixed models. The 'ended' method orders terms by the account for cluster of the model.
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<sup>1</sup> builtwards Inputation by Chained Equations (MCE) with 15 imputations.
<sup>1</sup> builtwards Inputation of the model.
<sup>1</sup> builtwards Inputations Were used with more than two levels. These methods were chosen to account for cluster of the model.
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Appendix (section 3): Univariate and Multivariate Analyses of Variables Influencing Respiratory Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis

				Complete c	ase analysis				In	nputed full sam	ple analysis	3
	Univariate analysis			Multivariate model <sup>2</sup>					Multivariate model <sup>2</sup>			
Predictors <sup>1</sup>	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р
Survey Day	10.95	5.05	23.74	<0.001	9.99	3.80	26.29	<0.001	1.09	0.79	1.50	0.5
Age	0.45	0.22	0.92	0.029								
Gender: Female	Reference											
Gender: Male	0.57	0.15	2.15	0.410								
Continent: Europe	Reference											
Continent: Africa	0.16	0.02	1.71	0.131								
Continent: Americas	0.56	0.10	3.22	0.513								
Continent: Asia	0.94	0.20	4.56	0.943								
Continent: Oceania	0.52	0.00	249.52	0.835								
Travel Purpose: Leisure/Tourist Travellers	Reference											
Travel Purpose: Visiting Friends and Relatives (VFR)	1.31	0.25	6.73	0.748								
Travel Purpose: Business/Corporate Travellers	0.41	0.05	3.60	0.425								
Travel Purpose: Other	0.41	0.00	48.58	0.712								
Smoking Status: Never Smoked	Reference											
Smoking Status: Current Smoker	1.42	0.15	13.16	0.757								
Smoking Status: Former Smoker	0.64	0.06	7.23	0.717								
Chronic Health Conditions: None	Reference											
Chronic Health Conditions: Yes	0.87	0.10	7.59	0.902								
Clouds (%)	0.92	0.72	1.18	0.509								
Humidity (%)	1.79	1.31	2.45	<0.001	1.50	1.05	2.14	0.026	1.10	0.98	1.24	0.10
Pressure (hPa)	2.11	1.30	3.43	0.002	1.91	1.11	3.29	0.019	1.12	0.81	1.54	0.4
Temperature (°C)	0.66	0.47	0.92	0.015	0.78	0.50	1.21	0.266	0.97	0.84	1.13	0.7
UV Index (UVI)	0.73	0.51	1.04	0.082								
Visibility (m)	0.89	0.72	1.09	0.256								
Wind Speed (m/s)	0.84	0.65	1.10	0.203								
Air Quality Components - CO (µg/m <sup>3</sup> )	1.15	0.97	1.35	0.099								
Air Quality Components - NH3 (µg/m <sup>3</sup> )	1.16	0.96	1.41	0.117		BMJ						
Air Quality Components - NO ( $\mu g/m^3$ )	1.09	0.95	1.25	0.225		Oper						
Air Quality Components - NO2 (µg/m <sup>3</sup> )	1.07	0.88	1.30	0.496		BMJ Open: first published as 10.1136/bm Protected by						
Air Quality Components - O3 (µg/m <sup>3</sup> )	0.91	0.68	1.21	0.510		t publ						
Air Quality Components - PM10 (µg/m <sup>3</sup> )	1.20	0.98	1.47	0.077		ished						
Air Quality Components - SO2 (µg/m <sup>3</sup> )	1.06	0.94	1.19	0.346		as 10 Pro						
Season: Summer	Reference					).1136 )tecte						
Season: Autumn	0.41	0.09	1.90	0.253		s 10.1136/bmjopen-2023-0830 Protected by copyright, inclu						
Season: Spring	1.18	0.39	3.58	0.776		jopen-2023-0830 / copyright, incl						
Season: Winter	0.56	0.16	1.97	0.364		2023-						

<sup>1</sup>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.

<sup>2</sup>The optimal model was determined using a combination of 'order' and 'backward' elimination, with the Akaike In a combination (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.

<sup>3</sup>Multivariate Imputation by Chained Equations (MICE) with 15 imputations were used with linear mixed 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 rip\_id in the data.

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Appendix (section 4): Univariate and Multivariate Analyses of Variables Influencing Dermatological Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis

			(	Complete c	ase analysis				Impu	ited full sam	ple analysis <sup>5</sup>	3
	Univariate ana	llysis			Multivariate r	nodel <sup>2</sup>			Multivariate n	nodel <sup>2</sup>		
Predictors <sup>1</sup>	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р
Survey Day	3.82	2.19	6.66	<0.001	3.36	1.63	6.92	0.001	1.69	1.05	2.70	0.029
Age	0.57	0.23	1.39	0.215								
Gender: Female	Reference											
Gender: Male	0.43	0.08	2.40	0.337								
Continent: Europe	Reference											
Continent: Africa	0.43	0.02	9.03	0.585								
Continent: Americas	1.34	0.15	12.29	0.799								
Continent: Asia	4.18	0.64	27.37	0.135								
Continent: Oceania	3.23	0.01	1009.68	0.689								
Travel Purpose: Leisure/Tourist Travellers	Reference											
Travel Purpose: Visiting Friends and Relatives (VFR)	0.23	0.01	4.72	0.342								
Travel Purpose: Business/Corporate Travellers	0.11	0.00	6.89	0.296								
Travel Purpose: Other	0.75	0.01	57.62	0.896								
Smoking Status: Never Smoked	Reference											
Smoking Status: Current Smoker	1.82	0.14	24.20	0.649								
Smoking Status: Former Smoker	0.56	0.02	13.41	0.722								
Chronic Health Conditions: None	Reference											
Chronic Health Conditions: Yes	0.20	0.00	15.67	0.466								
Clouds (%)	0.93	0.69	1.24	0.606								
Humidity (%)	1.21	0.83	1.76	0.315								
Pressure (hPa)	0.96	0.60	1.54	0.873								
Temperature (°C)	1.85	1.20	2.85	0.005	1.90	1.19	3.03	0.007	1.68	1.04	2.69	0.032
UV Index (UVI)	1.01	0.74	1.40	0.936								
Visibility (m)	1.02	0.78	1.34	0.887								
Wind Speed (m/s)	1.11	0.84	1.47	0.446								
Air Quality Components - CO (µg/m <sup>3</sup> )	1.03	0.87	1.23	0.703								
Air Quality Components - NH3 (µg/m <sup>3</sup> )	0.97	0.80	1.18	0.796		BA						
Air Quality Components - NO (µg/m <sup>3</sup> )	0.96	0.74	1.25	0.764		BMJ Open: first published as 10.1136/Bm						
Air Quality Components - NO2 ( $\mu g/m^3$ )	1.06	0.86	1.30	0.576		en: fii						
Air Quality Components - O3 (µg/m <sup>3</sup> )	1.19	0.87	1.63	0.266		rst pu						
Air Quality Components - PM10 (µg/m <sup>3</sup> )	1.06	0.87	1.29	0.574		blishe						
Air Quality Components - SO2 (µg/m <sup>3</sup> )	1.03	0.91	1.17	0.638		yd as						
Season: Summer	Reference				Reference	s 10.1136/gen			Reference			
Season: Autumn	0.01	0.00	0.43	0.019	0.01	36/990 1990	0.97	0.048	0.05	0.00	0.91	0.04
Season: Spring	0.38	0.10	1.48	0.163	0.78	njogen-2023-0; w copyright ir	3.84	0.761	0.56	0.15	2.06	0.4
Season: Winter	0.30	0.07	1.31	0.110	1.55	vriat 0027	8.76	0.620	0.51	0.12	2.21	0.4

<sup>1</sup>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.

