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

and disease outbreak news known as DONs (Daily Outbreak News) via API from WHO and updated in real-time.

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.

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	**Overall**, N = 609[1]	**Leisure/tourist travellers**, N = 401[1]	**Visiting friends and relatives (VFR)**, N = 99[1]	**Business/corporate travellers**, N = 80[1]	**Other**, N = 29[2]
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%)

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

[1]n (%)

[2]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

[3]Includes participants who completed the baseline questionnaire but did not complete any subsequent surveys.

[4]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,

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.

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**).

	Overall (N=3739)[a]		Africa (N=699)[a]		Americas (N=870)[a]		Asia (N=1006)[a]		Europe (N=1109)[a]		Oceania (N=55)[a]		Female (N=2175)[a]		Male (N=1564)[a]	
Symptoms	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]
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

	Overall (N=3739)[a]		Africa (N=699)[a]		Americas (N=870)[a]		Asia (N=1006)[a]		Europe (N=1109)[a]		Oceania (N=55)[a]		Female (N=2175)[a]		Male (N=1564)[a]	
Symptoms	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]
Out of Breath (Resting)	43	11,50	2	2,86	5	5,75	3	2,98	33	29,76	0	0,00	29	13,33	14	8,95
Out of Breath (Running)	78	20,86	6	8,58	13	14,94	15	14,91	44	39,68	0	0,00	56	25,75	22	14,07
Dermatologic	95	25,41	5	7,15	18	20,69	55	54,67	16	14,43	1	18,18	82	37,70	13	8,31
Rash	38	10,16	4	5,72	3	3,45	24	23,86	6	5,41	1	18,18	33	15,17	5	3,20
Itchy Insect Bite	64	17,12	4	5,72	14	16,09	32	31,81	13	11,72	1	18,18	54	24,83	10	6,39
Itchy (Other)	18	4,81	1	1,43	1	1,15	9	8,95	6	5,41	1	18,18	15	6,90	3	1,92
Sunburn	30	8,02	1	1,43	7	8,05	19	18,89	3	2,71	0	0,00	23	10,57	7	4,48
Itchy Red Eyes	17	4,55	0	0,00	3	3,45	8	7,95	6	5,41	0	0,00	15	6,90	2	1,28
General	158	42,26	21	30,04	35	40,23	63	62,62	39	35,17	0	0,00	115	52,87	43	27,49
Fever	49	13,11	4	5,72	10	11,49	17	16,90	18	16,23	0	0,00	33	15,17	16	10,23
Dizziness	63	16,85	4	5,72	10	11,49	30	29,82	19	17,13	0	0,00	44	20,23	19	12,15
Ear Ache	30	8,02	3	4,29	10	11,49	7	6,96	10	9,02	0	0,00	25	11,49	5	3,20
Headache	114	30,49	13	18,60	28	32,18	43	42,74	30	27,05	0	0,00	84	38,62	30	19,18
Pain in Eyes	36	9,63	6	8,58	5	5,75	14	13,92	11	9,92	0	0,00	19	8,74	17	10,87
Muscle Pain	47	12,57	5	7,15	11	12,64	16	15,90	15	13,53	0	0,00	26	11,95	21	13,43
Aching Limbs	53	14,17	5	7,15	11	12,64	23	22,86	14	12,62	0	0,00	31	14,25	22	14,07
Body (Other)	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00
Pain in 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
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

[a] Absolute Number of Surveys Completed

[b] Absolute Number of Reported Symptoms

[c] 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).

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 µg/m³) 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

	Complete case analysis								**Imputed full sample analysis[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*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**	**0.043**
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								

	Complete case analysis								Imputed full sample analysis[3]			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
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								
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**	**<0.001**
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

[1]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.

[2]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.

[3]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 http://www.icmje.org/disclosure-of-interest/ 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

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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

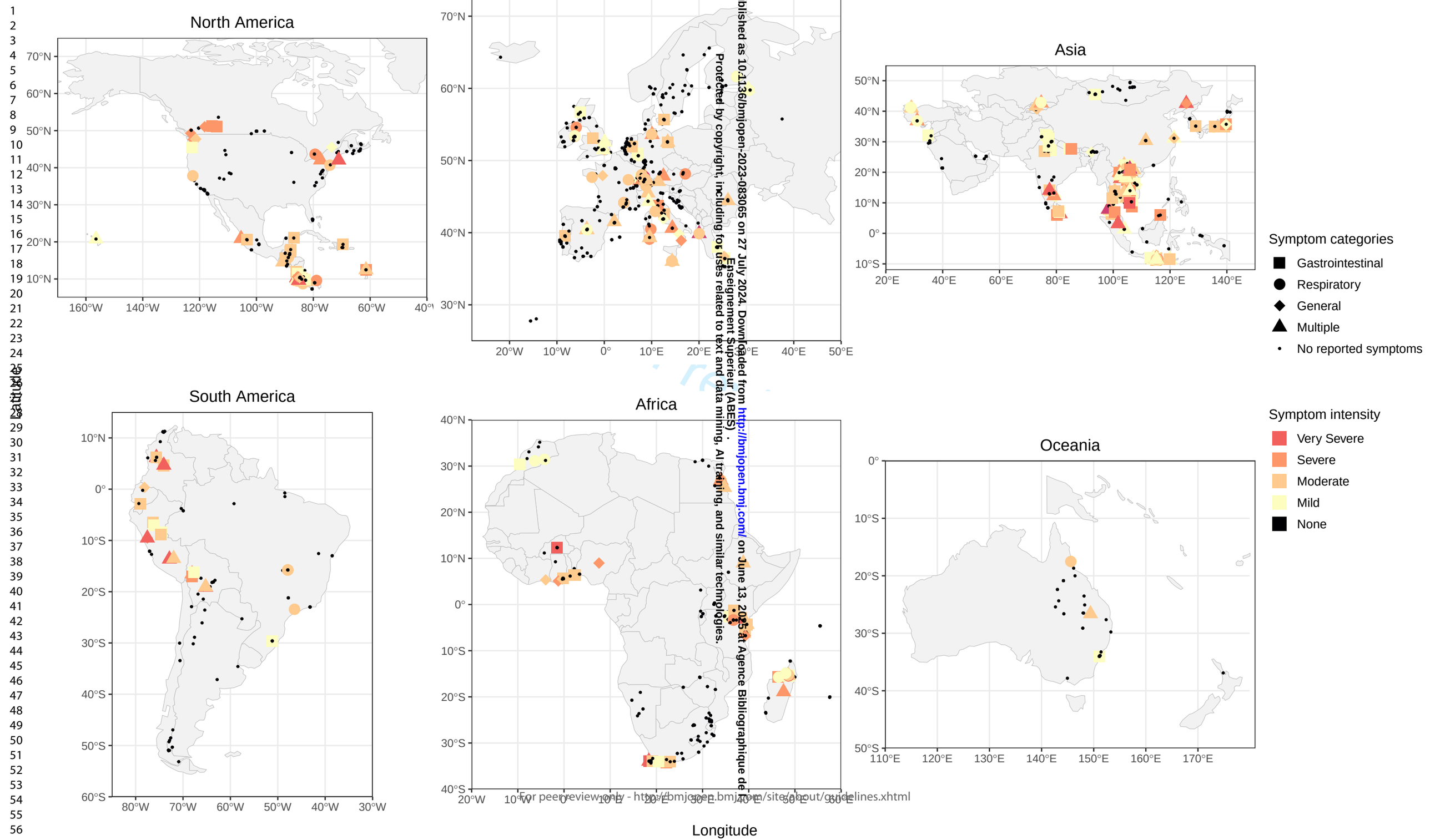
Appendix (section 1): Univariate and Multivariate Analyses of Variables Influencing Gastrointestinal Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis gastro_any_table_3.docx

