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Human gut microbiota composition associated with international travels

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A B S T R A C T

Objective: The objective of this study was to evaluate whether long stays in non-European countries influence the composition, diversity, and dynamics of gut microbiota, considering the potential impact of travelling, close contact with new people, and consumption of water and food.
Methods: Two prospective cohorts were analyzed: (i) A longitudinal cohort comprising long-term travellers who provided fecal samples before and after their travels. (ii) A cohort consisting of long-term travellers and recently arrived migrants from non-European countries, which was compared with non-traveller controls. Each participant self-collected fecal samples and provided demographic and epidemiological data. Microbiota was characterized through 16 S rRNA gene sequencing.
Results: The longitudinal cohort comprised 17 subjects. A trend toward higher bacterial diversity was observed after travelling (Shannon index 3.12*vs*3.26). When comparing 84 travellers/migrants with 97 non-travellers, a confirmed association of higher diversity levels with travelling was observed (Phylogenetic diversity: 22.1*vs*20.9). Specific genera enriched in travellers' gut microbiota were identified, including *Escherichia/Shigella, Bacteroides,* and *Parabacteroides*. The analysis revealed three major clusters with profound differences in their bacterial composition, which exhibited differential distribution between travellers and non-travellers (Adonis $P < 0.001$; $R2 = 30.6$ %). Two clusters were more frequently observed in travellers: The first cluster, characterized by dominance of *Escherichia/Shigella,* exhibited the lowest levels of richness and diversity. The second cluster, dominated by *Faecalibacterium* and *Bacteroides*, displayed the highest richness and diversity patterns.
Conclusion: These findings highlight the diverse impact of international travel on gut microbiota composition and underscore the importance of considering microbiota resilience and diversity in understanding the health implications.

1. Introduction

Globalization has facilitated increased interrelations between countries and people, leading to a significant surge in international travel in recent decades. By 2018, the global estimate of international travellers exceeded 1.4 billion [1].

Despite the undoubted benefits of cultural exchange, commercial associations, and tourism [2,3], travel also serves as a potent vector for the emergence and dissemination of infectious diseases by introducing microorganisms into new geographical areas. This cause-effect

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relationship has been glaringly evident in the recent COVID-19 pandemic and is anticipated to persist in the future [4,5].

Travellers' diarrhoea (TD) stands as a prevalent ailment among travellers, presenting a substantial health concern due to its frequency and economic repercussions [6]. Moreover, TD is intricately linked with the acquisition and spread of antimicrobial resistance (AMR) bacteria [7–9]. Although the carriage of specific bacteria and their genetic resistance traits is typically cleared shortly after return [7,9], there is a possibility of rapid transmission to the community prior to their eradication, thereby contributing to the propagation of AMR.

Recent research suggests that the gut microbiota can play a pivotal role in the susceptibility to TD and the acquisition and duration of AMR carriage during international travels [10,11]. There is a mounting body of evidence indicating that alterations in the diversity, richness, and abundance of gut microbiota are correlated with the dissemination of antimicrobial-resistant bacteria subsequent to travel.

In general, a lack of diversity in the microbiome appears to be associated with disease, while a healthy and resilient microbiome hinges upon high richness and biodiversity [12]. Over recent centuries, individuals from developed and industrialized nations have experienced a gradual decline in microbial diversity [13,14]. This decline in microbial diversity extends beyond infectious diseases and may also be implicated in various non-communicable diseases [12].

Travel, along with exposure to new people, traditions, cultures, and unfamiliar foods, can induce modifications in the gut microbiota and bacterial diversity, counteracting the negative consequences of microbial diversity loss described above. However, there has been a scarcity of studies evaluating the effects of travel on gut microbiome composition, aside from those focused on infection and AMR carriage and duration. Interestingly, a recent study found that travel to low or middle-income countries was not associated with significant changes in the taxonomic composition or diversity of the faecal microbiome, despite an observed increase in the acquisition of antibiotic resistance genes [15].

The objective of the present study was to assess whether the gut microbiota composition of generally healthy adults could be influenced by extended stays in non-European countries, and to examine which microorganisms are more frequently involved and their dynamics.

2. Materials and methods

2.1. Study design

Two prospective cohorts were analyzed in this study. The first was a longitudinal cohort comprising individuals over 18 years old residing in Catalonia who planned to travel abroad for more than 3 months within the following month. These individuals provided one fecal sample before travelling and another within the first month after returning, allowing for the evaluation of changes in microbiota between pre- and post-travel samples. The second cohort included individuals who had returned to Catalonia in the previous month after a long stay (>3 months) in a non-European country, new visitors, or migrants over 18 years old from non-European countries, and a group of individuals who had not travelled in the previous year. Participants provided a single self-collected fecal sample, and the gut microbiota compositions of travellers/migrants and individuals not exposed to travel were compared. An unsupervised clustering approach was used to evaluate the relationship between gut microbiota and travel, as well as other host characteristics. Recruitment took place between April 2019 and June 2022 at two centers of traveller attendance services and three different primary care centers.

2.2. Data collection

All subjects completed a baseline demographic and epidemiological survey. Additionally, subjects who had recently travelled from an extra-European country responded to a survey regarding the epidemiological characteristics of their stay abroad.

2.3. Sample collection

Rectal swabs were self-collected by participants following detailed instructions provided by a project member at each centre. ESwab® transport system (COPAN diagnostics, California, USA) was used. Details can be found in the Appendix.

2.4. DNA extraction and sequencing

DNA was extracted and isolated using the automated MagNA Pure Compact Instrument (Roche Diagnostics, Risch-Rotkreuz, Switzerland) after an enzymatic pre-treatment (details in Appendix). Amplicon sequencing of V3-V4 region from 16 S rRNA gene was performed using Illumina MiSeq (Illumina, San Diego, California, USA), as previously described [16]. Negative controls were also sequenced for controlling potential contamination.

2.5. Bioinformatics analyses

The DADA2 pipeline was followed to obtain exact amplicon sequence variants (ASVs) from raw reads [17]. Contaminant ASVs were detected and removed based on comparison of prevalence/abundance in negative controls and samples, as previously described [16,18].

