RESEARCH PAPER

Human Vaccines & Immunotherapeutics 9:3, 692–698; March 2013; © 2013 Landes Bioscience

Effectiveness of the WC/rBS oral cholera vaccine in the prevention of traveler's diarrhea

A prospective cohort study

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Keywords: Traveler's diarrhea, WC/rBS vaccine, effectiveness, cholera, preventive fraction, number needed to vaccinate

Objective: Traveler's diarrhea (TD) is the most frequent disease among people from industrialized countries who travel to less developed ones, especially sub-Saharan Africa, Southern Asia and South America. The most common bacteria causing TD is enterotoxigenic *Escherichia coli* (ETEC). The WC/rBS cholera vaccine (Dukoral®) has been shown to induce cross-protection against ETEC by means of the B subunit of the cholera toxin. The aim of the study was to evaluate the effectiveness of the WC/rBS cholera vaccine in preventing TD.

Methods: Between May 1 and September 30 (2007), people seeking pre-travel advice in ten Spanish international vaccination centers were included in a prospective cohort study of travelers to cholera risk countries. The incidence rates of TD were adjusted for variables whose frequencies were statistically different (entry point 0.10) between the vaccinated and non-vaccinated cohorts.

Findings: The vaccinated cohort (n = 544 travelers) included people vaccinated with the WC/rBS cholera vaccine, and the non-vaccinated cohort (n = 530 travelers) by people not vaccinated. The cumulative incidence rate of TD was 1.69 in vaccinated and 2.14 in non-vaccinated subjects. The adjusted relative risk of TD in vaccinated travelers was 0.72 (95% CI: 0.58–0.88) and the adjusted vaccination effectiveness was 28% (95% CI: 12–42).

Conclusions: The WC/rBS cholera vaccine prevents TD in 2 out of 7 travelers (preventive fraction: 28%). The number needed to vaccinate (NNV) to prevent 1 case of TD is 10.

Introduction

Traveler's diarrhea (TD) is the most common disease in people from industrialized countries who travel to less developed ones, especially to countries of sub-Saharan Africa, Southern Asia and South America. It affects 20–60% of travelers.[1-3] Diarrhea is the main reason for medical consultation among travelers and approximately 24 to 40 million people are affected worldwide each year.[1-4]

TD is a diarrheal syndrome that results from the ingestion of fecal contaminated food or water, and may appear during travel or during the following days.[1] It is defined as the daily passage of at least 3 loose or watery stools, which may occur in association with nausea, vomiting, abdominal cramping and/or dehydration. TD tends to be self-limiting and resolves spontaneously within 3–4 d in most cases. However, TD can last for weeks or months in up to 14% of cases.[1] Occasionally, it may result in post-infectious irritable bowel syndrome.[5] The onset of TD usually occurs within the first or second week of travel, but may occur at any time while traveling, and even some days after returning home. TD is rarely life threatening, but can be debilitating and incapacitating.[6] About 20% of patients must stay in bed for 1–2 d, 40% have to modify their planned itinerary and up to 1% require hospitalization.[7] Diarrhea can have more severe complications in some groups, including the elderly,[8] infants and young children,[9] immunocompromised patients[8] and pregnant women.[10]

TD is an infectious disease that may be caused by bacteria (60–85%), parasites (5–10%) or viruses (5–20%),[11,12] and varies widely according to geographical and seasonal factors.[13] Enterotoxigenic *Escherichia coli* (ETEC) is the most frequent causal agent, followed by *Campylobacter jejuni*, Shigella sp, Samonella sp and Vibrio sp.[14] The available scientific evidence shows that ETEC is responsible for 30–60% of all cases of TD depending on the season and the country visited.[15-17] The ratio of ETEC heat-labile toxin producers (LT-ETEC) and heat-stable producers (ST-ETEC) varies according to the study,[1,18] but up to

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Submitted: 10/19/12; Accepted: 10/29/12
http://dx.doi.org/10.4161/hv.23267

two thirds of cases of ETEC have been found to be LT-ETEC,[18] and it is estimated that every year 10 million cases of TD are caused by LT-ETEC.[19,20]

Despite the frequency of TD, there is no international consensus on its prevention. Pre-travel health education and counseling include recommendations on the safe consumption of water and food, but compliance is usually irregular. Some studies have suggested that hygienic measures can minimize, but not eliminate, the risk of TD.[8]

The molecular structure of the subunit of the *Vibrio cholerae* toxin is similar to the LT of ETEC. In vitro studies have suggested that serum antibodies against the cholera toxin induced by the WS/rBS cholera vaccine (Dukoral®, Crucell, Holland) can recognize and neutralize the LT of ETEC.[20] Therefore, this vaccine should prevent ETEC diarrhea.