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 table_4.docx



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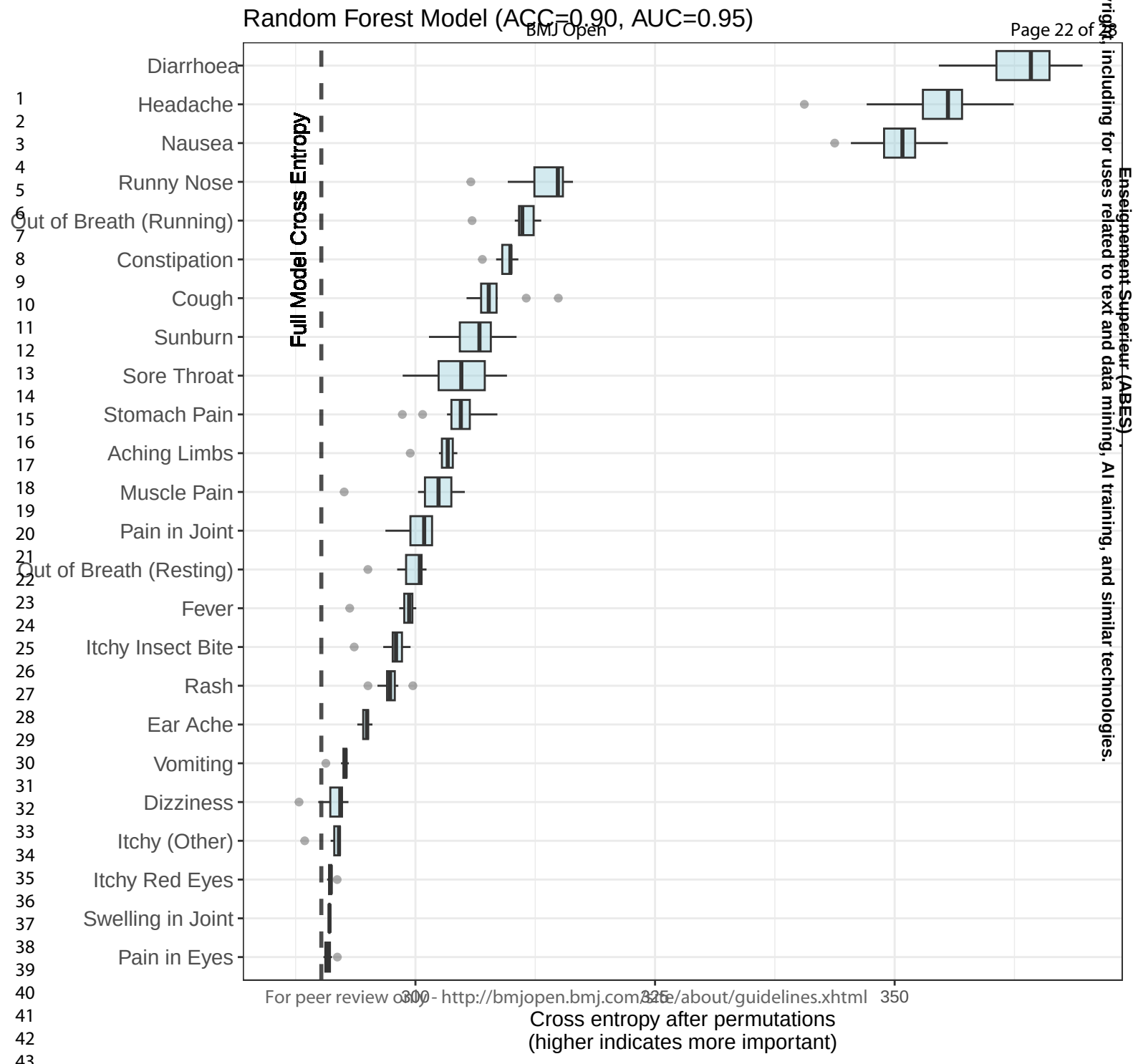

Appendix (section 1): Univariate and Multivariate Analyses of Variables Influencing Gastrointestinal Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis

	Complete case analysis								**Imputed full sample analysis[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
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								
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								
Travel Purpose: Leisure/Tourist Travellers	**Reference**											
Travel Purpose: Visiting Friends and Relatives (VFR)	0.40	0.14	1.16	0.091								
Travel Purpose: Business/Corporate Travellers	0.50	0.18	1.44	0.201								
Travel Purpose: Other	0.99	0.14	6.78	0.990								
Smoking Status: Never Smoked	**Reference**											
Smoking Status: Current Smoker	1.78	0.51	6.24	0.366								
Smoking 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								
Humidity (%)	1.19	0.97	1.46	0.101	1.12	0.91	1.39	0.279	**1.65**	**1.38**	**1.96**	**<0.001**
Pressure (hPa)	1.25	0.92	1.69	0.150								
Temperature (°C)	1.17	0.93	1.46	0.170								
UV Index (UVI)	1.05	0.90	1.22	0.546								
Visibility (m)	0.99	0.85	1.15	0.850								
Wind Speed (m/s)	0.93	0.78	1.11	0.412								
Air Quality Components - CO (µg/m³)	1.06	0.93	1.20	0.401								
Air Quality Components - NH3 (µg/m³)	**1.18**	**1.04**	**1.34**	**0.011**	**1.17**	**1.03**	**1.34**	**0.016**	**1.25**	**1.10**	**1.43**	**<0.001**
Air Quality Components - NO (µg/m³)	0.94	0.79	1.12	0.498								
Air Quality Components - NO2 (µg/m³)	1.13	0.97	1.31	0.112								
Air Quality Components - O3 (µg/m³)	0.88	0.72	1.06	0.175								
Air Quality Components - PM10 (µg/m³)	**1.16**	**1.01**	**1.35**	**0.042**								
Air Quality Components - SO2 (µg/m³)	1.02	0.87	1.20	0.818								
Season: Summer	**Reference**				**Reference**				Reference			
Season: Autumn	**2.86**	**1.33**	**6.13**	**0.007**	**2.57**	**1.15**	**5.72**	**0.021**	2.06	0.88	4.83	0.10
Season: Spring	1.92	0.99	3.72	0.053	1.86	0.91	3.78	0.088	1.68	0.80	3.50	0.2
Season: Winter	**2.15**	**1.06**	**4.36**	**0.035**	**3.13**	**1.45**	**6.74**	**0.004**	2.10	0.95	4.65	0.069

[1]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.

[2]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.

[3]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.

Appendix (section 2): 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[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
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/m³)	1.15	0.97	1.35	0.099								
Air Quality Components - NH3 (µg/m³)	1.16	0.96	1.41	0.117								
Air Quality Components - NO (µg/m³)	1.09	0.95	1.25	0.225								
Air Quality Components - NO2 (µg/m³)	1.07	0.88	1.30	0.496								
Air Quality Components - O3 (µg/m³)	0.91	0.68	1.21	0.510								
Air Quality Components - PM10 (µg/m³)	1.20	0.98	1.47	0.077								
Air Quality Components - SO2 (µg/m³)	1.06	0.94	1.19	0.346								
Season: Summer	**Reference**											
Season: Autumn	0.41	0.09	1.90	0.253								
Season: Spring	1.18	0.39	3.58	0.776								
Season: Winter	0.56	0.16	1.97	0.364								

[1]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.

[2]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.

[3]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 by trip_id in the data.