2.6. Statistical analyses

Statistical analyses were performed using the R program v4.1.0. Data description and differences on mean/medians or distribution was evaluated with standard statistical tests. Microbiota diversity analyses were conducted at the genus taxonomic rank, but some analyses were also performed at the ASV level. Samples were rarified up to 36,430 sequences (minimum sample depth) before alpha-diversity indexes calculation each sample and comparison between study groups. For beta-diversity, a Bray-Curtis dissimilarity matrix was calculated on relative abundance data. Significance of samples' clustering according to study groups was evaluated with PERMANOVA (Adonis). Differential abundance tests were performed by Wilcoxon with Benjamin-Hochberg correction for multiple-testing, ANCOM-BC and ALDEx2. Only significant taxa detected by two of these methods were considered. To identify clusters of samples according to their bacterial genera composition in an unsupervised approach, hierarchical clustering using a Bray-Curtis dissimilarity matrix was performed. The Silhouette index determined the optimal number of clusters. Alfa and beta-diversity was compared between clusters. Random Forest classification models were used to evaluate the discriminatory power of gut microbiota between clusters and to identify most important genera contributing to the discriminatory power. A detailed description can be found in Appendix.

3. Results

Globally, a total of 13,181,277 sequences were obtained from samples included in the study (median = 71,037 sequences, IQR = 55,402–89021, minimum = 36,430, maximum = 130,774), which was sufficient to capture the full diversity on gut microbiota from these subjects without losing any sample (Supplementary Fig. 1).

3.1. Longitudinal alterations in the composition of the gut microbiota among travellers

Seventeen individuals were enrolled in the longitudinal cohort, with a median age of 28 years (IQR: 22–38 years). The majority were female (n = 13, 76.5 %) and travelled to South America (n = 10), Asia (n = 5), and Africa (n = 2), with a median duration of 152.5 days (IQR: 113.8–187.0 days). Among them, two travellers had underlying medical

conditions, namely hypothyroidism and diabetes with hypertension, while eight had been prescribed antibiotics within the previous year. During their journeys, four individuals were administered antibiotics; three of them required hospital attention due to infectious gastrointestinal diseases. Furthermore, seven participants reported travel-related diarrhoea, with four presenting with unformed faeces or diarrhoea during the post-travel assessment, as delineated in Table 1.

Regarding to longitudinal cohort, rectal samples were obtained 14 days (IQR: 8–18 days) before travelling and 12 days (IQR: 9–16 days) after return. A total of 305 distinct genera were identified, comprising the gut microbiota of the analyzed travellers. However, only a subset of these genera exhibited notable relative abundances across the samples. Fig. 1A illustrates the mean abundance of principal bacterial genera detected in participants both before and after travelling, with *Ezakiella* (9.6 %, 6.3 %), *Bacteroides* (6.2 %, 8.3 %), *Faecalibacterium* (5.6 %, 6.6 %), and *Prevotella* (5.3 %, 4.3 %) emerging as predominant genera at both time points.

Diversity and richness of microbiota in pre- and post-travel specimens were assessed. Alpha-diversity analyses revealed a tendency towards increased bacterial diversity in the gut microbiota of individuals post-travel (Shannon index: median = 3.12 (3.0–3.2) vs. median = 3.26 (3.2–3.4), P = 0.09) (Fig. 1B). Conversely, beta-diversity analysis failed to unveil significant differences in the overall microbiota composition between all pre- and post-travel samples (Adonis P = 0.65, R2 = 2.1 %) (Fig. 1C). Nonetheless, despite the absence of consistent patterns of change among travellers, considerable inter-individual differences were noted, with a shared similarity between individual pre- and post-travel samples averaging at merely 0.51 (IQR: 0.41–0.59) as measured by 1-Bray-Curtis. Lastly, differential abundance testing did not identify any overrepresented genera associated with travelling.

Table 1
Characteristics of participants included in the longitudinal study.

Demographic and epidemiological characteristics	
Age, years (median, IQR)	28.0 (22.0–38.0)
Sex, female (%)	13/17 (76.5 %)
Weight, kg (median, IQR) (n = 15)	65.0 (52.5–71.5)
Height, cm (median, IQR) (n = 15)	167.0 (161.5–170.0)
BMI (mean, SD) (n = 15)	22.58 (20.9–24.6)
Frequent contact with animals (%)	8/15 (53.3)
Toxic habits	
Drug consumption (%)	2/15 (13.3)
Alcohol consumption (%)	10/15 (66.6)
Smoking habit (%)	3/14 (21.4)
Dietary habits	
Meat consumption (≥3 times a week) (%)	10/14 (71.4)
Vegetable consumption (≥3 times a week) (%)	12/14 (85.7)
Fruit consumption (≥3 times a week) (%)	8/14 (57.1)
Legumes consumption (≥3 times a week) (%)	10/14 (71.4)
Satured fats consumption (≥3 times a week) (%)	4/14 (28.6)
Fish consumption (≥3 times a week) (%)	8/14 (57.1)
Eggs consumption (≥3 times a week) (%)	8/14 (57.1)
Dairy products consumption (≥3 times a week) (%)	7/14 (50.0)
Vegetarian (%)	0/15 (0)
Disease history	
Underlying disease (%)[a]	2/15 (13.3)
Regular medication (%)[b]	3/15 (20.0)
Antibiotic use within the previous year (%)	8/15 (53.3)
Probiotic use within the previous year (%)	7/15 (46.7)
Surgery within the previous year (%)	1/15 (6.7)
Regular intake of herbal medicines (%)	1/15 (6.7)
Hospital admission within previous one year (%)	4/15 (26.7)
Travel information	
Region[c]	
Africa (%)	2/17 (11.8)
Asia (%)	5/17 (29.4)
North America (%)	0/17 (0)
South and Central America (%)	10/17 (58.8)
Purpose	
Education (%)	2/15 (13.3)
Cooperation (%)	5/15 (33.3)
Vacation (%)	4/15 (26.7)
Duration, days (median, IQR) (n = 14)	152.5 (113.8–187.0)
Travel into rural area (vs urban area) (%)	12/15 (80.0)
Accommodation (particular home) (%)	5/13 (38.5)
Close contact with native population (%)	13/15 (86.7)
Travel associated diarrhoea (%)	7/15 (46.7)
Antibiotic consumption (%)	4/15 (26.7)
Hospital attention (%)[d]	3/15 (20.0)
Faeces characteristics at visit after travel	
Unformed faeces or diarrhoea[e]	4/15 (27.7)
Rectal colonization by multidrug resistant strains before travel (%)	1/17 (5.9)
Rectal colonization by multidrug resistant strains after travel (%)	1/17 (5.9)

IQR, Interquartile range; SD, standard deviation; BMI; body mass index, kg, kilograms; cm, centimetre.