<sup>2</sup>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.

<sup>1</sup>The optimal model was determined using a combination of "orde" and "backward elimination, with the Akake Information Criterion (AIC) as the selection eriteria. The 'order' method orders terms by their contribution to the model, usaring that the model converges before performing backward elimination.
<sup>3</sup>Multivariate Inputation by Chained Equations (MICE) with 15 imputations were used with linear mixed 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 by the data. **Output Output Output**<

Appendix (section 5): Univariate and Multivariate Analyses of Variables Influencing General Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis

			C	complete ca	ise analysis				Impu	ted full sam	ple analysis <sup>3</sup>	
	Univariate analysis			Multivariate model <sup>2</sup>				Multivariate model <sup>2</sup>				
Predictors <sup>1</sup>	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р
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.
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 (°C)	0.89	0.66	1.22	0.473	0.75	0.54	1.04	0.086	0.96	0.83	1.11	0
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.
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 (µg/m <sup>3</sup> )	1.10	0.96	1.26	0.173								
Air Quality Components - NH3 (µg/m <sup>3</sup> )	1.10	0.93	1.30	0.270								
Air Quality Components - NO (µg/m³)	1.03	0.91	1.16	0.677		BMJ						
Air Quality Components - NO2 (µg/m <sup>3</sup> )	1.05	0.89	1.25	0.565		BMJ Open: first published as 10.1136/bm						
Air Quality Components - O3 (µg/m <sup>3</sup> )	1.09	0.85	1.40	0.507		: first						
Air Quality Components - PM10 (µg/m <sup>3</sup> )	1.12	0.94	1.32	0.196	1.08	<b>pub</b> .91	1.29	0.385	1.05	0.96	1.14	0.
Air Quality Components - SO2 (µg/m <sup>3</sup> )	1.02	0.93	1.12	0.719		shed						
Season: Summer	Reference				Prc	as 10						
Season: Autumn	0.59	0.17	2.01	0.399	Protected by copyright,	.1136						
Season: Spring	0.89	0.38	2.05	0.782	d by c	/bmjo						
Season: Winter	1.34	0.52	3.45	0.538	сору	jopen-2023-						

<sup>1</sup>Generalized Linear Mixed-Effects Models (GLMMs) were used to analyze our data, with trip\_id included as a random of fect to account for variations between trips.

<sup>1</sup> the optimal model was determined using a combination of 'order' and 'backward' elimination.
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	Item No	Recommendation	Don
Title and abstract	1	( <i>a</i> ) Indicate the study's design with a commonly used term in the title or the abstract	ln. 1-2
		( <i>b</i> ) Provide in the abstract an informative and balanced summary of what was done and what was found	ln. 3-11
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	ln. 168 182
Objectives	3	State specific objectives, including any prespecified hypotheses	ln. 184- 186
Methods			
Study design	4	Present key elements of study design early in the paper	ln. 198- 200
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	ln. 198- 225
Participants	6	( <i>a</i> ) Give the eligibility criteria, and the sources and methods of selection of participants	ln. 198- 208
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	ln. 227- 236
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	ln. 227- 236
Bias	9	Describe any efforts to address potential sources of bias	ln. 198- 225
Study size	10	Explain how the study size was arrived at	ln. 198- 225
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	ln. 227- 236
Statistical methods	12	( <i>a</i> ) Describe all statistical methods, including those used to control for confounding	ln. 227- 258
		(b) Describe any methods used to examine subgroups and interactions	ln. 242- 251
		(c) Explain how missing data were addressed	ln. 247- 251
		( <i>d</i> ) If applicable, describe analytical methods taking account of sampling strategy	Not Applical
		( <u>e</u> ) Describe any sensitivity analyses	Not Applical
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	ln. 265- 284
		(b) Give reasons for non-participation at each stage	ln. 227- 284

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		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical,	ln. 265-
		social) and information on exposures and potential confounders	311
		(b) Indicate number of participants with missing data for each variable	ln. 265-
		of interest	311
Outcome data	15*	Report numbers of outcome events or summary measures	ln. 316-
			344
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted	ln. 316-
		estimates and their precision (eg, 95% confidence interval). Make clear	344
		which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were	ln. 316-
		categorized	344
		(c) If relevant, consider translating estimates of relative risk into	Not
		absolute risk for a meaningful time period	Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and	ln. 316-
5		interactions, and sensitivity analyses	344
Discussion			
Key results	18	Summarise key results with reference to study objectives	ln. 349-
			361
Limitations	19	Discuss limitations of the study, taking into account sources of	ln. 431-
		potential bias or imprecision. Discuss both direction and magnitude of	449
		any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	ln. 363-
		limitations, multiplicity of analyses, results from similar studies, and	449
		other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	ln. 431-
			449
Other information			
Funding	22	Give the source of funding and the role of the funders for the present	ln. 492-
		study and, if applicable, for the original study on which the present article is based	496

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

# Surveillance of global, travel-related illness using a novel app: a multivariable, cross-sectional study

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3	1	Surveillance of global, travel-related illness using a novel app: a multivariable, cross-
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### Abstract

### **Introduction :**

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. 

### **Methods** :

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 April 2022 to July 2023. Participants >18 years of age travelled internationally and provided electronic 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 administered. Logistic mixed models examined factors relating to symptom presence, and a random forest model examined symptom impact. 

### **Results:**

- 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%). All continents were 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.

### **Conclusion:**

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.

Keywords: Travel, malaria, dengue, Travel-Related Illness, Mobile Applications

### **Trial Registration** This study was registered in the "ClinicalTrials.gov" database (identifier NCT04672577) (1)

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2 3	88	Strengths and limitations of this study
4	00	Strengths and minitations of this study
5 6	89	• Provides real-time surveillance data on travel-related illnesses through a "bottom-up"
7	90	approach.
8 9	91	• Links geolocation and environmental data with symptom reports for precise
10	92	epidemiological profiling and illness cluster identification.
11 12	93	• Utilizes a non-commercial digital tool for public health surveillance of travellers' health.
12 13	94	• To date, focuses mainly on European travellers which may influence the
14	95	representativeness of the data.
15 16	96	• The presence of missing data points could diminish the overall data quality.
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### 100 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(5). Surveillance networks that collate clinician verified data on travellers' illness such as EuroTravNet (1) or GeoSentinel (6) are limited by a lack of denominator data and also capture only a small portion of travel-related 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, guarantine 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 real-time 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 travel-related 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

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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. 