Appendix (section 3): 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[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
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/m³)	1.03	0.87	1.23	0.703								
Air Quality Components - NH3 (µg/m³)	0.97	0.80	1.18	0.796								
Air Quality Components - NO (µg/m³)	0.96	0.74	1.25	0.764								
Air Quality Components - NO2 (µg/m³)	1.06	0.86	1.30	0.576								
Air Quality Components - O3 (µg/m³)	1.19	0.87	1.63	0.266								
Air Quality Components - PM10 (µg/m³)	1.06	0.87	1.29	0.574								
Air Quality Components - SO2 (µg/m³)	1.03	0.91	1.17	0.638								
Season: Summer	**Reference**				**Reference**				Reference			
Season: Autumn	**0.01**	**0.00**	**0.43**	**0.019**	**0.01**	**0.00**	**0.97**	**0.048**	**0.05**	**0.00**	**0.91**	**0.043**
Season: Spring	0.38	0.10	1.48	0.163	0.78	0.26	3.84	0.761	0.56	0.15	2.06	0.4
Season: Winter	0.30	0.07	1.31	0.110	1.55	0.27	8.76	0.620	0.51	0.12	2.21	0.4

[1]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.

[2]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.

[3]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 at trip_id 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[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
Survey Day	**3.46**	**2.08**	**5.76**	**<0.001**	**2.51**	**1.39**	**4.52**	**0.002**	1.16	0.80	1.68	0.4
Age	**0.37**	**0.23**	**0.60**	**<0.001**								
Gender: Female	**Reference**											
Gender: Male	0.71	0.26	1.92	0.499								
Continent: Europe	**Reference**											
Continent: Africa	0.73	0.09	6.16	0.775								
Continent: Americas	1.97	0.35	11.06	0.442								
Continent: Asia	3.10	0.64	14.95	0.158								
Continent: Oceania	0.00	0.00		0.996								
Travel Purpose: Leisure/Tourist Travellers	**Reference**											
Travel Purpose: Visiting Friends and Relatives (VFR)	1.53	0.44	5.31	0.506								
Travel Purpose: Business/Corporate Travellers	0.59	0.13	2.63	0.492								
Travel Purpose: Other	1.44	0.11	18.72	0.782								
Smoking Status: Never Smoked	**Reference**											
Smoking Status: Current Smoker	3.15	0.67	14.87	0.146								
Smoking Status: Former Smoker	0.56	0.09	3.64	0.545								
Chronic Health Conditions: None	**Reference**											
Chronic Health Conditions: Yes	0.59	0.11	3.20	0.543								
Clouds (%)	1.07	0.85	1.35	0.573								
Humidity (%)	1.03	0.79	1.34	0.823								
Pressure (hPa)	1.00	0.85	1.16	0.956								
Temperature (°C)	0.89	0.66	1.22	0.473	0.75	0.54	1.04	0.086	0.96	0.83	1.11	0.6
UV Index (UVI)	1.17	0.95	1.43	0.144	1.23	0.99	1.52	0.058	1.03	0.91	1.16	0.7
Visibility (m)	1.01	0.81	1.27	0.898								
Wind Speed (m/s)	0.94	0.74	1.20	0.619								
Air Quality Components - CO (µg/m³)	1.10	0.96	1.26	0.173								
Air Quality Components - NH3 (µg/m³)	1.10	0.93	1.30	0.270								
Air Quality Components - NO (µg/m³)	1.03	0.91	1.16	0.677								
Air Quality Components - NO2 (µg/m³)	1.05	0.89	1.25	0.565								
Air Quality Components - O3 (µg/m³)	1.09	0.85	1.40	0.507								
Air Quality Components - PM10 (µg/m³)	1.12	0.94	1.32	0.196	1.08	0.91	1.29	0.385	1.05	0.96	1.14	0.3
Air Quality Components - SO2 (µg/m³)	1.02	0.93	1.12	0.719								
Season: Summer	**Reference**											
Season: Autumn	0.59	0.17	2.01	0.399								
Season: Spring	0.89	0.38	2.05	0.782								
Season: Winter	1.34	0.52	3.45	0.538								

[1]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.

[2]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.

[3]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 by trip_id in the data.

Appendix (section 5): 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	medical visit	none

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Done
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	X
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	x
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	x
Objectives	3	State specific objectives, including any prespecified hypotheses	x
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 recruitment, exposure, follow-up, and data collection	x
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	x
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	x
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	*x*
Bias	9	Describe any efforts to address potential sources of bias	x
Study size	10	Explain how the study size was arrived at	x
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	x
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	x
		(*b*) Describe any methods used to examine subgroups and interactions	x
		(*c*) Explain how missing data were addressed	x
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	na
		(*e*) Describe any sensitivity analyses	na
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	x
		(b) Give reasons for non-participation at each stage	x
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	x
		(b) Indicate number of participants with missing data for each variable of interest	x
Outcome data	15*	Report numbers of outcome events or summary measures	x
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	x

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

*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.

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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, cross-sectional 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 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.

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

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

Strengths and limitations of this study

- Provides real-time surveillance data on travel-related illnesses through a "bottom-up" approach.
- Links geolocation and environmental data with symptom reports for precise epidemiological profiling and illness cluster identification.
- Non-commercial, public health surveillance of travellers' health
- To date,focuses mainly on European travellers which may influence the representativeness of the data.
- The presence of missing data points could diminish the overall data quality.

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, quarantine protocols, and vaccination campaigns promptly, curbing the progression of diseases. Secondly, travellers' self-reports can provide valuable insights into environmental exposures, regional risk factors, and potential disease hotspots, aiding in targeted preventive strategies to protect vulnerable populations. Lastly, the system fosters a sense of shared responsibility among travellers in safeguarding public health.

The widespread adoption of smartphones and digital platforms presents an unprecedented opportunity to implement a bottom-up, self-reported, illness tracking system. By encouraging travellers to report their symptoms and health conditions in 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

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, 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 (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

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 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 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.

Role of the funding source

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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	Overall, N = 609[1]	Leisure/tourist travellers, N = 401[1]	Visiting friends and relatives (VFR), N = 99[1]	Business/corporate travellers, N = 80[1]	Other, N = 29[2]
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					

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

[1]n (%)

[2]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

[3]Includes participants who completed the baseline questionnaire but did not complete any subsequent surveys.

[4]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.

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**).

	Overall (N=3739)[a]		Africa (N=699)[a]		Americas (N=870)[a]		Asia (N=1006)[a]		Europe (N=1109)[a]		Oceania (N=55)[a]		Female (N=2175)[a]		Male (N=1564)[a]	
Symptoms	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]
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

	Overall (N=3739)[a]		Africa (N=699)[a]		Americas (N=870)[a]		Asia (N=1006)[a]		Europe (N=1109)[a]		Oceania (N=55)[a]		Female (N=2175)[a]		Male (N=1564)[a]	
Symptoms	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]
Out of Breath (Resting)	43	11,50	2	2,86	5	5,75	3	2,98	33	29,76	0	0,00	29	13,33	14	8,95
Out of Breath (Running)	78	20,86	6	8,58	13	14,94	15	14,91	44	39,68	0	0,00	56	25,75	22	14,07
Dermatologic	95	25,41	5	7,15	18	20,69	55	54,67	16	14,43	1	18,18	82	37,70	13	8,31
Rash	38	10,16	4	5,72	3	3,45	24	23,86	6	5,41	1	18,18	33	15,17	5	3,20
Itchy Insect Bite	64	17,12	4	5,72	14	16,09	32	31,81	13	11,72	1	18,18	54	24,83	10	6,39
Itchy (Other)	18	4,81	1	1,43	1	1,15	9	8,95	6	5,41	1	18,18	15	6,90	3	1,92
Sunburn	30	8,02	1	1,43	7	8,05	19	18,89	3	2,71	0	0,00	23	10,57	7	4,48
Itchy Red Eyes	17	4,55	0	0,00	3	3,45	8	7,95	6	5,41	0	0,00	15	6,90	2	1,28
General	158	42,26	21	30,04	35	40,23	63	62,62	39	35,17	0	0,00	115	52,87	43	27,49
Fever	49	13,11	4	5,72	10	11,49	17	16,90	18	16,23	0	0,00	33	15,17	16	10,23
Dizziness	63	16,85	4	5,72	10	11,49	30	29,82	19	17,13	0	0,00	44	20,23	19	12,15
Ear Ache	30	8,02	3	4,29	10	11,49	7	6,96	10	9,02	0	0,00	25	11,49	5	3,20
Headache	114	30,49	13	18,60	28	32,18	43	42,74	30	27,05	0	0,00	84	38,62	30	19,18
Pain in Eyes	36	9,63	6	8,58	5	5,75	14	13,92	11	9,92	0	0,00	19	8,74	17	10,87
Muscle Pain	47	12,57	5	7,15	11	12,64	16	15,90	15	13,53	0	0,00	26	11,95	21	13,43
Aching Limbs	53	14,17	5	7,15	11	12,64	23	22,86	14	12,62	0	0,00	31	14,25	22	14,07
Body (Other)	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00
Pain in 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
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

[a] Absolute Number of Surveys Completed

[b] Absolute Number of Reported Symptoms

[c] 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).