[a] hypotiroidism (1) diabetes plus hypertension (1).

[b] Antibiotic (1), Blood pressure medication (1), corticosteroids (1).

[c] East and South Asia (different countries) (4), Ecuador, Peru (3), South America (different countries) (2), Bolivia, Cuba, Gambia, Nepal, Ghana (1).

[d] 1 Diarrhoea, 2 Salmonella infection.

[e] Bristol scale.

3.2. Comparison of microbiota composition between non-travellers and travellers

Out of the 181 participants included in the cohort, 97 had not travelled while 84 had. The median age was 27 years (IQR: 23.0–34.0 years) for non-travellers and 29 years (IQR: 25–36.2 years) for travellers. Female participants predominated in both cohorts (63.8 % and 66.2 %, respectively). Table 2 delineates the epidemiological and demographic characteristics of individuals unexposed and exposed to travel. A higher proportion of travellers reported diarrhoea or unformed faeces during the visit compared to non-travellers (18 % vs 6.2 %, P = 0.025), while a lower proportion of travellers reported probiotic use in the previous year (13.3 % vs 44.4 %, P = 0.006). Travellers were obtained rectal samples 12.5 days (IQR 8.5–21) after return.

The principal genera identified in both non-travellers and travellers were Bacteroides (4.8 %, 10.1 %), *Ezakiella* (6.4 %, 5.1 %), *Escherichia/Shigella* (3.1 %, 8.4 %), *Prevotella* (4.8 %, 4.1 %), *Faecalibacterium* (4.0 %, 4.9 %), and *Porphyromonas* (5.2 %, 3.2 %) (Fig. 2A). These findings closely mirrored those obtained in the analysis of the longitudinal cohort, albeit with subtle differences such as the prominence of *Escherichia/Shigella* as a predominant bacterial genus, particularly among travellers.

Further disparities in gut microbiota composition were observed between non-travellers and travellers. A tendency towards higher phylogenetic diversity of genera was noted among travellers compared to non-travellers (Phylogenetic diversity: median = 17.9 (16.5–18.9) vs median = 17.4 (14.3–18.7), P = 0.06) (Fig. 2B). This trend achieved statistical significance at the ASV level, with a significantly greater number of ASVs associated with travel (Phylogenetic diversity: median = 22.1 (19.8–23.8) vs median = 20.9 (16.6–22.8), P = 0.02) (Supplementary Fig. 2).

Additionally, an overall bacterial genera profile of faecal samples was analyzed, revealing a significant clustering of samples based on the participants' travel status. This outcome underscores the impact of travel on gut microbiota composition (Adonis P < 0.001, R2 = 2.3 %) (Fig. 2C).

A deeper examination of individual genera confirmed significant overrepresentation of *Escherichia/Shigella* in the group of travelling subjects, as well as overrepresentation of *Bacteroides* and *Parabacteroides* genera in this same group compared to the non-travelling group (Fig. 2D and E). At the ASV level, *Escherichia/Shigella* ASV6391 and *Bacteroides thetaiotaomicron* ASV4473 were associated with the travelling group, while *Negativicoccus* ASV9351 was the only feature associated with the non-travelling group (Supplementary Fig. 2).