Recently, several studies have demonstrated that the WC/rBS cholera vaccine induces cross-protection against TD through the recombinant non-toxic B-subunit of the cholera toxin (CTB).[21-23] Although the vaccine has been approved in most Western countries for cholera prevention, only Sweden and Canada have also approved it for TD prevention.[24]

The aim of this study was to assess the protection conferred by the WC/rBS vaccine against TD in people traveling to cholera risk countries.

Results

Data from 1,271 travelers were obtained during pre-travel consultations in the 10 study centers. The number of travelers provided by each center ranged between 100 and 240. After returning home, 1,102 travelers were interviewed by phone. One hundred and 60 nine travelers were not interviewed due to the following reasons: wrong phone number, cancellation of trip, change in travel dates and returning after study closure and non-collaboration. After the phone interview, 28 travelers who did not meet all study criteria were excluded. Therefore, 1,074 travelers were finally analyzed, 544 in the vaccinated cohort and 530 in the non-vaccinated cohort.

Table 1 shows the general characteristics of the study population according to WC/rBS vaccination status. Globally, a total of 58.4% participants were female and the mean age was 35 ± 10 y. Sixty percent of travelers went to Africa. Half the trips lasted between two and four weeks and only 15% lasted > 4 weeks. Seventy-five percent of trips were for tourism and almost half were package tours. Most trips combined urban and rural areas. The most common types of accommodation were hotels, lodges and boats.

Only a small number of travelers reported they had never taken non-recommended drink or food. The worst compliance was with recommendations to avoid raw food, juices, or salads. Almost 20 percent of travelers were taking regular medication for various diseases and a similar proportion had suffered diarrhea during previous trips.

In the vaccinated cohort, a higher frequency of trips longer than 4 weeks ($p < 0.001$), trips to Asia ($p = 0.001$), trips for cooperation ($p < 0.001$), accommodation in private homes ($p < 0.001$) and suffering diarrhea during previous trips ($p = 0.014$) were observed (**Table 1**).

Table 2 shows the number of cases of TD, incidence rates and RR for each covariate. Diarrhea during the trip or within 7 d after returning was reported by 186 (34.2%) vaccinated and 199 (37.5%) non-vaccinated travelers. The crude TD incidence rate was 1.69 (95% CI: 1.45–1.94) in vaccinated and 2.14 (95% CI: 1.86–2.46) in non-vaccinated travelers. The unadjusted RR in the vaccinated cohort was 0.79 ($p = 0.018$). Diarrhea was more frequent in non-vaccinated travelers, travelers to Asia, people traveling for cooperation tasks, travelers accommodated in private homes and travelers reporting regular diarrhea. No association between compliance with hygienic measures and diarrhea was found.

Table 3 shows the adjusted risk of TD in vaccinated subjects: RR = 0.72 (95% CI: 0.58–0.88). The adjusted vaccination effectiveness in preventing TD was 28% (95% CI: 12–42%). Therefore, the WC/rBS cholera vaccine avoided around 2 out of 7 TD cases. The number of cases needed to vaccinate to avoid one case of TD was 10. The variables considered in the model were: age group, geographical area, type of trip, accommodation in private houses, ingestion of fresh juice or raw foods and diarrhea in previous trips.

Discussion

The protective efficacy of vaccines (protective value in persons vaccinated under optimum conditions) is evaluated before marketing by phase 3 controlled clinical trials.[23] If the results are positive, the vaccine is submitted to the regulatory agencies for approval.[27] Approval by the regulatory agency means the vaccine can be administered to the population for which it is indicated.