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 µg/m³) 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 2-5).

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

	Complete case analysis								**Imputed full sample analysis[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*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**	**0.043**
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								

	Complete case analysis								Imputed full sample analysis[3]			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*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**	**<0.001**
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

[1]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.

[2]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.

[3]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(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

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 (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.

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 http://www.icmje.org/disclosure-of-interest/ 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.

Ethics approval

This study was approved by the Swiss Ethics Committee (BASEC number 2020–02292)

Role of the Funder

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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

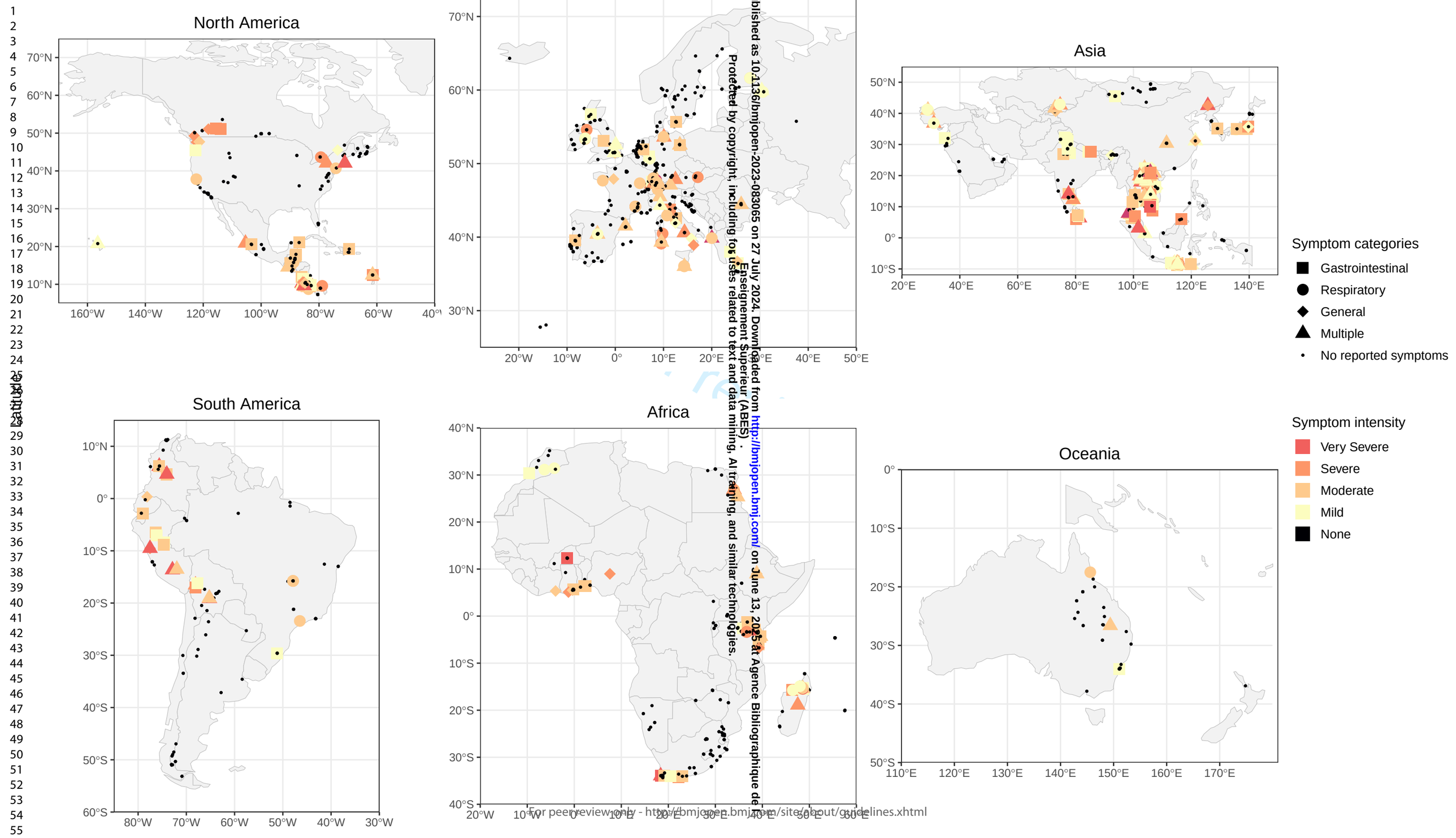
Appendix (section 1): Traveler Profile and Symptom Intensity Among Travelers Who Had a Medical Visit During Their Trip table_4.docx

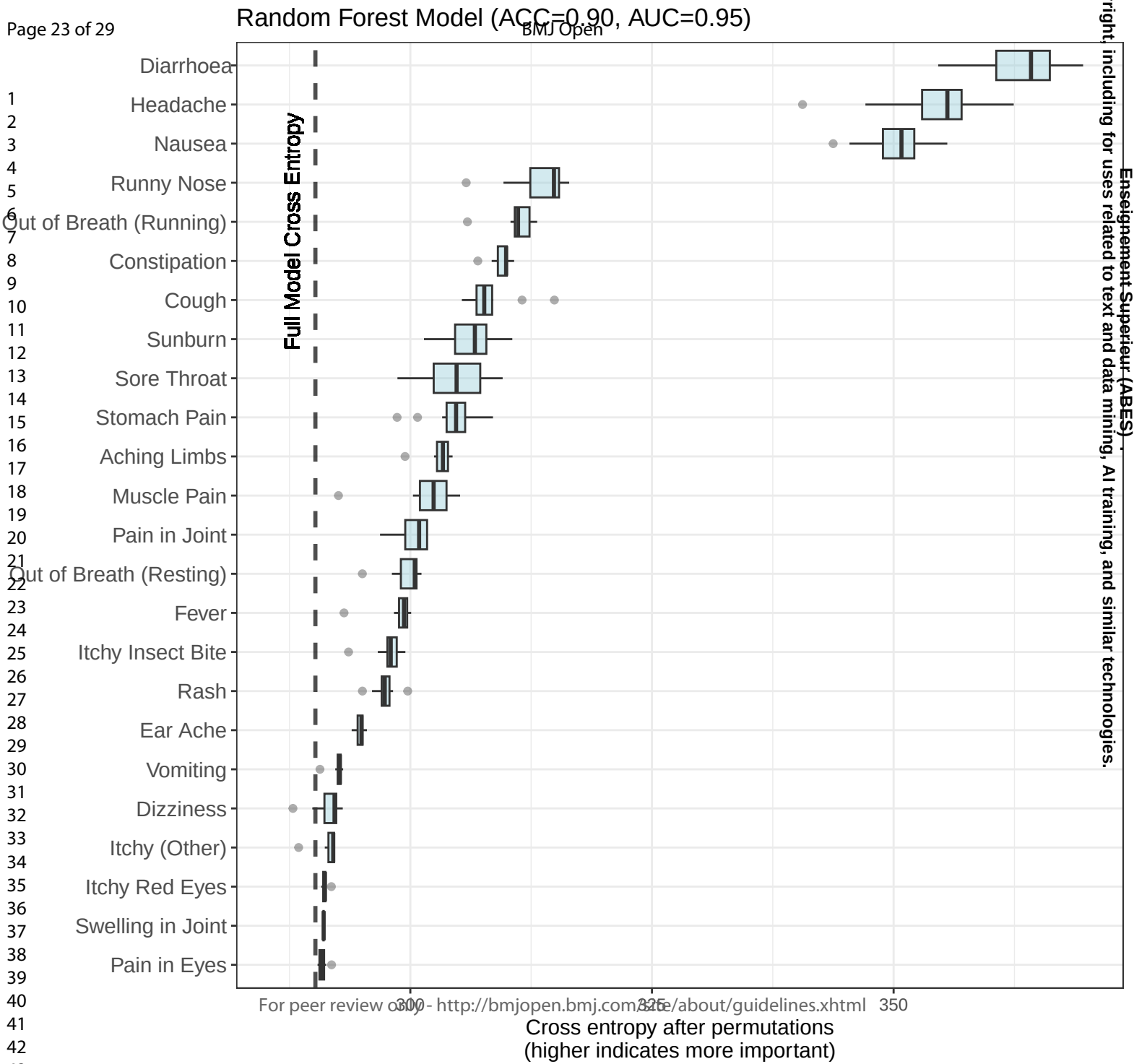
Appendix (section 2): Univariate and Multivariate Analyses of Variables Influencing Gastrointestinal Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis gastro_any_table_3.docx