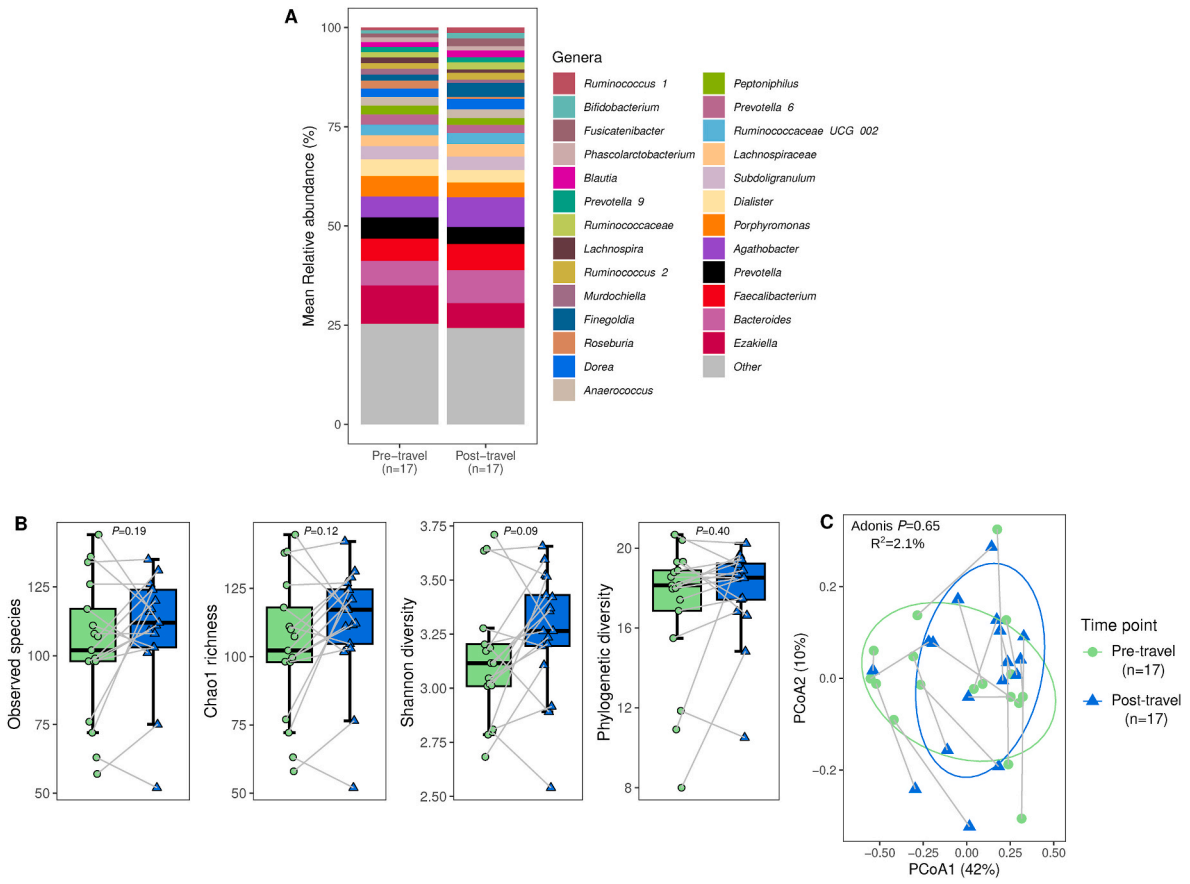

Fig. 1. Characterization of gut microbiota in pre-travel and post-travel samples from the longitudinal cohort's participants. (A) Mean relative abundance barplot of bacterial genera detected in pre-travel and post-travel samples. Other category agglomerates bacterial genera with absolute abundance in the dataset <1 %. (B) Boxplots with median and IQR representing the comparison of Observed species, Chao1 richness, Shannon and phylogenetic diversity indexes between pre-travel (green circles) and post-travel samples (blue triangles). Grey lines join paired samples. P-values derived from paired standard statistical tests. (C) Principal Coordinate Analyses ordination using a Bray-Curtis dissimilarity matrix that shows distribution of pre-travel (green circles) and post-travel (blue triangles) samples according to their gut microbiota composition. For clarity, ellipses are drawn containing at least 70 % of faecal samples from each time point and coloured accordingly. Grey lines join paired samples. P-value corresponds to Adonis PERMANOVA test on the time point variable.

3.3. Unsupervised clustering analysis of participants according to gut microbiota composition

A total of 11 clusters were optimal for segregating the faecal samples based on their microbiota profiles. However, only three of these clusters yielded sufficient samples for subsequent statistical analyses and were therefore considered (Fig. 3A).

Clusters 8, 10, and 11 were characterised by distinct genera. Cluster 8 was predominantly dominated by *Escherichia/Shigella*, with a mean relative abundance across the samples of 50.7 %. In Cluster 10, the primary genera detected were *Ezakiella*, *Porphyromonas*, and *Prevotella*, with mean relative abundances of 10.3 %, 9.2 %, and 7.7 %, respectively. Cluster 11 showcased *Bacteroides* and *Faecalibacterium* as the primary genera detected, with mean relative abundances of 11.1 % and 8.1 % (Fig. 3A).

Comparison of diversity metrics revealed significant differences in alpha-diversity among the three microbiota clusters. Cluster 11 exhibited the highest levels of richness and diversity, while the lowest levels were observed in Cluster 8. Cluster 10 displayed intermediate values between the other two clusters (Fig. 3B). Beta-diversity corroborated significant and profound differences in gut microbiota composition among the three clusters of samples (Adonis $P < 0.001$, $R2 = 30.6$ %), as depicted in the PCoA biplot (Fig. 3C).

We further discerned the most discriminative genera for the classification of samples within these clusters using Random Forest models. The initial model, exhibiting an AUC of 0.98 (95 % CI: 0.94–1.00), underscored *Escherichia/Shigella* and *Acinetobacter* as the foremost genera crucial for accurately classifying samples within Cluster 8 (Fig. 3D–I). The subsequent model, with an AUC of 0.99 (95 % CI: 0.98–1.00), highlighted *Peptoniphilus*, *Prevotella*, *Dialister*, and *Porphyromonas* as the most discriminating features associated with Cluster 10 (Fig. 3D–II). Notably, *Bacteroides* and *Faecalibacterium* emerged as the pivotal genera for classifying samples grouped under Cluster 11. This latter model exhibited an AUC of 0.97 (95 % CI: 0.94–0.99) (Fig. 3D–III).

The distribution of travellers and non-travellers across the clusters revealed an uneven distribution, reaffirming a robust correlation between travelling and gut microbiota composition. Two distinct microbiota profiles were discerned among travellers: both Clusters 8 and 11 demonstrated higher percentages of individuals who had travelled compared to Cluster 10 (Cluster 8: 80.0 %, Cluster 11: 58.0 %, Cluster 10: 33.3 %, $P = 0.001$) (Table 3).

Although there were some differences in host characteristics between clusters, these were relatively weak. Microbiota Cluster 8 exhibited a higher percentage of individuals with underlying diseases ($P = 0.03$) and individuals taking regular medication ($P = 0.007$), compared to Clusters 10 and 11 (Table 3). Additionally, South America was the preferred destination for 87.5 % of travellers from Cluster 8, as opposed to 60.0 % and 37.2 % of travellers from Clusters 10 and 11, respectively ($P = 0.01$) (Table 3). Furthermore, there was a significant difference in the distribution of sexes across clusters ($P = 0.02$), with a greater proportion of females in Cluster 8 compared to Clusters 10 and 11 (Table 3).

Table 2
Comparison of participants 'characteristics according to the antecedent of previous travel.

Variables	Non-travelers (n = 97)	Travelers (n = 84)	*P*-value
Demographic and epidemiological characteristics			
Age, years (median, IQR)	27.0 (23.0–34.0)	29.0 (25.0–36.2)	0.14
Sex, female (%)	53/83 (63.8)	53/80 (66.2)	0.87
BMI (median, IQR) (NT: n = 18, T: n = 69)[†]	22.3 (20.5–24.4)	23.7 (20.8–26.2)	0.27
Frequent contact with Animals (%)	18/18 (61.1)	43/75 (30.7)	**<0.001**
Toxic habits			
Drug consumption (%)	3/18 (16.7)	8/74 (10.8)	0.44
Alcohol consumption (%)	12/18 (66.7)	33/74 (44.6)	0.12
Smoking habit (%)	3/17 (17.6)	15/73 (20.5)	1.00
Dietary habits			
Meat consumption (≥3 times a week) (%)	11/17 (64.7)	45/60 (75.0)	0.59
Vegetable consumption (≥3 times a week) (%)	15/17 (88.2)	50/60 (83.3)	1.00
Fruit consumption (≥3 times a week) (%)	11/17 (64.7)	48/60 (80.0)	0.21
Legumes consumption (≥3 times a week) (%)	12/17 (70.6)	35/60 (58.3)	0.53
Satured fats consumption (≥3 times a week) (%)	4/17 (23.5)	16/60 (26.7)	1.00
Fish consumption (≥3 times a week) (%)	8/17 (47.0)	24/60 (40.0)	0.81
Eggs consumption (≥3 times a week) (%)	9/17 (53.0)	42/60 (70.0)	0.31
Dairy products consumption (≥3 times a week) (%)	9/17 (53.0)	42/60 (70.0)	0.31
Vegetarian (%)	0/7 (0)	1/31 (3.2)	1.00
Clinical characteristics			
Underlying diseases (%)	3/18 (16.7)	18/74 (24.3)	0.75
Regular medication (%)	3/18 (16.7)	14/75 (18.7)	1.00
Antibiotic use within the last year before sample collection (%)	10/18 (55.5)	26/75 (34.7)	0.17
Probiotic use within the last year before sample collection (%)	8/18 (44.4)	10/75 (13.3)	**0.006**
Surgery within the last year before sample collection (%)	1/18 (5.6)	1/75 (1.3)	0.35
Regular intake of herbal medicines within the last year before sample collection (%)	1/18 (5.6)	7/75 (9.3)	1.00
Hospital admission within the last year before sample collection (%)	5/18 (27.8)	9/75 (12.0)	0.14
Diarrhoea or unformed faeces at the visit time (%)[&]	6/97 (6.2)	11/61 (18.0)	**0.02**

