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Adherence to hepatitis A travel health guidelines: A cross-sectional seroprevalence study in Dutch travelling families - The Dutch travel Vaccination Study (DiVeST)

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ABSTRACT

Background: This Dutch travel Vaccination Study (DiVeST) aimed to study adherence or compliance to Dutch travel health guidelines in travelling families and to identify risk groups to provide better advice and protection for international travellers.

Methods: Between 2016 and 2018, family members who travelled to Eastern Europe or outside Europe during the preceding year were recruited via Dutch secondary schools. The vaccination status of the travellers was assessed using questionnaires and vaccination records and hepatitis A virus antibody concentrations in dried blood spot (DBS) eluates. Subgroups of travellers with lower adherence to guidelines were identified.

Results: Of the 246 travellers that participated in this study, 155 (63%) travelled to destinations for which the HAV vaccination was recommended. Of these 155 travellers, 56 (36%) said they visited a pre-travel clinic, and 64 of them (41%) showed a valid HAV vaccination in their vaccination records. Of the 145 travellers with available DBS eluates, anti-HAV antibodies were detected in 98 (68%) of them.

Conclusions: We found that adherence to travel health guidelines, in terms of HAV vaccination, was suboptimal. According to our results, specific attention should be paid to children, persons visiting friends and relatives and those who travel relatively short distances.

1. Introduction

The dynamic field of travel medicine has undergone some serious changes during the past 10 years. Currently, in many Western European countries, the total number of people travelling internationally is equal to, or even exceeds, the respective number of inhabitants in those countries [1]. And not only has the number of travellers increased, the distance that these people travel has also increased significantly. Remote areas are becoming more accessible, while flights are becoming more and more affordable. Nowadays, the accessibility of air traffic makes it possible to travel to the other side of the world in a matter of hours. A few decades ago this would have taken several days [2]. The growing number of people able to travel now goes hand-in-hand with an increased exposure to infectious diseases. Furthermore, the ease of international travel and the wide availability of "last-minute" trips nowadays can make people unaware of the necessity to take pre-travel precautions.

Travellers are increasingly at risk of exposure to pathogens that they have never encountered before. The risk of infection varies greatly per country and so can the appropriate preventive measurements recommended before travelling. International travel health guidelines are available and the vaccinations recommended will depend on travellers' health, risk behaviour, length of stay, and, most importantly, travel destination. Furthermore, recommendations may differ between various international guidelines, reflecting differences of risk assessments between countries, vaccination programmes and national policies.

Abbreviations: CLIA, chemiluminescent immunoassay; DBS, dried blood spot; DTP, diphtheria, tetanus and polio; ELISA, enzyme linked immunosorbent assay; HAV, Hepatitis A virus; LCR, Landelijk Coördinatiecentrum Reizigersadvisering (Dutch National Coordination Centre for Travellers' Health Advice); NIP, Nationwide Immunization Program; PTA, pre-travel advice; VFR, visiting friends and relatives; VPD, vaccine-preventable diseases

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The Dutch National Coordination Centre for Travellers' Health Advice (Landelijk Coördinatiecentrum Reizigersadvisering, LCR) has developed guidelines to optimally protect travellers living in the Netherlands [3]. These guidelines are updated annually. However, based on several survey studies, it is clear that about one third of Dutch travellers are unaware of the risk of contracting infectious diseases.

When visiting countries in which these diseases are endemic [4,5]. Focusing on risk destinations that are relatively close to home for example, such as Croatia, Turkey and Morocco, up to 64% of Dutch travellers are unaware of the recommended vaccinations [4]. Travellers visiting friends and relatives (VFR) are particularly at risk, as they often make the journey without getting pre-travel advice, then spend a longer period of time abroad, often in close contact with the local inhabitants. This puts them at greater risk of contracting infectious diseases [6,7]. Young travellers also constitute a significant risk category, as many parents assume that their children are sufficiently protected by the Nationwide Immunization Program (NIP). This includes the diphtheria, tetanus and polio (DTP) vaccination, but not the other frequently recommended travel vaccinations, such as hepatitis A [8]. Given that survey-only research is prone to contain bias, we studied adherence to travel health guidelines adding serological data.