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





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	medical visit	none

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

	Complete case analysis								**Imputed full sample analysis[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
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								
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								
Travel Purpose: Leisure/Tourist Travellers	**Reference**											
Travel Purpose: Visiting Friends and Relatives (VFR)	0.40	0.14	1.16	0.091								
Travel Purpose: Business/Corporate Travellers	0.50	0.18	1.44	0.201								
Travel Purpose: Other	0.99	0.14	6.78	0.990								
Smoking Status: Never Smoked	**Reference**											
Smoking Status: Current Smoker	1.78	0.51	6.24	0.366								
Smoking 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								
Humidity (%)	1.19	0.97	1.46	0.101	1.12	0.91	1.39	0.279	**1.65**	**1.38**	**1.96**	**<0.001**
Pressure (hPa)	1.25	0.92	1.69	0.150								
Temperature (°C)	1.17	0.93	1.46	0.170								
UV Index (UVI)	1.05	0.90	1.22	0.546								
Visibility (m)	0.99	0.85	1.15	0.850								
Wind Speed (m/s)	0.93	0.78	1.11	0.412								
Air Quality Components - CO (µg/m³)	1.06	0.93	1.20	0.401								
Air Quality Components - NH3 (µg/m³)	**1.18**	**1.04**	**1.34**	**0.011**	**1.17**	**1.03**	**1.34**	**0.016**	**1.25**	**1.10**	**1.43**	**<0.001**
Air Quality Components - NO (µg/m³)	0.94	0.79	1.12	0.498								
Air Quality Components - NO2 (µg/m³)	1.13	0.97	1.31	0.112								
Air Quality Components - O3 (µg/m³)	0.88	0.72	1.06	0.175								
Air Quality Components - PM10 (µg/m³)	**1.16**	**1.01**	**1.35**	**0.042**								
Air Quality Components - SO2 (µg/m³)	1.02	0.87	1.20	0.818								
Season: Summer	**Reference**				**Reference**				Reference			
Season: Autumn	**2.86**	**1.33**	**6.13**	**0.007**	**2.57**	**1.15**	**5.72**	**0.021**	2.06	0.88	4.83	0.10
Season: Spring	1.92	0.99	3.72	0.053	1.86	0.91	3.78	0.088	1.68	0.80	3.50	0.2
Season: Winter	**2.15**	**1.06**	**4.36**	**0.035**	**3.13**	**1.45**	**6.74**	**0.004**	2.10	0.95	4.65	0.069

[1]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.

[2]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.

[3]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.

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[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
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/m³)	1.15	0.97	1.35	0.099								
Air Quality Components - NH3 (µg/m³)	1.16	0.96	1.41	0.117								
Air Quality Components - NO (µg/m³)	1.09	0.95	1.25	0.225								
Air Quality Components - NO2 (µg/m³)	1.07	0.88	1.30	0.496								
Air Quality Components - O3 (µg/m³)	0.91	0.68	1.21	0.510								
Air Quality Components - PM10 (µg/m³)	1.20	0.98	1.47	0.077								
Air Quality Components - SO2 (µg/m³)	1.06	0.94	1.19	0.346								
Season: Summer	**Reference**											
Season: Autumn	0.41	0.09	1.90	0.253								
Season: Spring	1.18	0.39	3.58	0.776								
Season: Winter	0.56	0.16	1.97	0.364								

[1]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.

[2]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.

[3]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 by trip_id in the data.

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[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
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/m³)	1.03	0.87	1.23	0.703								
Air Quality Components - NH3 (µg/m³)	0.97	0.80	1.18	0.796								
Air Quality Components - NO (µg/m³)	0.96	0.74	1.25	0.764								
Air Quality Components - NO2 (µg/m³)	1.06	0.86	1.30	0.576								
Air Quality Components - O3 (µg/m³)	1.19	0.87	1.63	0.266								
Air Quality Components - PM10 (µg/m³)	1.06	0.87	1.29	0.574								
Air Quality Components - SO2 (µg/m³)	1.03	0.91	1.17	0.638								
Season: Summer	**Reference**				**Reference**				Reference			
Season: Autumn	**0.01**	**0.00**	**0.43**	**0.019**	**0.01**	**0.00**	**0.97**	**0.048**	**0.05**	**0.00**	**0.91**	**0.043**
Season: Spring	0.38	0.10	1.48	0.163	0.78	0.16	3.84	0.761	0.56	0.15	2.06	0.4
Season: Winter	0.30	0.07	1.31	0.110	1.55	0.27	8.76	0.620	0.51	0.12	2.21	0.4

[1]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.

[2]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.

[3]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 at trip_id in the data.

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[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
Survey Day	**3.46**	**2.08**	**5.76**	**<0.001**	**2.51**	**1.39**	**4.52**	**0.002**	1.16	0.80	1.68	0.4
Age	**0.37**	**0.23**	**0.60**	**<0.001**								
Gender: Female	**Reference**											
Gender: Male	0.71	0.26	1.92	0.499								
Continent: Europe	**Reference**											
Continent: Africa	0.73	0.09	6.16	0.775								
Continent: Americas	1.97	0.35	11.06	0.442								
Continent: Asia	3.10	0.64	14.95	0.158								
Continent: Oceania	0.00	0.00		0.996								
Travel Purpose: Leisure/Tourist Travellers	**Reference**											
Travel Purpose: Visiting Friends and Relatives (VFR)	1.53	0.44	5.31	0.506								
Travel Purpose: Business/Corporate Travellers	0.59	0.13	2.63	0.492								
Travel Purpose: Other	1.44	0.11	18.72	0.782								
Smoking Status: Never Smoked	**Reference**											
Smoking Status: Current Smoker	3.15	0.67	14.87	0.146								
Smoking Status: Former Smoker	0.56	0.09	3.64	0.545								
Chronic Health Conditions: None	**Reference**											
Chronic Health Conditions: Yes	0.59	0.11	3.20	0.543								
Clouds (%)	1.07	0.85	1.35	0.573								
Humidity (%)	1.03	0.79	1.34	0.823								
Pressure (hPa)	1.00	0.85	1.16	0.956								
Temperature (°C)	0.89	0.66	1.22	0.473	0.75	0.54	1.04	0.086	0.96	0.83	1.11	0.6
UV Index (UVI)	1.17	0.95	1.43	0.144	1.23	0.99	1.52	0.058	1.03	0.91	1.16	0.7
Visibility (m)	1.01	0.81	1.27	0.898								
Wind Speed (m/s)	0.94	0.74	1.20	0.619								
Air Quality Components - CO (µg/m³)	1.10	0.96	1.26	0.173								
Air Quality Components - NH3 (µg/m³)	1.10	0.93	1.30	0.270								
Air Quality Components - NO (µg/m³)	1.03	0.91	1.16	0.677								
Air Quality Components - NO2 (µg/m³)	1.05	0.89	1.25	0.565								
Air Quality Components - O3 (µg/m³)	1.09	0.85	1.40	0.507								
Air Quality Components - PM10 (µg/m³)	1.12	0.94	1.32	0.196	1.08	0.91	1.29	0.385	1.05	0.96	1.14	0.3
Air Quality Components - SO2 (µg/m³)	1.02	0.93	1.12	0.719								
Season: Summer	**Reference**											
Season: Autumn	0.59	0.17	2.01	0.399								
Season: Spring	0.89	0.38	2.05	0.782								
Season: Winter	1.34	0.52	3.45	0.538								