4. Discussion

The findings of this study underscore the significant impact of international travel on gut microbiota composition. Generally, higher prevalence of diarrhoea or non-formed faeces among travellers compared to non-travellers, particularly among those returning from Southern Asian and South American countries. In addition, *Escherichia/shigella, Bacteroides* and *Parabacteroides* were more abundant in travellers' gut microbiota.

Escherichia/Shigella, Bacteriodes and *Parabacteroides* are important pathobionts of the human gut microbiome. They can maintain an equilibrium with the rest of the gut microbiota and establish beneficial relationships with their host. Especially, a protective role has been attributed to *Bacteroides* and *Parabacteroides* by a wide range of mechanisms including modulation of immune cells, colonization resistance or secretion of short fatty acid chains, important for the gut barrier integrity [19,20]. However, under certain circumstances, this equilibrium can disappear and evolve to cause significant pathology. These genera have been implicated in numerous infections and non-infectious diseases as gastrointestinal disorders, but also cardiologic, metabolic and neurological diseases [20–23].

Immune system alterations may induce the transition to invasion and pathogenic states of these bacteria, but in many cases, it may be a result of the ecological context, driven by factors such as medications, diet, etc. Therefore, the relation of such bacteria with host health or disease states cannot be fully understood without contextualizing them in the ecological niche of the gut nor without additional information on epidemiological and clinical factors concerning the host. In this regard, the unsupervised clustering of samples according to gut microbiota composition and its relation with host characteristics helped us to go deeper into this issue.

Travelling was associated to two different profiles of gut microbiota in our study; some individuals exhibited a gut microbiota characterized by low diversity and richness, dominated by *Escherichia/Shigella*, while others benefited from a rich and diverse microbiota profile, enriched with *Faecalibacterium* and *Bacteroides*.

Regarding the low diversity pattern, the literature widely reports *Escherichia coli* and *Shigella* species as the main causative agents of Travellers' Diarrhoea (TD) and antibiotic resistance [24–27]. Higher rates of TD have been identified in travellers visiting South America [25,27], which coincided with the geographical destination most frequently observed among participants with a low diversity microbiota pattern. Additionally, immunosuppressed individuals and those with underlying chronic diseases exhibited this low diversity pattern more frequently, possibly due to the lack of a healthy gut microbiome which acts as the first barrier to restrict incoming pathogen colonization.

The intestinal colonization by *Escherichia/Shigella* species in this context is worrisome. *E. coli* has been described to produce metabolites as ethanol that can increase intestinal permeability and enhance inflammatory states when secreted in large amounts [28]. *Escherichia/-Shigella* overrepresentation together with decreased beneficial bacteria, such as *Blautia* or *Faecalibacterium*, and decreased alpha-diversity has been associated with dysbiosis and a proinflammatory microbiota [29], in a similar manner to what we found in this low diversity pattern. In addition, *E. coli* has been described to produce biofilm that can enhance the chronicity of this infection and serve as genetic reservoir for antibiotic resistance. Maintaining long-term inflammation and dysbiotic states in the gut have been implicated in the development of gastrointestinal disorders including chronic gastritis, inflammatory bowel disease, colorectal cancer, among others [30].

A novel finding of this study was the identification of a second gut microbiota pattern, more frequently associated with migrants, characterized by high richness and diversity levels, as well as high abundance of beneficial genera, as *Faecalibacterium*, related to intestinal inflammation prevention and gastrointestinal homeostasis [31]. A second important genera detected in this microbiota pattern was *Bacteroides*, suggesting that a mutualistic relation with the host may be established in this context of ecological diversity and richness [20].

This second gut microbiota profile associated to travel may be partly explained by the low-income destination of most participants. Industrialization is known to have a significant inverse relationship with microbial diversity [13,14]. Direct and indirect social transmission through contact with native populations from less-resourced countries might also constitute a pathway for acquiring new bacteria and increasing gut microbiota diversity. The horizontal transmission of microorganisms that comprise the human adult microbiome is an emerging field of interest; it has been recently described that subjects sharing the same environment have a similar microbiota composition, sharing up to 50 % of the taxa when close contact is produced, regardless of relatedness [19,32].