**Methods** 

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

Patient and Public Involvement

The public was involved in this study as pilot participants, giving feedback for the ITIT app, suggesting improvements and modifications, and demonstrating study feasibility(9). A feedback button on the app allows for participants to give input throughout their participation. 

Recruitment 

Participants were recruited from April 1st 2022 to July 15th 2023 through a convenience sampling approach in travel clinics in Switzerland, Berlin, Amsterdam 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 seven-point Likert scale ranging from no impact on activities to hospitalisation. The daily survey can be filled out in less than a minute. 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 

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the World Health Organization (WHO), 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 the WHO and updated in real-time. 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 Zürich, Switzerland. The climate information is fed via the weather API from OpenWeatherMap and includes data on temperature, weather, humidity, and air quality. These linked data were tied to the daily surveys and tagged with anonymised participant and trip IDs, as participants were able to take part in the study for multiple trips. 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 analyse participants' daily surveys, taking into account the clustering of data by individual trips. These models assessed the influence of various factors on the likelihood of symptom expression, both overall and within four symptom subcategories (11). Univariate analysis was conducted 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.

225 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.

13 229

# 15 230 **Results** 16

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 1). 

239	Table 1. Sociodemographic characteristics of	TITIT participants ( $n = 609$ ).
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Characteristic	<b>Overall</b> , N = 609 <sup>1</sup>	Leisure/tourist travellers, N = 401 <sup>1</sup>	Visiting friends and relatives (VFR), N = 99 <sup>1</sup>	Business/corporate travellers, N = 80 <sup>1</sup>	<b>Other</b> , N 29 <sup>2</sup>
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

Characteristic	<b>Overall</b> , N = 609 <sup>1</sup>	Leisure/tourist travellers, N = 401 <sup>1</sup>	Visiting friends and relatives (VFR), N = 99 <sup>1</sup>	Business/corporate travellers, N = 80 <sup>1</sup>	<b>Other</b> , N = 29 <sup>2</sup>
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 <sup>3</sup>					
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 <sup>4</sup>					
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%)

¹n (%)

<sup>2</sup>Includes specific groups of travellers who do not fit into the previously defined categories. These travellers attended mass gathering events such as the Hajj, Olympics, or World Cup, or were involved in research, education, humanitarian work, or other activities

<sup>3</sup>Includes participants who completed the baseline questionnaire but did not complete any subsequent surveys.

<sup>4</sup>Includes participants who completed at least one survey.

Overall, there were 2905 daily symptom surveys with associated location data filled out by participants. Figure 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 (section 1*). Some initial symptom clusters can be visually identified, including groups of symptoms around southeast Asia, and central America, as well as southern Europe. 

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

ł	279	Table 2. Absolute number and incidence rate of symptoms reported by travellers using the ITIT
) :	280	app, stratified by sex and location of travel (n=3739).

(N=3739 <i>n<sup>b</sup> L</i> 48 66,3 04 27,5	<i>IR</i> ° 66,33	Africa (N=699) <sup>a</sup> // 2 60,09 1 30,04		Americas (N=870) <sup>a</sup> <i>IR</i> <sup>c</sup> 72,41	n <sup>b</sup>	Asia (N=1006)ª <i>IR</i> °	n <sup>b</sup>	Europe (N=1109) <sup>a</sup> <i>IR</i> <sup>c</sup>	n <sup>b</sup>	Oceania (N=55)ª <i>IR</i> °	n <sup>b</sup>	Female (N=2175) <sup>a</sup> <i>IR</i> <sup>c</sup>	n <sup>b</sup>	Mal (N=1564)
48 66,3 04 <b>27</b> ,8	6,33 27,81	2 60,09 1 30,04	63				n <sup>b</sup>	IR∘	n <sup>b</sup>	IR⁰	n <sup>b</sup>	IR°	n <sup>b</sup>	IR
04 27,8	27,81	1 30,04		72,41	125									
,			21		.20	124,25	17	15,33	1	18,18	170	78,16	78	49,8
20 5,3	5,35			24,14	59	58,65	3	2,71	0	0,00	81	37,24	23	14,7
		2 2,86	7	8,05	11	10,93	0	0,00	0	0,00	11	5,06	9	5,75
43 38,2	38,25	5 35,77	41	47,13	71	70,58	5	4,51	1	18,18	95	43,68	48	30,69
97 52,6	52,69	6 51,50	57	65,52	91	90,46	13	11,72	0	0,00	127	58,39	70	44,7
43 11,5	1,50	2 2,86	4	4,60	30	29,82	7	6,31	0	0,00	31	14,25	12	7,6
18 58,3	58,30	4 34,33	30	34,48	70	69,58	92	82,96	2	36,36	141	64,83	77	49,23
58 42,2	12,26	8 25,75	20	22,99	52	51,69	66	59,51	2	36,36	95	43,68	63	40,28
14 30,4	30,49	5 7,15	12	13,79	37	36,78	60	54,10	0	0,00	81	37,24	33	21,10
64 43,8	13,86	0 28,61	24	27,59	57	56,66	61	55,00	2	36,36	99	45,52	65	41,50
58 14	4	42,26 11 30,49	42,26 18 225,75 30,49 5 7,15	42,26         18         25,75         20           30,49         5         7,15         12	42,26         18         25,75         20         22,99           30,49         5         7,15         12         13,79	42,26         18         25,75         20         22,99         52           30,49         5         7,15         12         13,79         37	42,26         18         25,75         20         22,99         52         51,69           30,49         5         7,15         12         13,79         37         36,78	42,26         18         25,75         20         22,99         52         51,69         66           30,49         5         7,15         12         13,79         37         36,78         60	42,26         18         25,75         20         22,99         52         51,69         66         59,51           30,49         5         7,15         12         13,79         37         36,78         60         54,10	42,26       18       25,75       20       22,99       52       51,69       66       59,51       2         30,49       5       7,15       12       13,79       37       36,78       60       54,10       0	42,26       18       25,75       20       22,99       52       51,69       66       59,51       2       36,36         30,49       5       7,15       12       13,79       37       36,78       60       54,10       0       0,00	42,26       18       25,75       20       22,99       52       51,69       66       59,51       2       36,36       95         30,49       5       7,15       12       13,79       37       36,78       60       54,10       0       0,00       81	42,26       18       25,75       20       22,99       52       51,69       66       59,51       2       36,36       95       43,68         30,49       5       7,15       12       13,79       37       36,78       60       54,10       0       0,000       81       37,24	42,26       18       25,75       20       22,99       52       51,69       66       59,51       2       36,36       95       43,68       63         30,49       5       7,15       12       13,79       37       36,78       60       54,10       0       0,00       81       37,24       33