[1]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.

[2]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.

[3]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 by trip_id in the data.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Done
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	ln. 1-2
		(*b*) 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	(*a*) 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	(*a*) 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
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not Applicable
		(*e*) Describe any sensitivity analyses	Not Applicable
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

		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	ln. 265-311
		(b) Indicate number of participants with missing data for each variable of interest	ln. 265-311
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 estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	ln. 316-344
		(*b*) Report category boundaries when continuous variables were categorized	ln. 316-344
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	ln. 316-344
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 potential bias or imprecision. Discuss both direction and magnitude of any potential bias	ln. 431-449
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	ln. 363-449
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 study and, if applicable, for the original study on which the present article is based	ln. 492-496

*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.

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

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

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

Strengths and limitations of this study

- Provides real-time surveillance data on travel-related illnesses through a "bottom-up" approach.
- Links geolocation and environmental data with symptom reports for precise epidemiological profiling and illness cluster identification.
- Utilizes a non-commercial digital tool for public health surveillance of travellers' health.
- To date, focuses mainly on European travellers which may influence the representativeness of the data.
- The presence of missing data points could diminish the overall data quality.

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, quarantine protocols, and vaccination campaigns promptly, curbing the progression of diseases. Secondly, travellers' self-reports can provide valuable insights into environmental exposures, regional risk factors, and potential disease hotspots, aiding in targeted preventive strategies to protect vulnerable populations. Lastly, the system fosters a sense of shared responsibility among travellers in safeguarding public health.

The widespread adoption of smartphones and digital platforms presents an unprecedented opportunity to implement a bottom-up, self-reported, illness tracking system. By encouraging travellers to report their symptoms and health conditions in 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

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, 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 (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

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.

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	Overall, N = 609[1]	Leisure/tourist travellers, N = 401[1]	Visiting friends and relatives (VFR), N = 99[1]	Business/corporate travellers, N = 80[1]	Other, N = 29[2]
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					

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

[1]n (%)

[2]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

[3]Includes participants who completed the baseline questionnaire but did not complete any subsequent surveys.

[4]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.

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.

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**).

	Overall (N=3739)[a]		Africa (N=699)[a]		Americas (N=870)[a]		Asia (N=1006)[a]		Europe (N=1109)[a]		Oceania (N=55)[a]		Female (N=2175)[a]		Male (N=1564)[a]	
Symptoms	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]
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

	Overall (N=3739)[a]		Africa (N=699)[a]		Americas (N=870)[a]		Asia (N=1006)[a]		Europe (N=1109)[a]		Oceania (N=55)[a]		Female (N=2175)[a]		Male (N=1564)[a]	
Symptoms	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]	*n*[b]	*IR*[c]
Out of Breath (Resting)	43	11,50	2	2,86	5	5,75	3	2,98	33	29,76	0	0,00	29	13,33	14	8,95
Out of Breath (Running)	78	20,86	6	8,58	13	14,94	15	14,91	44	39,68	0	0,00	56	25,75	22	14,07
Dermatologic	95	25,41	5	7,15	18	20,69	55	54,67	16	14,43	1	18,18	82	37,70	13	8,31
Rash	38	10,16	4	5,72	3	3,45	24	23,86	6	5,41	1	18,18	33	15,17	5	3,20
Itchy Insect Bite	64	17,12	4	5,72	14	16,09	32	31,81	13	11,72	1	18,18	54	24,83	10	6,39
Itchy (Other)	18	4,81	1	1,43	1	1,15	9	8,95	6	5,41	1	18,18	15	6,90	3	1,92
Sunburn	30	8,02	1	1,43	7	8,05	19	18,89	3	2,71	0	0,00	23	10,57	7	4,48
Itchy Red Eyes	17	4,55	0	0,00	3	3,45	8	7,95	6	5,41	0	0,00	15	6,90	2	1,28
General	158	42,26	21	30,04	35	40,23	63	62,62	39	35,17	0	0,00	115	52,87	43	27,49
Fever	49	13,11	4	5,72	10	11,49	17	16,90	18	16,23	0	0,00	33	15,17	16	10,23
Dizziness	63	16,85	4	5,72	10	11,49	30	29,82	19	17,13	0	0,00	44	20,23	19	12,15
Ear Ache	30	8,02	3	4,29	10	11,49	7	6,96	10	9,02	0	0,00	25	11,49	5	3,20
Headache	114	30,49	13	18,60	28	32,18	43	42,74	30	27,05	0	0,00	84	38,62	30	19,18
Pain in Eyes	36	9,63	6	8,58	5	5,75	14	13,92	11	9,92	0	0,00	19	8,74	17	10,87
Muscle Pain	47	12,57	5	7,15	11	12,64	16	15,90	15	13,53	0	0,00	26	11,95	21	13,43
Aching Limbs	53	14,17	5	7,15	11	12,64	23	22,86	14	12,62	0	0,00	31	14,25	22	14,07
Body (Other)	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00
Pain in 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
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

[a] Absolute Number of Surveys Completed

[b] Absolute Number of Reported Symptoms

[c] 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).

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 µg/m³) 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 2-5).

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

	Complete case analysis								**Imputed full sample analysis[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*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**	**0.043**
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								

	Complete case analysis								Imputed full sample analysis[3]			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*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**	**<0.001**
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

[1]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.

[2]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.

[3]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 (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,

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.

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 http://www.icmje.org/disclosure-of-interest/ 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.

Ethics approval

This study was approved by the Swiss Ethics Committee (BASEC number 2020–02292)

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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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, prospective, cohort study. New Microbes New Infect. 2022 Mar;46:100967.