After a vaccine is licensed, if hypotheses emerge on possible new indications, dosages and implementation strategies, new controlled clinical trials are unlikely for ethical and practical reasons.[27] To test these hypotheses, observational epidemiological studies (cohort or case control) are normally performed in people vaccinated in daily clinical practice or public health programs.[27] However, these studies do not measure vaccine efficacy but vaccine effectiveness i.e., the protective value of vaccination in routine conditions of application in public or private primary care or public health programs, in conditions that differ substantially from those of controlled clinical trials.[27] Not surprisingly, the epidemiological evidence provided by these studies is inferior to that of the gold standard of controlled clinical trials but may be the only feasible alternative.[27]

This is the case of our study. The WC/rBS vaccine is marketed in Spain for use in international travelers to geographic areas with a risk of cholera. Due to the similarity of the *V. cholerae* toxin to that of ETEC, the main bacterium causing TD, it has been hypothesized that the vaccine could be effective in preventing TD. Since the geographic areas at risk for TD largely overlap with endemic cholera areas, it would not be ethical to conduct a controlled clinical trial to evaluate the protective efficacy of the vaccine in travelers to risk areas.

Table 1. Baseline characteristics of participants according to WC/rBS vaccination status

		WC/rBS vaccination			
		YES[a]	NO[a]	p	Total
		N (%)[b]	N (%)[b]		N (%)
DEMOGRAPHIC VARIABLES					
Sex	Male	231 (42.5%)	215 (40.6%)		446 (41.6%)
	Female	312 (57.5%)	314 (59.4%)	> 0.05	626 (58.4%)
Age (years)	< 30	173 (31.9%)	188 (35.5%)		361 (33.7%)
	30–44	270 (49.7%)	243 (45.9%)		513 (47.9%)
	≥ 45	100 (18.4%)	98 (18.5%)	> 0.05	198 (18.5%)
TRAVEL CHARACTERISTICS					
Travel duration (weeks)	< 2	160 (29.4%)	210 (39.6%)		370 (34.5%)
	2–4	282 (51.8%)	259 (48.9%)		541 (50.4%)
	> 4	102 (18.8%)	61 (11.5%)	< 0.001	163 (15.2%)
Geographical area	Africa	299 (55.0%)	345 (65.1%)		644 (60.0%)
	Asia	245 (45.0%)	185 (34.9%)	0.001	430 (40.0%)
Type of trip	Organized	220 (40.4%)	69 (13.0%)	< 0.001	178(16.6%)
	Individual	215 (39.5%)	60 (11.3%)		153 (14.2%)
	Cooperation	109 (20.0%)	182 (34.3%)		324 (30.2%)
Travel area	Urban	93 (17.1%)	60 (11.3%)		153 (14.2%)
	Rural	142 (26.1%)	182 (34.3%)		324 (30.2%)
	Urban and rural	309 (56.8%)	288 (54.3%)	> 0.05	597 (55.6%)
Accommodation	Hotel/ship/lodge/ hostel	424 (77.9%)	450 (84.9%%	0.01	874 (81.4%)
	Private home	120 (22.1%)	80 (15.1%)		200 (18.6%)
HEALTH STATUS					
Regular diarrhea	Yes	22 (4.1%)	20 (3.8%)	0.05	42 (3.9%)
	No	521 (95.9%)	509 (96.2%)		1030 (96.1%)
Diarrhea in previous trips	Yes	108 (19.9%)	79 (15.0%)	0.014	187 (17.5%)
	No	387 (71.3%)	417 (79.0%)		804 (75.1%)
	No recall	48 (8.8%)	32 (6.1%)		80 (7.5%)

[a]Total: Vaccinated, 544 (50.6%); Non-vaccinated, 530 (49.4%); [b]Row percentages; VFR: Visit to friends or relatives.

Alternatively, we designed a prospective cohort study whose main endpoint was the incidence of all-cause diarrhea, as the observational nature of the study meant that the causative agents of diarrhea of patients could not be investigated.

The global incidence of TD incidence found (35.8%) is consistent with the reported value range for high-risk areas.[1,24,28]

The risk of diarrhea was greater in younger travelers, people traveling for cooperative reasons, travelers to Asian countries and those who stayed in private houses; all these factors have been reported by other authors.[28-30]

Our results show an independent, significant protective effect of the WC/rBS vaccine against TD. The risk of diarrhea was 28% lower in vaccinated travelers after adjusting for other factors associated with gastrointestinal problems during the trip.