2																		
3			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) <sup>a</sup>		Male (N=1564) <sup>a</sup>	
5 6	Symptoms	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR°	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	n <sup>b</sup>	IR∘	
7 8 9	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	
10 11 12	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	
13	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	
14	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	
15 16 17	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	
18	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	
19	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	
20 21	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	
22 23	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	
24	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	
25 26	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	
27	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	
28 29	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	
30	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	
31	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	
32 33	Aching												,					
34	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	
35	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	
36 37	Pain in Joint	33	8,83	10	14,31	2	2,30	16	15,90	5	4,51	0	0,00	23	10,57	10	6,39	
38 39	Swelling in Joint	10	2,67	4	5,72	1	1,15	2	1,99	3	2,71	0	0,00	8	3,68	2	1,28	
40																		

<sup>a</sup> Absolute Number of Surveys Completed

<sup>b</sup> Absolute Number of Reported Symptoms

° Incidence Rate per 1000 Completed Surveys

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 (see Table 3).

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291 292 When examining symptom categories separately, the multivariate models using MICE showed 293 different factors as being associated with symptom presence. Duration of travel, higher humidity 294 and atmospheric ammonia (NH3 µg/m<sup>3</sup>) were associated with gastrointestinal symptom presence, 295 whereas for respiratory symptoms and general symptoms, no factor was significantly associated 296 with symptom presence in the imputed model. Duration of travel, higher temperatures and 297 travelling in summer versus autumn were associated with higher incidence of dermatological 298 symptoms (Appendix 2-5). 299

Table 3: Univariate and multivariate analyses of variables influencing symptom expression using
 complete case analysis and imputed full sample analysis

			С	omplete c	ase analysis				Imputed full sample analysis <sup>3</sup>					
	Univariate a	nalysis			Multivariate	e model <sup>2</sup>			Multivaria	te model <sup>2</sup>				
Predictors <sup>1</sup>	Odds Ratios	Lower Cl	Upper Cl	p	Odds Ratios	Lower Cl	Upper Cl	p	Odds Ratios	Lower Cl	Upper Cl	p		
Survey Day	3.72	2.65	5.22	<0.001	3.10	2.13	4.51	<0.001	1.26	1.01	1.57	0.04		
Age	0.44	0.33	0.59	<0.001										
Gender: Female	Reference													
Gender: Male	0.63	0.36	1.09	0.100										
Continent: Europe	Reference													
Continent: Africa	0.80	0.36	1.80	0.592										
Continent: Americas	1.78	0.84	3.76	0.134										
Continent: Asia	3.90	1.95	7.82	<0.001										
Continent: Oceania	0.56	0.04	6.99	0.650										
Travel Purpose: Leisure/Tourist Travellers	Reference													
Travel Purpose: Visiting Friends and Relatives (VFR)	0.86	0.41	1.80	0.689										
Travel Purpose: Business/Corporate Travellers	0.41	0.18	0.92	0.030										
Travel Purpose: Other	0.52	0.11	2.56	0.423										
Smoking Status: Never Smoked	Reference													
Smoking Status: Current Smoker	2.13	0.83	5.45	0.115										
Smoking Status: Former Smoker	0.78	0.28	2.15	0.633										
Chronic Health Conditions: None	Reference													
Chronic Health Conditions: Yes	0.70	0.29	1.72	0.441										

			C	omplete o	case analysis				Impu	ted full sar	nple analy	sis <sup>3</sup>
	Univariate	analysis			Multivariat	e model <sup>2</sup>			Multivariate	e model <sup>2</sup>		
Predictors <sup>1</sup>	Odds Ratios	Lower Cl	Upper Cl	p	Odds Ratios	Lower Cl	Upper Cl	p	Odds Ratios	Lower Cl	Upper Cl	p
Clouds (%)	0.97	0.84	1.12	0.669								
Humidity (%)	1.25	1.07	1.46	0.005	1.16	0.99	1.37	0.069	1.76	1.53	2.02	<0.00
Pressure (hPa)	1.06	0.93	1.20	0.372								
Temperature (°C)	0.97	0.81	1.15	0.690								
UV Index (UVI)	0.97	0.85	1.10	0.633								
Visibility (m)	0.97	0.86	1.09	0.579								
Wind Speed (m/s)	0.90	0.78	1.03	0.139	0.91	0.78	1.05	0.179	0.98	0.84	1.14	0.8
Air Quality Components - CO (μg/m³)	1.02	0.91	1.14	0.691								
Air Quality Components - NH3 (µg/m³)	1.10	0.98	1.24	0.105								
Air Quality Components - NO (µg/m³)	0.98	0.87	1.11	0.733								
Air Quality Components - NO2 (µg/m³)	1.03	0.90	1.16	0.692								
Air Quality Components - Ο3 (μg/m³)	0.94	0.81	1.10	0.444								
Air Quality Components - PM10 (µg/m³)	1.08	0.95	1.23	0.229								
Air Quality Components - SO2 (µg/m³)	1.02	0.93	1.12	0.732								
Season: Summer	Reference	)			Reference				Reference			
Season: Autumn	1.33	0.73	2.41	0.347	1.27	0.66	2.45	0.468	0.93	0.49	1.75	0.8
Season: Spring	1.25	0.75	2.10	0.390	1.63	0.92	2.88	0.096	1.26	0.73	2.18	0.4
Season: Winter	1.85	1.09	3.14	0.023	2.79	1.51	5.13	0.001	1.51	0.85	2.69	0.2

<sup>1</sup>Generalized Linear Mixed-Effects Models (GLMMs) were used to analyse our data, with trip\_id included as a random effect to account for variations between trips.

<sup>2</sup>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.

<sup>3</sup>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.

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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 2).

#### 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 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'. 

With regard to possible participation bias, the target population for the ITIT project is all travellers who cross an international border and travel for 2 days or longer. Travellers do not form a homogenous group but rather encompass many types of travellers who are categorised by their purpose of travel - these include: tourists, visiting friends and relatives (VFR), migrants, business travellers, visitors to mass events/other. This paper includes all these traveller types with tourists (66%), VFR (16%) and business travellers (13%) and a small number of mass gathering visitors. The proportions of these traveller types within the ITIT cohort corresponds with other papers on travel-related illness (1,12) (tourists 51%, VFR 14%, business 11%) and (5) (tourists 63%, VFR 16.3% and business 14%). To avoid sex bias, this study evaluates data on approximately equal numbers of men and women, wide range of ages and there are also short- and long-term travellers. In ITIT we aimed to include short haul travel including travel to bordering countries in Europe. This is important as travel anywhere can be associated with infection dissemination. Our travellers were recruited mainly from travel clinics who see all the types of travellers listed above so our participants do reflect the traveling public in general. One possible bias may be 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 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 travel medicine professionals) 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 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 (16); however, the higher proportion of fever in women contrast with 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 2-5) and larger numbers of travellers are needed to further elucidate these associations. Increased duration of travel increases the probability of symptom reporting (17). 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 (18). For travel consultations, this could mean that different illnesses and preventative measures should be emphasised depending on the season at the destination. Consistent with previous studies and observed in our results, older travellers exhibit fewer symptoms, likely due to their better adherence with travel health recommendations and prevention strategies (19). 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 self-treatments 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 or more likely to report symptoms. Ongoing recruitment will focus on recruiting larger numbers and a broader range of travellers and the creation of large datasets with possible Artificial Intelligence applications. 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,

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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
location-associated 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 (20-22). In an analogous manner, ITIT, using self-reported 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. 