Serosurveillance data is widely available for NIP and some other infectious diseases, but these data only reflect the immune status of the general population [9]. Furthermore, plenty of data about specific outbreaks is also available [10–12]. However, information about the vaccination coverage in the healthy travelling populations, based on seroprevalence of vaccine-preventable diseases (VPD), is limited. Prior survey studies provide an indication of the frequency of pre-travel consultations. However, this is not representative of the number of unprotected travellers, as frequent travellers can be protected by vaccinations received in the past. The duration of protection offered by vaccines can range from a year to lifelong [3]. Besides, individuals who were born in an endemic country or who have lived abroad for a certain period could very well be protected by childhood vaccinations or natural infection, which means they would be in compliance with recommendations found in travel health guidelines when travelling to certain destinations [13]. In other words, not visiting a travel clinic prior to travel does not automatically mean that someone is travelling unprotected. Moreover, travellers can sometimes forget that they have received vaccinations [14] or vaccination records can be lost, all of which means that data from survey-only studies can be unreliable. Therefore, in carrying out the Dutch travel Vaccination Study (DiVeST) our objective was to do unbiased research into: (1) the vaccination status, and (2) the seroprotection rate of travelling families living in the Netherlands. Given that we did not want to rely solely on vaccination registration, because of potential loss of valuable information we strived to increase the reliability of the vaccination status data by collecting dry blood spots. This, so as to obtain insights in the presence of antibodies. Given that all travellers between the ages of 12 and 16 attend secondary school [15] it stands to reason that families travelling to any destination, by any mode of transport and with any opinion about the need to be vaccinated, can be reached via secondary schools. This made these schools a highly suitable source of data for this study.

The hepatitis A virus (HAV) vaccination is a widely advised travel vaccination - recommended according to the LCR guidelines in 184 out of the 227 (81%) defined destinations for which a vaccination is recommended [3]. Furthermore, the HAV vaccination is not included in the Dutch NIP. Therefore, using HAV as a representative VPD, HAV vaccination status and HAV seroprotection rates would provide valuable insights in the adherence to travel health guidelines in healthy Dutch travelling families [16–18]. Within the context of DiVeST, it was our intention to determine the proportion of Dutch travelling family members that adhere to travel health guidelines and identify risk groups among those that don't adhere. The overriding objective of all this was to provide better advice to international travellers and offer protection to more of them.

2. Material and methods

2.1. Study population

This cross-sectional study was conducted in secondary schools throughout the Netherlands between September 2016 and December 2018 Travellers, consisting of school personnel and students and their family members who visited an Eastern European or non-European country in the preceding year were recruited. Eastern Europe is in this study defined as Albania, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech, Estonia, Greece, Hungary, Kosovo, Latvia, Lithuania, Macedonia, Moldova, Montenegro, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, Turkey, and Ukraine. To ensure we recruited a sufficient number of travellers who should have been vaccinated according to Dutch travel health guidelines, travellers to Western European countries were excluded. Thirty-seven schools were approached, based on their respective locations (population density), type of school (public or denominational) and education level. After receiving permission and confirmation of participation in the study from school principals, we visited the applicable schools on plenary evenings or approached students' families via e-mail. Once participants had given written consent, anonymised demographic data, health data and vaccination and travel history were collected with OpenClinica, an electronic data-management application. Where available, copies of vaccination records were obtained. Additionally, dried blood spots were collected to ascertain vaccination status.

2.2. Sample collection

Following a finger prick (with a BD Lancet Device), capillary blood was collected on filter paper cards (Whatman™ Protein Saver™ 903™), dried for at least two hours and stored in foil bags with a small packet of desiccant for a maximum of three weeks at room temperature. Subsequently, these foil bags were placed in a freezer at minus 80° Celsius until they could be tested.

2.3. Elution of DBS samples

The filter paper cards were thawed and dried blood spots (DBS) were punched from these cards with a 12.7 mm or 6 mm diameter paper-hole punch. A 12.7 mm diameter spot was considered to contain 26 μL of serum and a 6 mm spot 5 μL. The spots were 1:6 eluted in phosphate buffered saline (PBS) with 2% fetal bovine serum (FBS) and incubated overnight on a rotating device in a room kept at 4° Celsius. The next day the supernatant was transferred to a cone vial and the paper spots were squeezed to get the maximum volume out of the DBS. Eluates were centrifuged prior to testing.

2.4. Laboratory testing

Given that the standard clinical test for HAV serology is the anti-HAV chemiluminescent immunoassay (CLIA), this test was used for the first screening of the eluates from all the DBS cards that were properly filled. The test was performed following the instructions of the manufacturer (DiaSorin LIAISON®). The limit of detection of this assay is a HAV antibody concentration of 18 micro international units per millilitre (mIU/ml), with a range of 15.5–21.5 mIU/ml. However, because of the 1:6 dilution factor, we had to maintain a cut-off of 108 mIU/ml for the CLIA of this study with a range of 93–129 mIU/ml.