Because the WC/rBS vaccine is only approved for cholera prophylaxis in Spain, our study only included travelers to zones where cholera is endemic, in order to achieve a sufficient sample. The lack of microbiological confirmation of TD cases made it impossible to estimate vaccine effectiveness only for LT-ETEC or other etiological agents.

Several studies have also shown the efficacy (clinical trials) or effectiveness (observational epidemiological studies) of cross protection of the WC/rBS vaccine against ETEC diarrhea (**Table 4**).[31-36]

The first demonstration of vaccine cross-protection in the setting of a clinical trial was in 1985. The study followed over 50000 women and children from a rural area of Bangladesh for 3 mo. Two or 3 vaccine doses had an efficacy of 67% ($p < 0.01$).[31] However, this study included only local people, who had high-risk exposure and high natural immunity, and therefore the

Table 2. Frequency of traveler's diarrhea and crude rates per 100 person-days according to study variables

		Cases	Person-days	Rate/100 d	95%CI 100 d°	Non adjusted rate ratios RR	95%CI	p-value
WC/rBS vaccination	Yes	186	11025	1.69	(1.45–1.94)	0.79	(0.64–0.96)	0.018
	No	199	9286	2.14	(1.86–2.46)	1		
	Total	385	20311	1.85	(1.71–2.09)			
DEMOGRAPHIC VARIABLES								
Sex	Male	151	8518	1.77	(1.51–2.07)	1		0.280
	Female	234	11793	1.98	(1.74–2.25)	0.89	(0.72; 1.09)	
Age (years)	< 30	182	6446	2.82	(2.43–3.26)	1		0.000
	30–44	165	10036	1.64	(1.40–1.91)	0.58	(0.47; 0.72)	
	≥ 45	38	3829	0.99	(0.71–1.34)	0.35	(0.24; 0.49)	
TRAVEL CHARACTERISTICS								
Trip duration (weeks)	< 2	90	5426	1.66	(1.34–2.03)	1		0.208
	2–4	214	10390	2.06	(1.79–2.35)	1.24	(0.97; 1.59)	
	> 4	81	4495	1.80	(1.44–2.23)	1.08	(0.80; 1.46)	
Geographical area	Africa	173	12422	1.39	(1.19–1.61)	1		0.000
	Asia	212	7889	2.69	(2.34–3.07)	1.93	(1.58; 2.36)	
Type of travel	Organized	137	8938	1.53	(1.29–1.80)	1		0.003
	Individual	162	7372	2.19	(1.88–2.56)	1.43	(1.14; 1.80)	
	Cooperation	86	4001	2.15	(1.73–2.64)	1.40	(1.06; 1.83)	
Travel area	Urban	64	2839	2.25	(1.75–2.86)	1		0.010
	Rural	92	6131	1.50	(1.21–1.83)	0.66	(0.48; 0.91)	
	Urban and rural	229	11341	2.01	(1.77–2.29)	0.89	(0.68; 1.18)	
Accommodation	Hotel/ship/lodge/others	291	16152	1.80	(1.60–2.01)	1		0.027
	Private house	94	4159	2.26	(1.84–2.75)	1.25	(0.99; 1.58)	
HEALTH STATUS								
Regular diarrhea	No	362	19757	1.83	(1.65–2.02)	1		0.002
	Yes	23	554	4.15	(2.69–6.13)	2.26	(1.49; 3.45)	
Diarrhea in previous trip	Yes	79	3628	2.18	(1.73–2.70)	1		0.151
	No	275	15274	1.80	(1.60–2.02)	0.83	(0.65; 1.07)	
	Do not recall	31	1409	2.20	(1.52–3.08)	1.01	(0.66; 1.52	

results cannot be extrapolated to travelers. During 1991, a prospective double blind study included 615 Finnish tourists traveling to Morocco. After returning home, they were followed for 12 mo. Global vaccine efficacy was 23% (95% CI = 16–30%) for TD and 60% (95% CI = 52–68%) for ETEC.[32] In US young adult tourists to Mexico, vaccine efficacy against ETEC was 50% (95% CI = 14–71%),[33] although the vaccine was not administered as recommended, with the first and second doses being taken after arriving in Mexico. As a consequence, 74% of diarrheas occurred within the 7 d after vaccination, when protection was not yet established.