# <sup>19</sup> 412 **Conclusion** 20

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. 

# 30 419 CRediT author statement

32 420

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. 

# **Declaration of interests**

43 428 44 420

429 All authors have completed the ICMJE uniform disclosure form

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435 Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any

56 439 discrepancies from the study as planned have been explained.

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4	440 441	Data Availability
5	442	Data Availability
6	442	Restrictions apply to the availability of the data that support the findings of this study, and so are
7	444	not publicly available. Some data can be made available from the authors upon reasonable request
8 9	444	and with permission of Prof. Patricia Schlagenhauf.
10	445	and with permission of Fior. Fathera Semagennaur.
11	440 447	Ethias annual
12		Ethics approval
13	448	This study was approved by the Swigs Ethics Committee (DASEC symbol 2020, 02202)
14	449	This study was approved by the Swiss Ethics Committee (BASEC number 2020–02292)
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16 17	451	Role of the Funder
17 18	452	
19	453	This study was funded by the Swiss National Science Foundation, Switzerland (grant number
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21	455	interpretation of data, or the writing of this manuscript.
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Appendix 

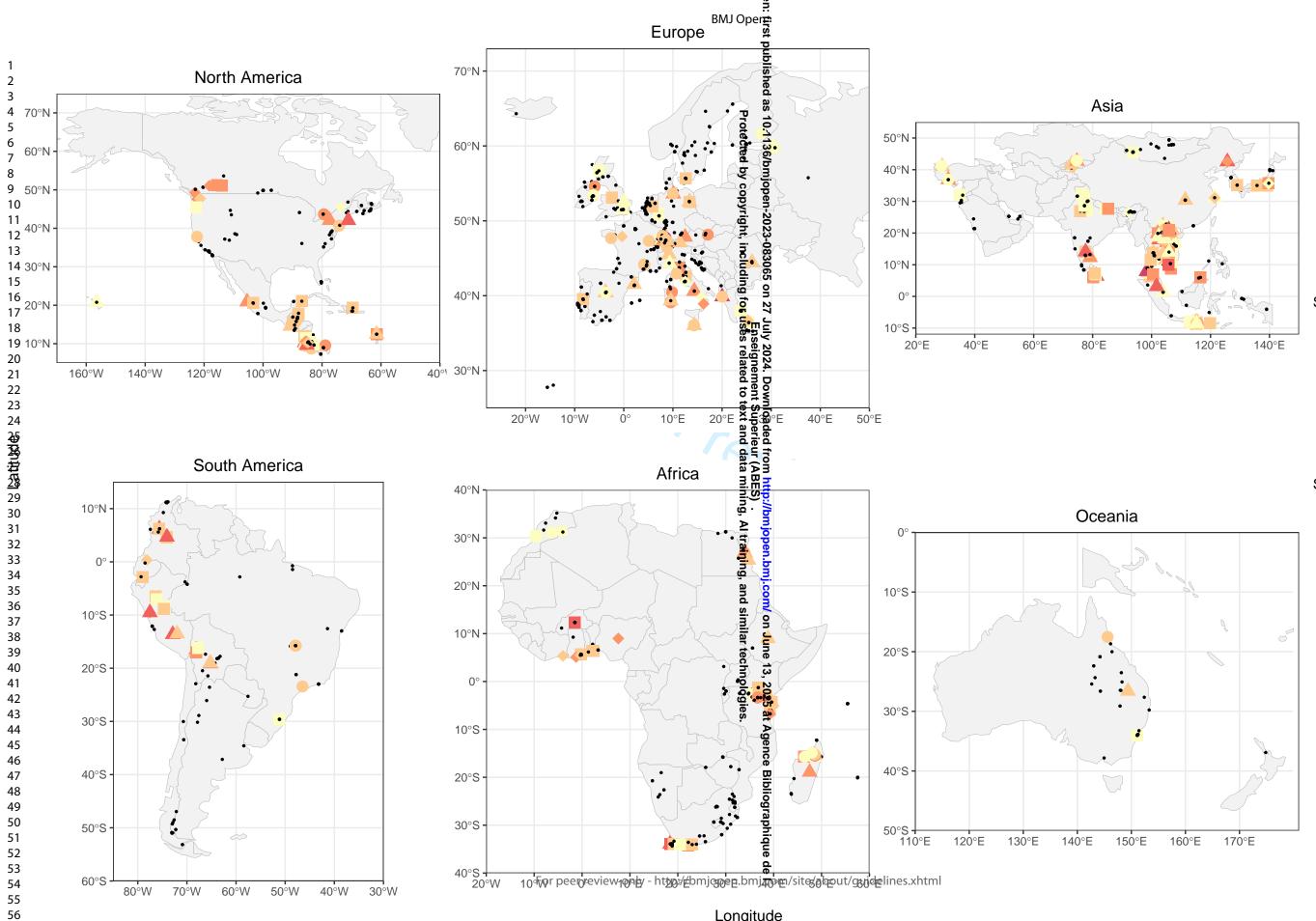
Appendix (section 1): Traveler Profile and Symptom Intensity Among Travelers Who Had a *Medical Visit During Their Trip* table 4.docx 

Appendix (section 2): Univariate and Multivariate Analyses of Variables Influencing Gastrointestinal Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis gastro any table 3.docx 

Appendix (section 3): Univariate and Multivariate Analyses of Variables Influencing Respiratory Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis respi any table 3.docx 

Appendix (section 4): Univariate and Multivariate Analyses of Variables Influencing Dermatological Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis skin any table 3.docx 

Appendix (section 5): Univariate and Multivariate Analyses of Variables Influencing General Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis body any table 3.docx 