Appendix

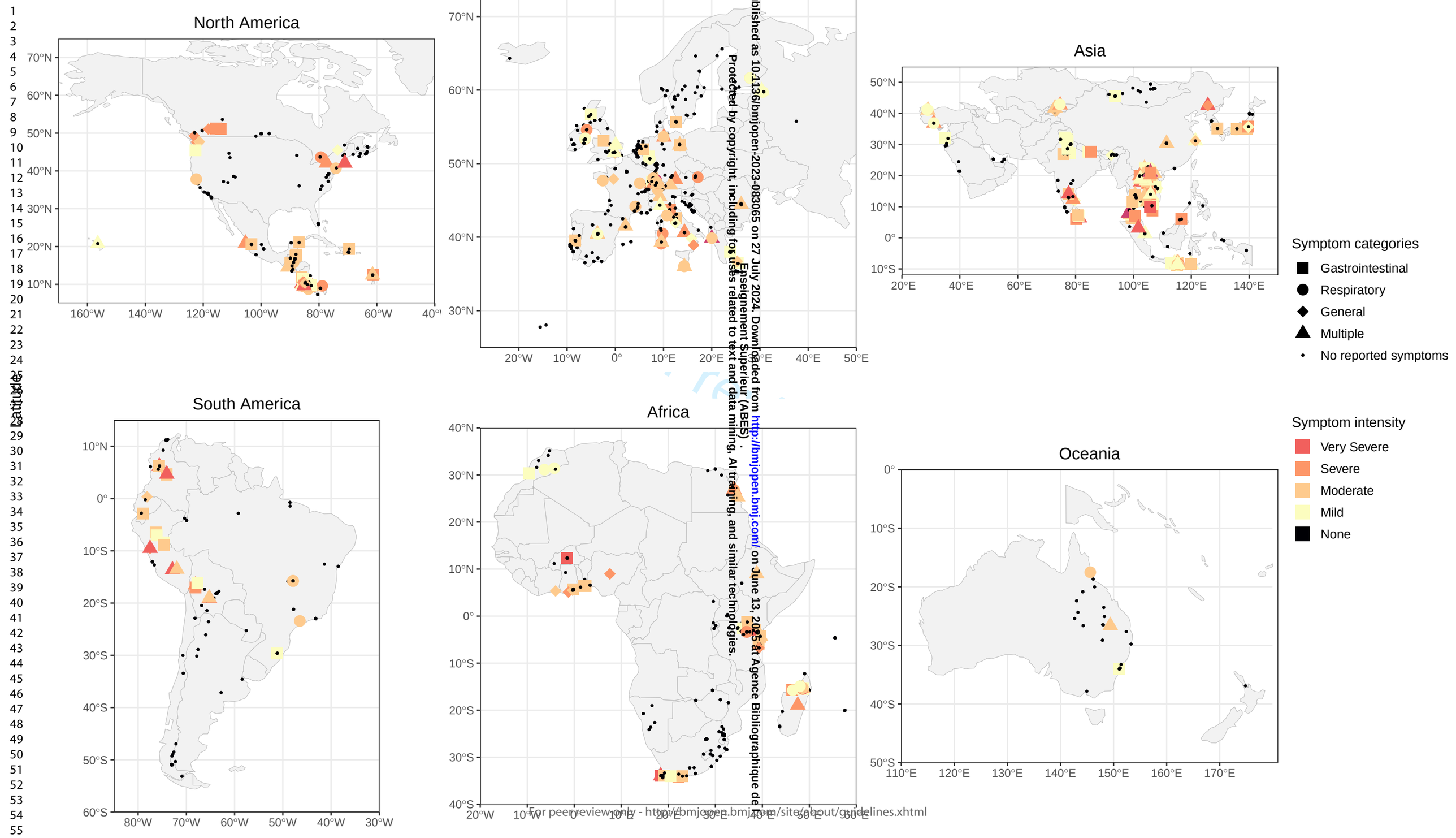
Appendix (section 1): Traveler Profile and Symptom Intensity Among Travelers Who Had a Medical Visit During Their Trip table_4.docx

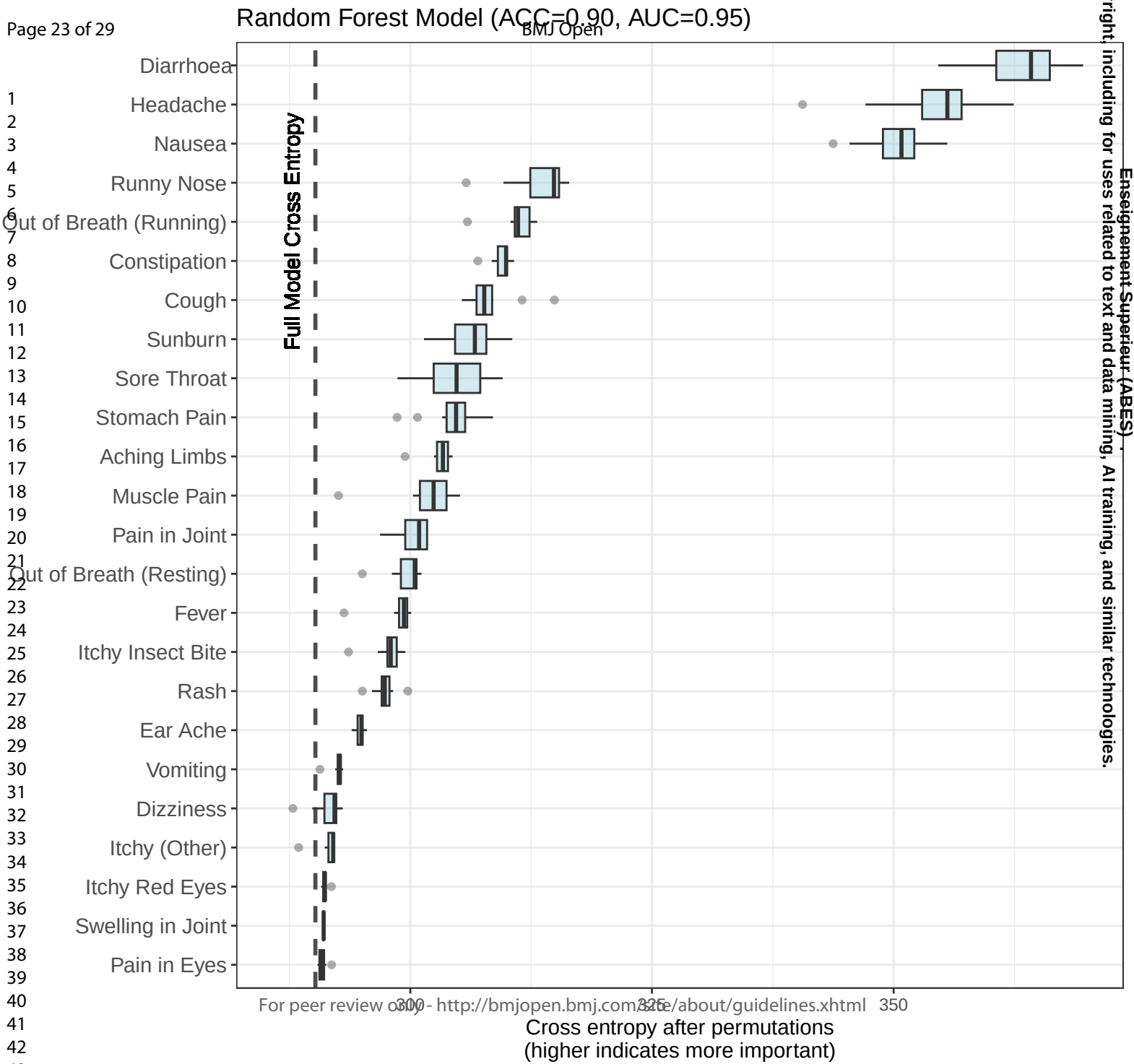
Appendix (section 2): Univariate and Multivariate Analyses of Variables Influencing Gastrointestinal Symptom Expression Using Complete Case Analysis and Imputed Full Sample Analysis gastro_any_table_3.docx