The effectiveness of the WC/rBS vaccine in preventing TD has been evaluated in two Spanish observational studies. In 2007, López-Gigosos et al. observed a TD risk reduction of 43% (95% CI = 15–62%) in vaccinated travelers, with a shorter duration of diarrhea episodes.[34-36] In 2009, Ramon et al., in a cohort study including travelers from Barcelona, estimated a vaccine effectiveness against TD of 57% in high-risk travelers.[35] These figures are slightly higher than those found in our study, although methodological differences may explain this. First, the retrospective design, with a loss of more than 20% of travelers during the follow-up in the study by Ramon et al. study.[35] Second, both studies only included travelers from a single IVC and, according to the inclusion criteria, the a priori risk of TD was higher.

Like all observational epidemiological studies, our study had strengths and weakness and may have been subject to selection and information bias and to confounding.

One of the main strengths points of the study is its prospective design, which minimizes information and recall bias. The Oxford Center for Evidence-Based Medicine (http://www.cebm.net/) classifies cohort studies as having a level of evidence of 2b, which is the category immediately below randomized clinical trials. In addition, the study was multicenter, which confers external validity, favoring the inclusion of travelers with different profiles, vaccination criteria and preventive advice, according to

Table 3. Adjusted risk of traveler's diarrhea in the multivariate analysis

		Adjusted RR	95% CI	p-value	Vaccination effectiveness	95% CI
WCr/BS vaccination	Yes	1				
	No	0.72	(0.58- 0.88)	0.002	28%	(12–42)

Table 4. Published Studies on the Efficacy/Effectiveness of the WC/rBS Vaccine against Traveler's Diarrhea

Author (year)	Design	Type of population	N	Country of origin	Efficacy/effectiveness
Clemens (1988)	Clinical trial	Native	50000	India	67% against LT-ETEC
Peltola (1991)	Clinical trial	Travelers	615	Finland	60% against LT-ETEC 23% global
Scerpella (1995)	Clinical trial	Travelers	502	USA	50% against ETEC
Lopez-Gigosos (2007)	Retrospective cohort study	Travelers	237	Spain	43% global
Ramon (2009)	Retrospective cohort study	Travelers	658	Spain	57% global
Present study	Prospective cohort study	Travelers	1074	Spain	28% global

the center. The study cohort was large and there were few losses during follow-up (87% of travelers reported information after their return). However, the information was obtained by phone interview, which could be a limitation, even though a standard questionnaire was used and the interviewers were trained, and the robustness of the results is supported by their similarity to most published studies.

All TD studies have a common bias: the study population is composed only of travelers who attend vaccination centers, and this group is probably not representative of all travelers.[37] Travelers who ask for pre-travel advice are probably more aware of risks, more compliant with hygienic measures and have higher immunization levels than those who do not. Therefore, lower disease incidence might be expected in travelers attending vaccination centers.

Another possible bias is that mild forms of cholera may have been mistaken for TD. In this case, vaccinated subjects could have been protected, at least in part, against cholera while non-vaccinated subjects were not. This could have overestimated the effectiveness of vaccination. This situation would have occurred mainly in travelers to endemic areas of Asia. The magnitude of this bias depends on the actual incidence of mild cholera in travelers to endemic areas. Cholera has traditionally been considered an uncommon disease in travelers. However, recent data suggest that the contribution of cholera to TD is underestimated, as more than 90% of cases are mild or moderate, self-limiting and indistinguishable from other causes of TD.[38] Enterotoxigenic *V. cholerae* serogroup O1 biotype El Tor is the cause of the ongoing pandemics. It provokes mild, asymptomatic cases of cholera more frequently than the classic biotype responsible for previous pandemics.[39]

Methods

A prospective cohort study was conducted from May 1 to September 30, 2007. People seeking pre-travel counseling in ten international vaccination centers (IVC) from various Spanish regions were included. These IVC are part of a national public network formed by 68 centers at the time of the study, which assist travelers asking for pre-travel prevention services (vaccinations, antimalarial prophylaxis and health education).

This study was approved by the Clinical Research Ethics Committee, Hospital Clínico Universitario, Valencia, Spain).