Our findings suggest that long-term travellers would benefit from the use of probiotics, given the clinical risks of TD and the association of this disease with travellers in our study. Some probiotics have already been proved to be effective in preventing TD [33]. Moreover, a dysbiotic state was identified in the gut microbiota of some subjects with chronic and immunocompromised conditions that travelled to South America, indicating that these subjects might also benefit from probiotic administration. Nevertheless, the promotion of beneficial microbiota profiles by

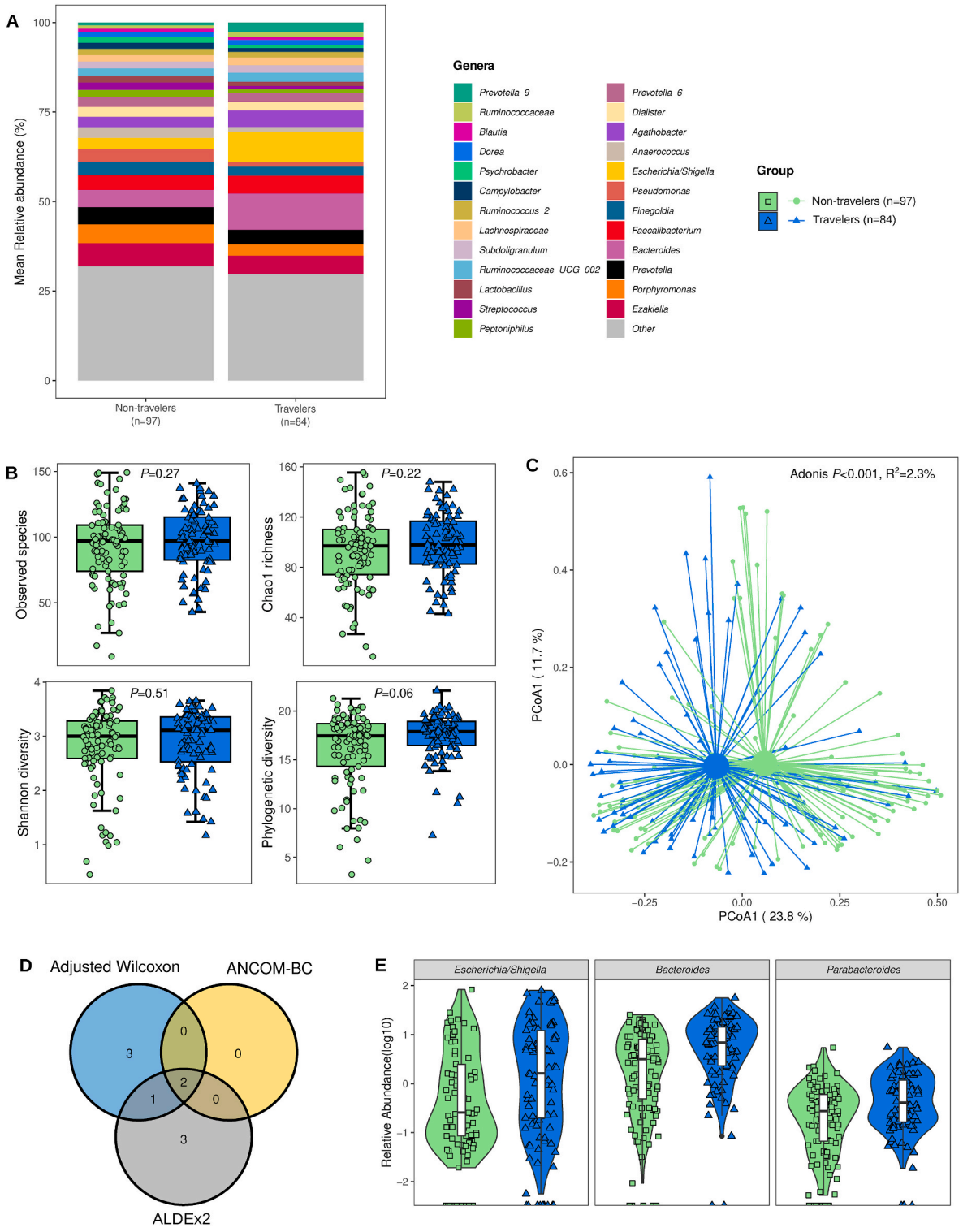

Fig. 2. Characterization of gut microbiota according to the antecedent of previous travel in subjects from the prospective cohort stuy. (A) Mean relative abundance barplot of bacterial genera detected in non-travellers' and travellers's samples. Other category agglomerates bacterial genera with absolute abundance in the dataset <1 %. (B) Boxplots with median and IQR representing the comparison of Observed species, Chao1 richness, Shannon and phylogenetic diversity indexes between samples from non-travellers (green circles) and travellers (blue triangles). P-values derived from standard statistical tests. (C) Principal Coordinate Analyses ordination using a Bray-Curtis dissimilarity matrix that shows distribution of samples from non-travellers (green circles) and travellers (blue triangles) according to their gut microbiota composition. For clarity, samples of each group are connected with their corresponding centroids using the function "ordispider" (Vegan R package). P-value corresponds to Adonis PERMANOVA test on the traveller-exposure group. (D) Venn diagram showing unique and shared genera identified as differentially abundant by group of study using three different statistical tests, including Adjusted Wilcoxon, ANCOM-BC and ALDEx2. (E) Boxplots with median and IQR depicting the comparison of bacterial genera relative abundances according to antecedent of previous travelling. Only taxa identified by at least two differential abundance tests were considered significant and ploted.