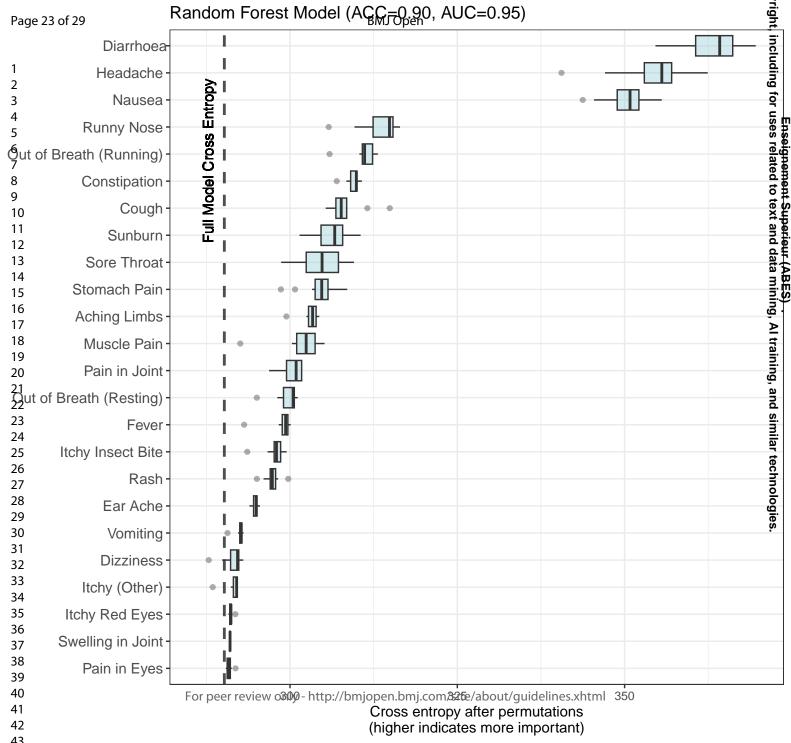
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#### Symptom categories

- Gastrointestinal
- Respiratory
- General ٠
- Multiple
- No reported symptoms

### Symptom intensity

- Very Severe
- Severe
- Moderate
- Mild
- None



Appendix (section 1): Traveler Profile and Symptom Intensity Among Travelers Who Had a Medical Visit During Their Trip

	Traveller 1	Traveller 2	Traveller 3	Traveller 4
Traveller Profile				
Age	36	56	24	41
Gender	Female	Male	Male	Male
Destination	Thailand	Argentina	Thailand	Albania
Travel Purpose	Leisure/tourist travellers	Leisure/tourist travellers	Leisure/tourist travellers	Leisure/tourist travellers
Smoking Status	Not smoking	Former smoker	Not smoking	Former smoker
Health Chronic	None	Heart disease	None	High blood pressure
Day(s) into Travel	42	1	1	4
Symptoms Intensity				
Nausea	medical visit	none	medical visit	none
Vomiting	none	none	medical visit	none
Stomach Pain	none	none	medical visit	none
Diarrhea	none	none	medical visit	none
Cough	none	medical visit	none	moderate
Sore Throat	none	moderate	none	very bad
Runny Nose	none	moderate	none	medical visit
Out of Breath (Resting)	none	mild	none	bad
Out of Breath (Running)	none	moderate	none	bad
Rash	mild	none	none	none
Dizziness	moderate	none	medical visit	none
Headache	mild	none	medical visit	bad
Eye Pain	none	none	medical visit	mild
Muscle Pain	none	none	medical visit	very bad
Aching Limbs	none	none	Enedical visit	none

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 Interview

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Appendix (section 2): Univariate and Multivariate Analyses of Variables Influencing Gastrointestinal Symptom Exp	pression Using Complete Case Analysis and Imputed
Full Sample Analysis	

	T.T	1:-		compiete	case analysis	- 1-12		<b>Imputed full sample analysis<sup>3</sup></b> Multivariate model <sup>2</sup>				
	Univariate ana				Multivariate m							
Predictors <sup>1</sup>	Odds Ratios	Lower CI	Upper CI		Odds Ratios	Lower CI	Upper CI		Odds Ratios	Lower CI		<i>p</i>
urvey Day	3.03	2.09	4.38	<0.001	3.06	1.99	4.71	<0.001	1.36	1.03	1.79	0.028
se l E l	0.69	0.47	1.01	0.053								
Gender: Female	Reference	0.00	1.04	0.164								
Gender: Male	0.59	0.28	1.24	0.164								
Continent: Europe	Reference			0.007								
Continent: Africa	4.10	1.49	11.31	0.006								
Continent: Americas	5.02	1.88	13.41	0.001								
Continent: Asia	13.25	5.33	32.95	<0.001								
ontinent: Oceania	1.37	0.05	41.32	0.856								
Travel Purpose: Leisure/Tourist Travellers	Reference											
ravel Purpose: Visiting Friends and elatives (VFR)	0.40	0.14	1.16	0.091								
Travel Purpose: Business/Corporate Travellers	0.50	0.18	1.44	0.201								
ravel Purpose: Other	0.99	0.14	6.78	0.990								
moking Status: Never Smoked	Reference											
moking Status: Current Smoker	1.78	0.51	6.24	0.366								
moking Status: Former Smoker	1.83	0.53	6.36	0.340								
hronic Health Conditions: None	Reference											
hronic Health Conditions: Yes	0.84	0.25	2.77	0.770								
Clouds (%)	1.06	0.89	1.26	0.536								
Iumidity (%)	1.19	0.97	1.46	0.101	1.12	0.91	1.39	0.279	1.65	1.38	1.96	<0.00
ressure (hPa)	1.25	0.92	1.69	0.150								
Semperature (°C)	1.17	0.93	1.46	0.170								
JV Index (UVI)	1.05	0.90	1.22	0.546								
visibility (m)	0.99	0.85	1.15	0.850								
Vind Speed (m/s)	0.93	0.78	1.11	0.412								
Air Quality Components - CO (µg/m <sup>3</sup> )	1.06	0.93	1.20	0.401								
ir Quality Components - NH3 (µg/m <sup>3</sup> )	1.18	1.04	1.34	0.011	1.17	1.03	1.34	0.016	1.25	1.10	1.43	<0.001
ir Quality Components - NO ( $\mu g/m^3$ )	0.94	0.79	1.12	0.498		BMJ						
ir Quality Components - NO2 ( $\mu$ g/m <sup>3</sup> )	1.13	0.97	1.31	0.112		Oper						
ir Quality Components - O3 (µg/m <sup>3</sup> )	0.88	0.72	1.06	0.175		n: firs						
ir Quality Components - PM10 (µg/m <sup>3</sup> )	1.16	1.01	1.35	0.042		t publ						
ir Quality Components - SO2 (µg/m <sup>3</sup> )	1.02	0.87	1.20	0.818		ished						
eason: Summer	Reference				Reference	las 10 Pro			Reference			
eason: Autumn	2.86	1.33	6.13	0.007	2.57	BMJ Open: first published as 10.1136/b	5.72	0.021	2.06	0.88	4.83	0.10
Season: Spring	1.92	0.99	3.72	0.053	1.86	ă <b>15</b> 9.9 19	3.78	0.088	1.68	0.80	3.50	0.2
Season: Winter	2.15	1.06	4.36	0.035	3.13	9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	6.74	0.004	2.10	0.95	4.65	0.069