Study subjects. The vaccinated cohort included travelers who received the WC/rBS cholera vaccine and who traveled to countries at risk of cholera. Travelers were considered as vaccinated if they took oral doses of the vaccine with a minimum interval between doses of one week with the second dose being taken at least 7 d before beginning the trip. The non-vaccinated cohort included travelers who did not receive the WC/rBS vaccine because health personal considered that the type of trip involved a low risk of cholera, and going to the same countries that the vaccinated cohort.

A case of TD was defined as a traveler who reported ≥ 3 non-solid stools in a 24-h period with or without other signs or symptoms, including abdominal cramps, nausea, vomiting, fever, tenesmus, fecal urgency or bloody fever, during a trip to the countries mentioned below or within 7 d after returning home.[25]

The inclusion criteria were:

- Age ≥ 18 y;
- Native and/or resident of the European Union, United States, or Canada;
- To have planned a trip to Africa (except South Africa), Bangladesh, India, or Indonesia;
- Planned stay of ≥ 7 d in the chosen country;
- Absence of severe gastrointestinal disease or chronic diarrhea;
- Absence of relevant background disease;
- No current corticosteroid or immunosuppressive treatment;
- Written informed consent

Demographic, epidemiological and clinical variables. In the pre-travel IVC visit, data were recorded using a specially-designed questionnaire, including

• Register and demographic variables (consultation date, date and place of birth, sex)

• Planned travel data (departure and return dates, countries to visit and type of trip)

• Clinical data (medical history, current diseases, drug therapies)

• Vaccinations (vaccination history and vaccines recommended in each center for the specific trip)

Between 7 and 14 d after the planned return day, two trained health professionals interviewed vaccinated and non-vaccinated cohorts by phone to collect information on the following variables:

• Trip data and preparation: countries visited, type of trip (package tour, individual, international cooperation, others), scope of trip (urban, rural, or both), reason for the trip (tourism, work, visiting relatives and cooperative tasks), type of stay (hotel, hostel, camp site, family or friend's house), vaccines administered, anti-malarial agents, other medication.

• During the trip: ingestion of non-recommended food and drink (non-bottled water, ice cubes, unsafe juices or fruits, raw food, salads, etc.)

• During the trip and within 7 d after the return: occurrence of TD, onset and duration of diarrhea, limitations on activity, fever, medical care and treatment prescribed.

Sample size. Estimating a risk difference (RD) of having TD of 20%, a risk ratio (RR) of 1.5, a statistical power of 90% and a statistical significance of 0.05, a sample size of 1,002 travelers was required.[26] In each IVC, consecutive travelers who complied with the inclusion criteria were included until the assigned number was obtained.

Statistical analysis. A descriptive analysis was made of all study variables. Cohorts were compared using contingency tables and the Chi^2 test.

The incidence rate of TD was calculated as the number of cases of diarrhea (people with one or more episodes of acute diarrhea) divided by the sum of travel days. The incidence rates and 95% confidence intervals (CI) were calculated for all variables and statistical significance was obtained using a univariate Poisson model.

A multivariate Poisson regression model using log-incidence rates as the outcome variable was constructed. For confounding variables related to diarrhea, forward selection with an entry p value of 0.10 based on the likelihood ratio test was performed. The statistical analysis was performed using Stata 10.0 (STATA. Stata 10. Stata Corporation. College Station, USA, 2004).

Vaccination effectiveness was estimated as 1 – RR from the final fitted model. The number needed to vaccinate (NNV) was calculated as the reciprocal of the absolute risk reduction expressed as a proportion per 100.

Conclusion

The results of our study suggest that WC/rBS vaccination of travelers to high-risk areas is associated with an absolute reduction of 28% in the risk of all-cause TD diarrhea. The vaccine has the potential to avoid 2 out of 7 cases of TD. In addition, vaccination of 10 travelers avoids 1 case, one of the lowest NNV found in licensed preventive vaccines.

Although the effectiveness of the WC/rBS vaccine against TD is low compared with other vaccines typically administered to travelers such as yellow fever or hepatitis A, the high frequency of the disease clearly justifies the vaccination of travelers as the protective potential in terms of reduction of cases of TD is substantial.

The World Health Organization (WHO) recently outlined the effectiveness and usefulness of the WC/rBS vaccine against ETEC diarrhea.[39]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors would like to thank all the travelers involved in the study for their kind collaboration.

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