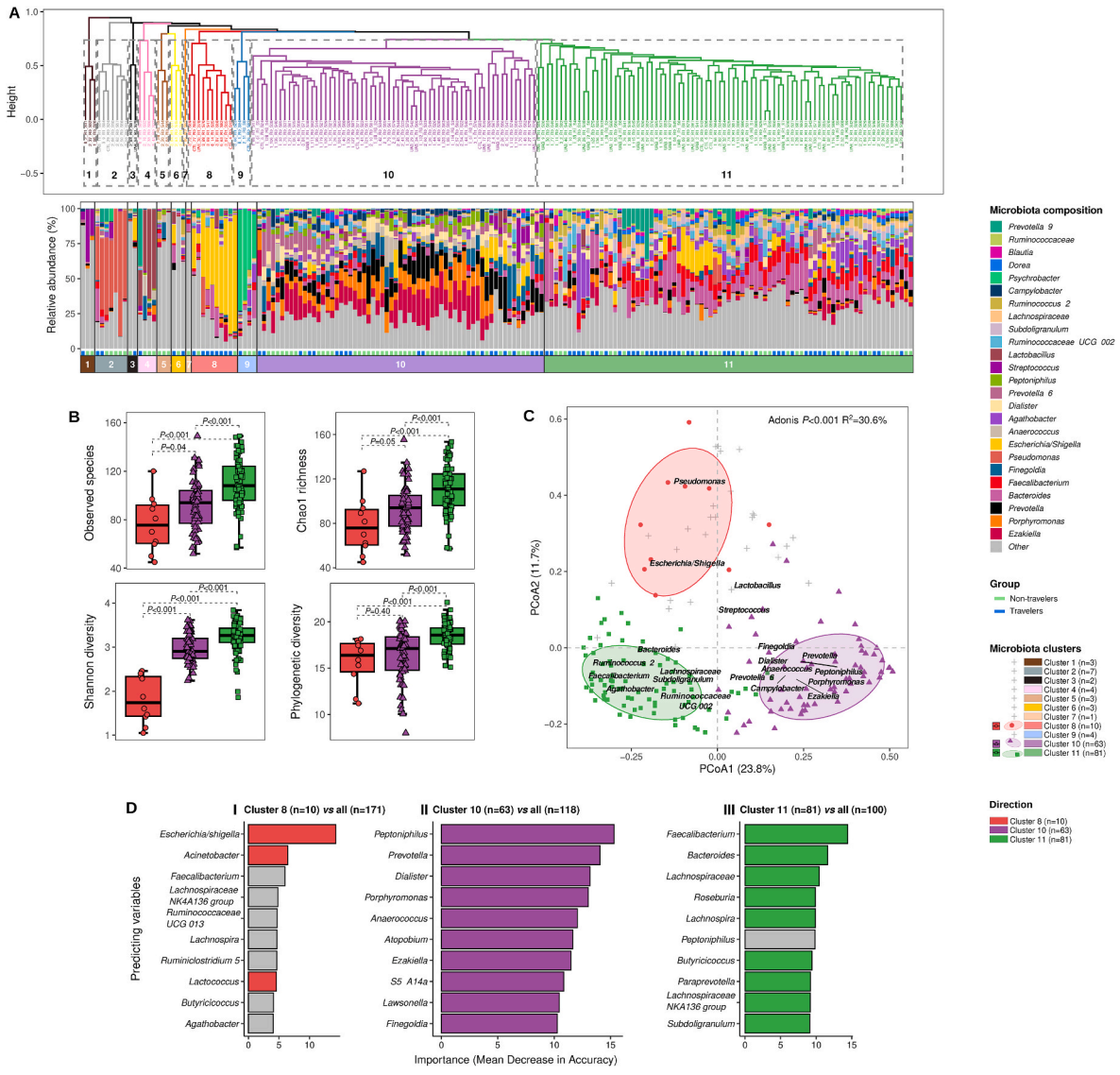

Fig. 3. Characterization of gut microbiota from clusters of samples identified using an unsupervised hierarchical clustering analysis on the prospective study cohort. (A) Dendrogram visualizing an average linkage hierarchical clustering of subjects using a Bray–Curtis dissimilarity matrix. The branches of the tree structure were coloured according to the clusters identified and dashed lines delimited the clusters. Stacked bar charts show the relative abundance of the genera with absolute abundance in the dataset higher than 1 %. Other category agglomerates bacterial genera with absolute abundance in the dataset <1 %. Information on the antecedent of previous travel is showed below the stacked bar chart (non-travellers; green, travellers; blue). Silhouette index identified an optimal number of 11 clusters and only three of them had enough number of samples for statistical analyses; Cluster 8, Cluster 10 and Cluster 11. (B) Boxplots with median and IQR representing the comparison of Observed species and Shannon diversity indexes between samples from Cluster 8 (red circles), Cluster 10 (purple triangles) and Cluster 11 (green squares). P-values derived from standard statistical tests. (C) Principal Coordinate Analyses ordination biplot using a Bray-Curtis dissimilarity matrix that shows distribution of samples from Cluster 8 (red circles), Cluster 10 (purple triangles) and Cluster 11 (green squares) according to their gut microbiota composition as well as the position of the main bacterial genera detected (absolute abundance >1 %). For clarity, ellipses are drawn containing at least 70 % of faecal samples from cluster and coloured accordingly. P-value corresponds to Adonis PERMANOVA test on the clustering variable. (D) RF models were built for distinguishing I. samples from Cluster 8 from the rest of samples, II. samples from Cluster 10 from the rest of samples and III. samples from Cluster 11 from the rest of samples. The contribution of the variables to the performance of the three models is shown in I, II and III through the representation of the mean decrease in Gini index of each variable. The direction of the association to Cluster 8 (red), Cluster 10 (pruple) or Cluster 11 (green) was established post-hoc using Cliff's delta test.

probiotics among travellers subjects should be further investigated. What does seem clearer is the importance of diet, which not only shapes microbial composition of gut microbiome, but also its metabolic activity [34]. A balanced diet with high fiber intake, avoiding high fat and fast foods, has been described to be a key stone for a healthy and functional microbiome resilient to perturbations [21,35].

This study has several limitations. Firstly, due to a low proportion of travellers sampled before travelling, the longitudinal cohort study did not allow for a definitive assessment of the association between travel and specific microbiota patterns. Additionally, inadequate statistical power precluded a multivariate analysis to comprehensively characterize the factors influencing the observed microbiota profiles. Future studies with larger participant cohorts are needed to explore the impact of various factors such as diet, travel type, specific destination countries (rather than regional aggregates), migrant and traveller's conditions, and other modifiable characteristics on microbiome patterns. Secondly, we could not determine the antimicrobial resistance gene profile of travellers and non-travellers subjects due to the use of a 16 S rRNA gene sequencing approach. Thirdly, while the gut microbiome can undergo changes over time, our study only conducted a single assessment within

Table 3
Comparison of participants 'characteristics among the three major clusters identified.

MAIN GROUPING VARIABLE	Cluster 8 (n = 10)	Cluster 10 (n = 63)	Cluster 11 (n = 81)	*P*-value
Traveller (%)	8/10 (80.0)	21/63 (33.3)	47/81 (58.0)	**0.001**