<sup>2</sup>The optimal model was determined using a combination of 'order' and 'backward' elimination, with the Akaike Indernet in Criterion (AIC) as the selection criteria. The 'order' method orders terms by <sup>1</sup> be grinnal model was determined using a combination of 'vde' and 'backward elimination, with the Adaka Lefterminiation, with the Adaka Lefterminiation of the model, ensuing that the model converges before performing backward elimination.
<sup>1</sup> builtwards Inputation by Chained Equacions (MCE) with 15 imputations were used with linear mixed models. The 'ended' method orders terms by the account for cluster of the model.
<sup>1</sup> builtwards Inputation by Chained Equacions (MCE) with 15 imputations were used with linear mixed models. The 'ended' method orders terms by the account for cluster of the model.
<sup>1</sup> builtwards Inputation by Chained Equacions (MCE) with 15 imputations were used with linear mixed models. These methods were chosen to account for cluster of the model.
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<sup>1</sup> builtwards Inputation by Chained Equacions (MCE) with 15 imputations were used with inear mixed models. These methods were chosen to account for cluster of the model.
<sup>1</sup> builtwards Inputation by Chained Equations (MCE) with 15 imputations.
<sup>2</sup> builtwards Inputation of the model.
<sup>2</sup> builtwards Inputations Were used with more than two levels. These methods were chosen to account for cluster of the model.
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<sup>4</sup> builtwards Input termine of the model their contribution to the model, ensuring that the model converges before performing backward elimination. for 

Appendix (section 3): Univariate and Multivariate Analyses of Variables Influencing Respiratory Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis

	Complete case analysis								Imputed full sample analysis <sup>3</sup>				
Predictors <sup>1</sup>	Univariate analysis			Multivariate model <sup>2</sup>					Multivariate model <sup>2</sup>				
	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	
Survey Day	10.95	5.05	23.74	<0.001	9.99	3.80	26.29	<0.001	1.09	0.79	1.50	0.5	
Age	0.45	0.22	0.92	0.029									
Gender: Female	Reference												
Gender: Male	0.57	0.15	2.15	0.410									
Continent: Europe	Reference												
Continent: Africa	0.16	0.02	1.71	0.131									
Continent: Americas	0.56	0.10	3.22	0.513									
Continent: Asia	0.94	0.20	4.56	0.943									
Continent: Oceania	0.52	0.00	249.52	0.835									
Travel Purpose: Leisure/Tourist Travellers	Reference												
Travel Purpose: Visiting Friends and Relatives (VFR)	1.31	0.25	6.73	0.748									
Travel Purpose: Business/Corporate Travellers	0.41	0.05	3.60	0.425									
Travel Purpose: Other	0.41	0.00	48.58	0.712									
Smoking Status: Never Smoked	Reference												
Smoking Status: Current Smoker	1.42	0.15	13.16	0.757									
Smoking Status: Former Smoker	0.64	0.06	7.23	0.717									
Chronic Health Conditions: None	Reference												
Chronic Health Conditions: Yes	0.87	0.10	7.59	0.902									
Clouds (%)	0.92	0.72	1.18	0.509									
Humidity (%)	1.79	1.31	2.45	<0.001	1.50	1.05	2.14	0.026	1.10	0.98	1.24	0.10	
Pressure (hPa)	2.11	1.30	3.43	0.002	1.91	1.11	3.29	0.019	1.12	0.81	1.54	0.4	
Temperature (°C)	0.66	0.47	0.92	0.015	0.78	0.50	1.21	0.266	0.97	0.84	1.13	0.7	
UV Index (UVI)	0.73	0.51	1.04	0.082									
Visibility (m)	0.89	0.72	1.09	0.256									
Wind Speed (m/s)	0.84	0.65	1.10	0.203									
Air Quality Components - CO ( $\mu$ g/m <sup>3</sup> )	1.15	0.97	1.35	0.099									
Air Quality Components - NH3 (µg/m <sup>3</sup> )	1.16	0.96	1.41	0.117		BMJ							
Air Quality Components - NO ( $\mu g/m^3$ )	1.09	0.95	1.25	0.225		Oper							
Air Quality Components - NO2 (µg/m <sup>3</sup> )	1.07	0.88	1.30	0.496		ı: first							
Air Quality Components - O3 (µg/m <sup>3</sup> )	0.91	0.68	1.21	0.510		t publ							
Air Quality Components - PM10 (µg/m <sup>3</sup> )	1.20	0.98	1.47	0.077		ished							
Air Quality Components - SO2 (µg/m <sup>3</sup> )	1.06	0.94	1.19	0.346		BMJ Open: first published as 10.1136/bm Protected by							
Season: Summer	Reference					s 10.1136/bmjopen-2023-0830 Protected by copyright, inclu							
Season: Autumn	0.41	0.09	1.90	0.253		√bmja d by c							
Season: Spring	1.18	0.39	3.58	0.776		jopen-2023-0830 / copyright, inclu							
Season: Winter	0.56	0.16	1.97	0.364		2023: ight,							

<sup>1</sup>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.

<sup>2</sup>The optimal model was determined using a combination of 'order' and 'backward' elimination, with the Akaike In a combination (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.

<sup>3</sup>Multivariate Imputation by Chained Equations (MICE) with 15 imputations were used with linear mixed 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 rip\_id in the data.

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Appendix (section 4): Univariate and Multivariate Analyses of Variables Influencing Dermatological Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis