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





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	medical visit	none

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

	Complete case analysis								**Imputed full sample analysis[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
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								
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								
Travel Purpose: Leisure/Tourist Travellers	**Reference**											
Travel Purpose: Visiting Friends and Relatives (VFR)	0.40	0.14	1.16	0.091								
Travel Purpose: Business/Corporate Travellers	0.50	0.18	1.44	0.201								
Travel Purpose: Other	0.99	0.14	6.78	0.990								
Smoking Status: Never Smoked	**Reference**											
Smoking Status: Current Smoker	1.78	0.51	6.24	0.366								
Smoking 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								
Humidity (%)	1.19	0.97	1.46	0.101	1.12	0.91	1.39	0.279	**1.65**	**1.38**	**1.96**	**<0.001**
Pressure (hPa)	1.25	0.92	1.69	0.150								
Temperature (°C)	1.17	0.93	1.46	0.170								
UV Index (UVI)	1.05	0.90	1.22	0.546								
Visibility (m)	0.99	0.85	1.15	0.850								
Wind Speed (m/s)	0.93	0.78	1.11	0.412								
Air Quality Components - CO (µg/m³)	1.06	0.93	1.20	0.401								
Air Quality Components - NH3 (µg/m³)	**1.18**	**1.04**	**1.34**	**0.011**	**1.17**	**1.03**	**1.34**	**0.016**	**1.25**	**1.10**	**1.43**	**<0.001**
Air Quality Components - NO (µg/m³)	0.94	0.79	1.12	0.498								
Air Quality Components - NO2 (µg/m³)	1.13	0.97	1.31	0.112								
Air Quality Components - O3 (µg/m³)	0.88	0.72	1.06	0.175								
Air Quality Components - PM10 (µg/m³)	**1.16**	**1.01**	**1.35**	**0.042**								
Air Quality Components - SO2 (µg/m³)	1.02	0.87	1.20	0.818								
Season: Summer	**Reference**				**Reference**				Reference			
Season: Autumn	**2.86**	**1.33**	**6.13**	**0.007**	**2.57**	**1.15**	**5.72**	**0.021**	2.06	0.88	4.83	0.10
Season: Spring	1.92	0.99	3.72	0.053	1.86	0.91	3.78	0.088	1.68	0.80	3.50	0.2
Season: Winter	**2.15**	**1.06**	**4.36**	**0.035**	**3.13**	**1.45**	**6.74**	**0.004**	2.10	0.95	4.65	0.069

[1]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.

[2]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.

[3]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.

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[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
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/m³)	1.15	0.97	1.35	0.099								
Air Quality Components - NH3 (µg/m³)	1.16	0.96	1.41	0.117								
Air Quality Components - NO (µg/m³)	1.09	0.95	1.25	0.225								
Air Quality Components - NO2 (µg/m³)	1.07	0.88	1.30	0.496								
Air Quality Components - O3 (µg/m³)	0.91	0.68	1.21	0.510								
Air Quality Components - PM10 (µg/m³)	1.20	0.98	1.47	0.077								
Air Quality Components - SO2 (µg/m³)	1.06	0.94	1.19	0.346								
Season: Summer	**Reference**											
Season: Autumn	0.41	0.09	1.90	0.253								
Season: Spring	1.18	0.39	3.58	0.776								
Season: Winter	0.56	0.16	1.97	0.364								

[1]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.

[2]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.

[3]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 by trip_id in the data.

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[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
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/m³)	1.03	0.87	1.23	0.703								
Air Quality Components - NH3 (µg/m³)	0.97	0.80	1.18	0.796								
Air Quality Components - NO (µg/m³)	0.96	0.74	1.25	0.764								
Air Quality Components - NO2 (µg/m³)	1.06	0.86	1.30	0.576								
Air Quality Components - O3 (µg/m³)	1.19	0.87	1.63	0.266								
Air Quality Components - PM10 (µg/m³)	1.06	0.87	1.29	0.574								
Air Quality Components - SO2 (µg/m³)	1.03	0.91	1.17	0.638								
Season: Summer	**Reference**				**Reference**				Reference			
Season: Autumn	**0.01**	**0.00**	**0.43**	**0.019**	**0.01**	**0.00**	**0.97**	**0.048**	**0.05**	**0.00**	**0.91**	**0.043**
Season: Spring	0.38	0.10	1.48	0.163	0.78	0.16	3.84	0.761	0.56	0.15	2.06	0.4
Season: Winter	0.30	0.07	1.31	0.110	1.55	0.27	8.76	0.620	0.51	0.12	2.21	0.4

[1]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.

[2]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.

[3]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 at trip_id in the data.

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[3]**			
	Univariate analysis				Multivariate model[2]				Multivariate model[2]			
Predictors[1]	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*	*Odds Ratios*	*Lower CI*	*Upper CI*	*p*
Survey Day	**3.46**	**2.08**	**5.76**	**<0.001**	**2.51**	**1.39**	**4.52**	**0.002**	1.16	0.80	1.68	0.4
Age	**0.37**	**0.23**	**0.60**	**<0.001**								
Gender: Female	**Reference**											
Gender: Male	0.71	0.26	1.92	0.499								
Continent: Europe	**Reference**											
Continent: Africa	0.73	0.09	6.16	0.775								
Continent: Americas	1.97	0.35	11.06	0.442								
Continent: Asia	3.10	0.64	14.95	0.158								
Continent: Oceania	0.00	0.00		0.996								
Travel Purpose: Leisure/Tourist Travellers	**Reference**											
Travel Purpose: Visiting Friends and Relatives (VFR)	1.53	0.44	5.31	0.506								
Travel Purpose: Business/Corporate Travellers	0.59	0.13	2.63	0.492								
Travel Purpose: Other	1.44	0.11	18.72	0.782								
Smoking Status: Never Smoked	**Reference**											
Smoking Status: Current Smoker	3.15	0.67	14.87	0.146								
Smoking Status: Former Smoker	0.56	0.09	3.64	0.545								
Chronic Health Conditions: None	**Reference**											
Chronic Health Conditions: Yes	0.59	0.11	3.20	0.543								
Clouds (%)	1.07	0.85	1.35	0.573								
Humidity (%)	1.03	0.79	1.34	0.823								
Pressure (hPa)	1.00	0.85	1.16	0.956								
Temperature (°C)	0.89	0.66	1.22	0.473	0.75	0.54	1.04	0.086	0.96	0.83	1.11	0.6
UV Index (UVI)	1.17	0.95	1.43	0.144	1.23	0.99	1.52	0.058	1.03	0.91	1.16	0.7
Visibility (m)	1.01	0.81	1.27	0.898								
Wind Speed (m/s)	0.94	0.74	1.20	0.619								
Air Quality Components - CO (µg/m³)	1.10	0.96	1.26	0.173								
Air Quality Components - NH3 (µg/m³)	1.10	0.93	1.30	0.270								
Air Quality Components - NO (µg/m³)	1.03	0.91	1.16	0.677								
Air Quality Components - NO2 (µg/m³)	1.05	0.89	1.25	0.565								
Air Quality Components - O3 (µg/m³)	1.09	0.85	1.40	0.507								
Air Quality Components - PM10 (µg/m³)	1.12	0.94	1.32	0.196	1.08	0.91	1.29	0.385	1.05	0.96	1.14	0.3
Air Quality Components - SO2 (µg/m³)	1.02	0.93	1.12	0.719								
Season: Summer	**Reference**											
Season: Autumn	0.59	0.17	2.01	0.399								
Season: Spring	0.89	0.38	2.05	0.782								
Season: Winter	1.34	0.52	3.45	0.538								

[1]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.

[2]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.

[3]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 by trip_id in the data.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Done
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	ln. 1-2
		(*b*) 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	(*a*) 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	(*a*) 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
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not Applicable
		(*e*) Describe any sensitivity analyses	Not Applicable
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

		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	ln. 265-311
		(b) Indicate number of participants with missing data for each variable of interest	ln. 265-311
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 estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	ln. 316-344
		(*b*) Report category boundaries when continuous variables were categorized	ln. 316-344
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	ln. 316-344
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 potential bias or imprecision. Discuss both direction and magnitude of any potential bias	ln. 431-449
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	ln. 363-449
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 study and, if applicable, for the original study on which the present article is based	ln. 492-496

*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.