Demographic and epidemiological characteristics	Cluster 8 (n = 10)	Cluster 10 (n = 63)	Cluster 11 (n = 81)	*P*-value
Age, years (median, IQR)	28 (24–40.5)	26 (22–31)	29 (25–38)	0.11
Sex, female (%)	8/8 (100.0)	40/58 (69.0)	40/73 (54.8)	**0.02**
BMI (median, IQR) (Cl8: n = 6, Cl10: n = 23, Cl11:n = 51)[†]	24.2 (22.0–26.4)	22.1(20.5–24.1)	23.8 (21.2–27.2)	0.21
Number of cohabitants (median, IQR) (Cl8: n = 3, Cl10: n = 8, Cl11:n = 22)[†]	2 (1.5–3)	3.5 (3–4.25)	3 (2–4)	0.31
Frequent contact with Animals (%)	1/8 (12.5)	17/24 (70.8)	41/52 (78.8)	0.001
Toxic habits				
Drug consumption (%)	0/7 (0)	3/24 (12.5)	8/52 (15.4)	0.88
Alcohol consumption (%)	0/7 (0)	14/24 (58.3)	29/52 (55.8)	**0.01**
Smoking habits (%)	1/7 (14.3)	8/23 (34.8)	9/51 (17.6)	0.22
Dietary habits				
Meat consumption (≥3 times a week) (%)	2/2 (100)	14/22 (63.6)	38/48 (79.2)	0.28
Vegetable consumption (≥3 times a week) (%)	2/2 (100)	18/22 (81.8)	40/48 (83.3)	1.00
Fruit consumption (≥3 times a week) (%)	2/2 (100)	14/22 (63.6)	38/48 (79.2)	0.28
Legumes consumption (≥3 times a week) (%)	2/2 (100)	14/22 (63.6)	28/48 (58.3)	0.58
Satured fats consumption (≥3 times a week) (%)	1/2 (50)	6/22 (27.3)	13/48 (27.1)	0.78
Fish consumption (≥3 times a week) (%)	1/2 (50)	10/22 (45.4)	20/48 (41.7)	0.90
Eggs consumption (≥3 times a week) (%)	2/2 (100)	11/22 (50.0)	35/48 (72.9)	0.11
Dairy products consumption (≥3 times a week) (%)	2/2 (100)	16/22 (72.7)	29/48 (60.4)	0.42
Vegetarian (%)	0/1 (0)	0/8 (0)	1/27 (3.7)	1.00
Clinical characteristics				
Underlying disease (%)	4/7 (57.1)	6/24 (25.0)	7/52 (13.5)	**0.03**
Regular medication (%)	5/8 (62.5)	2/24 (8.3)	9/52 (17.3)	**0.007**
Antibiotic use within the last year before the sample collection (%)	2/8 (25.0)	10/24 (41.7)	21/52 (40.4)	0.75
Probiotic use within the last year before the sample collection (%)	1/8 (12.5)	8/24 (33.3)	9/52 (17.3)	0.26
Surgery within the last year before the sample collection (%)	0/8 (0)	0/24 (0)	2/52 (3.8)	1.00
Regular intake of herbal medicines the last year before the sample collection (%)	1/8 (12.5)	2/24 (8.3)	5/52 (9.6)	1.00
Hospital admission within the year before sample collection (%)	0/8 (0)	6/24 (25.0)	7/52 (13.5)	0.26
Number of stools/day (median, IQR) (Cl8: n = 0, Cl10: n = 2, Cl11:n = 6)[†]	–	2.5 (1.75–3.25)	4 (2.5–4.75)	0.39*
Diarrhoea or unformed faeces at the visit time (%)[&]	0/5 (0)	3/56 (5.3)	13/74 (17.6)	0.10

Travel information (Travelers group)	Cluster 8 (n = 8)	Cluster 10 (n = 21)	Cluster 11 (n = 47)	P-value
Region				
Africa (%)	0/8 (0)	3/20 (15.0)	7/43 (16.3)	0.69
Asia (%)	1/8 (12.5)	3/20 (15.0)	14/43 (32.6)	0.33
North and Centre America (%)	0/8 (0)	2/20 (10.0)	6/43 (13.9)	0.86
South america (%)	7/8 (87.5)	12/20 (60.0)	16/43 (37.2)	**0.01**
Purpose				
Education (%)	1/1	10/14 (71.4)	27/42 (64.3)	0.75*
Cooperation (%)	0/1	3/14 (21.4)	2/42 (4.8)	**0.09***
Vacation (%)	0/1	1/14 (7.1)	8/42 (19.0)	0.42*
Familiar visiting (%)	0/1	0/14 (0)	5/42 (11.9)	0.32*
Type of traveller, new inmigrant (%)	1/8 (12.5)	8/21 (38.1)	26/47 (55.3)	**0.06**
Duration, days (median, IQR) (Cl8: n = 0, Cl10: n = 7, Cl11: n = 14)[†]	–	172 (146–210)	122 (55–166.5)	0.11*
Accomodation (shelter, camping, farm) (%)	0/1	5/15 (33.3)	9/39 (35.9)	0.62*
Antibiotic consumption (%)	0/8	3/17 (17.6)	4/42 (7.1)	0.49

the first month after arrival, without subsequent evaluations. Therefore, potential fluctuations before or after rectal sample collection may not have been captured. Finally, most participants were recruited during the exceptional period of the SARS-CoV-2 pandemic, suggesting caution when generalizing the results beyond that period.

In conclusion, the information provided by the two cohorts analyzed in this study adds new evidences on the relation of gut microbiome diversity and composition with the international travels, identifying two distinct travel-associated microbiota patterns influenced by travellers' epidemiological background. Whether preventive specific measures may be recommended to stimulate favorable microbiome patterns before or after travelling is a question that will be addressed in future studies.

Data availability statement

Raw sequence files have been deposited in the European Nucleotide Archive (ENA) at EMBL-EBI under accession number PRJEB72871. Supplementary data are available in the article's supplementary files.

Ethics statementstatement

This research was approved by the Ethics Committee of Fundació Parc Taulí (ref. 2,017,653) and conducted in compliance with the World Medical Association's Declaration of Helsinki. All participants provided written consent to participate in the study.

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CRediT authorship contribution statement

D. Henares: Investigation, Methodology, Writing – original draft. **V. Monsalvez:** Data curation, Investigation, Writing – review & editing.

Pedro Brotons: Methodology, Validation, Writing – review & editing. **Maria Luisa Machado:** Investigation. **Silvia Capilla:** Investigation, Methodology, Validation. **Aina Gomila-Grange:** Investigation. **Paula Bierge:** Investigation. **Meritxell Cubero:** Investigation, Methodology. **Oscar Q. Pich:** Investigation, Methodology, Supervision. **Ana Requena-Méndez:** Funding acquisition, Methodology, Project administration. **C. Muñoz-Almagro:** Supervision, Validation, Writing – review & editing. **O. Gasch:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Oriol Gasch reports financial support was provided by Carlos III Health Institute, Spain. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2024.102747.

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