	Complete case analysis						Imputed full sample analysis <sup>3</sup>						
	Univariate analysis				Multivariate model <sup>2</sup>					Multivariate model <sup>2</sup>			
Predictors <sup>1</sup>	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	
Survey Day	3.82	2.19	6.66	<0.001	3.36	1.63	6.92	0.001	1.69	1.05	2.70	0.029	
Age	0.57	0.23	1.39	0.215									
Gender: Female	Reference												
Gender: Male	0.43	0.08	2.40	0.337									
Continent: Europe	Reference												
Continent: Africa	0.43	0.02	9.03	0.585									
Continent: Americas	1.34	0.15	12.29	0.799									
Continent: Asia	4.18	0.64	27.37	0.135									
Continent: Oceania	3.23	0.01	1009.68	0.689									
Travel Purpose: Leisure/Tourist Travellers	Reference												
Travel Purpose: Visiting Friends and Relatives (VFR)	0.23	0.01	4.72	0.342									
Travel Purpose: Business/Corporate Travellers	0.11	0.00	6.89	0.296									
Travel Purpose: Other	0.75	0.01	57.62	0.896									
Smoking Status: Never Smoked	Reference												
Smoking Status: Current Smoker	1.82	0.14	24.20	0.649									
Smoking Status: Former Smoker	0.56	0.02	13.41	0.722									
Chronic Health Conditions: None	Reference												
Chronic Health Conditions: Yes	0.20	0.00	15.67	0.466									
Clouds (%)	0.93	0.69	1.24	0.606									
Humidity (%)	1.21	0.83	1.76	0.315									
Pressure (hPa)	0.96	0.60	1.54	0.873									
Temperature (°C)	1.85	1.20	2.85	0.005	1.90	1.19	3.03	0.007	1.68	1.04	2.69	0.032	
UV Index (UVI)	1.01	0.74	1.40	0.936									
Visibility (m)	1.02	0.78	1.34	0.887									
Wind Speed (m/s)	1.11	0.84	1.47	0.446									
Air Quality Components - CO (µg/m <sup>3</sup> )	1.03	0.87	1.23	0.703									
Air Quality Components - NH3 (µg/m <sup>3</sup> )	0.97	0.80	1.18	0.796		B							
Air Quality Components - NO (µg/m <sup>3</sup> )	0.96	0.74	1.25	0.764		do rw							
Air Quality Components - NO2 ( $\mu g/m^3$ )	1.06	0.86	1.30	0.576		BMJ Open: first published as 10.1136/Bm							
Air Quality Components - O3 (µg/m <sup>3</sup> )	1.19	0.87	1.63	0.266		rst pu							
Air Quality Components - PM10 (µg/m <sup>3</sup> )	1.06	0.87	1.29	0.574		blish							
Air Quality Components - SO2 (µg/m <sup>3</sup> )	1.03	0.91	1.17	0.638		ed as							
Season: Summer	Reference				Reference	10.11 <sup>7</sup> rotec			Reference				
Season: Autumn	0.01	0.00	0.43	0.019	0.01	s 10.1136/gen	0.97	0.048	0.05	0.00	0.91	0.04	
Season: Spring	0.38	0.10	1.48	0.163	0.78	njogen-2023-0; w copyright ir	3.84	0.761	0.56	0.15	2.06	0.4	
Season: Winter	0.30	0.07	1.31	0.110	1.55	vria)	8.76	0.620	0.51	0.12	2.21	0.4	

<sup>1</sup>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.

<sup>2</sup>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.

<sup>1</sup>The optimal model was determined using a combination of "orde" and "backward elimination, with the Akake Information Criterion (AIC) as the selection eriteria. The 'order' method orders terms by their contribution to the model, usaring that the model converges before performing backward elimination.
<sup>3</sup>Multivariate Inputation by Chained Equations (MICE) with 15 imputations were used with linear mixed 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 by the data. **Output Output Output**<

Appendix (section 5): Univariate and Multivariate Analyses of Variables Influencing General Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis

	Complete case analysis							Imputed full sample analysis <sup>3</sup>					
	Univariate analysis			Multivariate model <sup>2</sup>				Multivariate model <sup>2</sup>					
Predictors <sup>1</sup>	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	Odds Ratios	Lower CI	Upper CI	р	
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.	
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 (°C)	0.89	0.66	1.22	0.473	0.75	0.54	1.04	0.086	0.96	0.83	1.11	0	
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.	
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 (µg/m <sup>3</sup> )	1.10	0.96	1.26	0.173									
Air Quality Components - NH3 (µg/m <sup>3</sup> )	1.10	0.93	1.30	0.270									
Air Quality Components - NO (µg/m³)	1.03	0.91	1.16	0.677		BMJ							
Air Quality Components - NO2 (µg/m <sup>3</sup> )	1.05	0.89	1.25	0.565		BMJ Open: first published as 10.1136/bm							
Air Quality Components - O3 (µg/m <sup>3</sup> )	1.09	0.85	1.40	0.507		: first							
Air Quality Components - PM10 (µg/m <sup>3</sup> )	1.12	0.94	1.32	0.196	1.08	<b>pub</b> .91	1.29	0.385	1.05	0.96	1.14	0	
Air Quality Components - SO2 (µg/m <sup>3</sup> )	1.02	0.93	1.12	0.719		shed							
Season: Summer	Reference				Prc	as 10							
Season: Autumn	0.59	0.17	2.01	0.399	Protected by copyright,	.1136							
Season: Spring	0.89	0.38	2.05	0.782	d by c	/bmjo							
Season: Winter	1.34	0.52	3.45	0.538	сору	jopen-2023-							

<sup>1</sup>Generalized Linear Mixed-Effects Models (GLMMs) were used to analyze our data, with trip\_id included as a random of fect to account for variations between trips.

<sup>1</sup> the optimal model was determined using a combination of 'order' and 'backward' elimination.
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	Item No	Recommendation						
Title and abstract	1	( <i>a</i> ) Indicate the study's design with a commonly used term in the title or the abstract	ln. 1-2					
		( <i>b</i> ) Provide in the abstract an informative and balanced summary of what was done and what was found	ln. 3-11					
Introduction								
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	ln. 168 182					
Objectives	3	State specific objectives, including any prespecified hypotheses	ln. 184- 186					
Methods								
Study design	4	Present key elements of study design early in the paper						
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	ln. 198- 225					
Participants	6	( <i>a</i> ) Give the eligibility criteria, and the sources and methods of selection of participants	ln. 198- 208					
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable						
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group						
Bias	9	Describe any efforts to address potential sources of bias						
Study size	10	Explain how the study size was arrived at						
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why						
Statistical methods	12	( <i>a</i> ) Describe all statistical methods, including those used to control for confounding	236 ln. 227- 258					
		(b) Describe any methods used to examine subgroups and interactions	ln. 242- 251					
		(c) Explain how missing data were addressed	ln. 247- 251					
		( <i>d</i> ) If applicable, describe analytical methods taking account of sampling strategy	Not Applical					
		$(\underline{e})$ Describe any sensitivity analyses	Not Applical					
Results								
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	ln. 265- 284					
		(b) Give reasons for non-participation at each stage	ln. 227- 284					

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		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical,	ln. 265-
		social) and information on exposures and potential confounders	311
		(b) Indicate number of participants with missing data for each variable	ln. 265-
		of interest	311
Outcome data	15*	Report numbers of outcome events or summary measures	ln. 316-
			344
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted	ln. 316-
		estimates and their precision (eg, 95% confidence interval). Make clear	344
		which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were	ln. 316-
		categorized	344
		(c) If relevant, consider translating estimates of relative risk into	Not
		absolute risk for a meaningful time period	Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and	ln. 316-
5		interactions, and sensitivity analyses	344
Discussion			
Key results	18	Summarise key results with reference to study objectives	ln. 349-
			361
Limitations	19	Discuss limitations of the study, taking into account sources of	ln. 431-
		potential bias or imprecision. Discuss both direction and magnitude of	449
		any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	ln. 363-
		limitations, multiplicity of analyses, results from similar studies, and	449
		other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	ln. 431-
			449
Other information			
Funding	22	Give the source of funding and the role of the funders for the present	ln. 492-
		study and, if applicable, for the original study on which the present article is based	496

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.