Generally, used cut-offs range from 10 to 33 mIU/ml [19,20], but it is known that during the maintained protective periods of vaccines titres are much higher than the cut-offsThe concentration of HAV antibodies is at least 100 mIU/ml in 95% of the population in the first six months after primary vaccination, at least 1000 mIU/ml in 95% of the population up to 15 years after secondary vaccination and 1000–10,000 mIU/ml up to nine years after natural infection [21–23].

Table 1
Travellers' characteristics, categorised by pre-travel health advice.

	PTA+ n = 155 (63%)	PTA- n = 73 (30%)	PTA+/- n = 17 (7%)	Total n = 246° (100%)	p-value
Sex					0.348
Female	36 (49.3)	90 (58.1)	11 (64.7)	137 (55.9)	
Age (in years)					0.909
11–18	44 (28.4)	24 (32.9)	5 (29.4)	73 (29.8)	
> 18-35	7 (4.5)	3 (4.1)	2 (11.8)	12 (4.9)	
> 35-65	102 (65.8)	45 (61.6)	10 (58.8)	157 (64.1)	
> 65	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.4)	
Education level (child)[a]					0.031
VMBO	28 (18.1)	17 (23.3)	0 (0.0)	45 (18.4)	
HAVO	46 (29.7)	13 (17.8)	7 (41.2)	66 (26.9)	
VWO	76 (49.0)	35 (47.9)	8 (47.1)	119 (48.6)	
Highest level of education (parent)[b]					0.036
Secondary school	9 (8.2)	2 (4.2)	1 (8.3)	12 (7.1)	
MBO	10 (9.1)	15 (31.9)	1 (8.3)	26 (15.4)	
HBO	40 (36.4)	12 (25.5)	5 (41.7)	57 (33.7)	
WO	46 (41.8)	18 (38.3)	5 (41.7)	69 (40.8)	
Nationality					0.099
Other than Dutch or dual	16 (10.3)	4 (5.5)	0 (0.0)	20 (8.2)	
Medical history					0.392
Immunocompromised	3 (1.9)	0 (0.0)	0 (0.0)	3 (1.2)	

°For one participant the travel destination was not clear, so he could not be included in one of the PTA categories.
[a] VMBO stands for pre-vocational secondary education, HAVO stands for secondary general education and VWO stands for pre-university education level.
[b] MBO stands for senior secondary vocational education and training, HBO stands for higher professional education and WO stands for university level [44].

With a cut-off of 108 mIU/ml, the CLIA might not have been able to detect all positive samples, especially the ones there longer than 6 months after primary vaccination. Therefore, we subsequently tested all negative and equivocal eluates in the CLIA with a commercial enzyme-linked immunosorbent assay (ELISA) (DiaSorin® ETI-AB-HAVK PLUS). Also, because the CLIA needs an input volume of at least 240 µL per sample, the eluates from DBS cards that were sparsely filled were tested with the ELISA, as the input needed for this is only 50 µL. The ELISA was carried out according to the instructions of the manufacture, with additional dilutions of the calibrator. This resulted in a cut-off value of 10mIU/ml, leading to a cut-off of 60 mIU/ml due to the dilution factor. Therefore, equivocal samples (values 20% from the cut-off) were also considered positive (> 48 mIU/ml). Thus, we considered DBS eluates negative if both the CLIA and ELISA gave a negative result, or if the ELISA gave a negative result and the sample was not tested with the CLIA. DBS eluates were considered positive if either the CLIA or the ELISA gave a positive or an equivocal result. So, samples that were tested negative or equivocal with the CLIA, but gave a positive or equivocal result in the ELISA, were considered positive. This was because the cut-off of the ELISA was closer to the correlate of protection (Supplemental Fig. 1).

2.5. Definitions

Travellers were categorised according to the pre-travel HAV vaccination recommendation of the LCR as this would pertain to the (last) trip they made to an Eastern European country or a country outside Europe.

- PTA+ (pre-travel advice positive): travellers who visited a destination for which a pre-travel HAV vaccination is recommended.
- PTA- (pre-travel advice negative): travellers who visited a destination for which a pre-travel HAV vaccination is NOT recommended.
- PTA+/- (pre-travel advice depends): travellers who visited a destination (South Africa or Israel) for which a pre-travel HAV vaccination is only recommended under certain circumstances.

2.6. Data analysis

The study population was described using descriptive statistics. Categorical variables were compared between categories with chi-square tests and continuous variables with Mann-Whitney tests. The following baseline variables were analysed: sex, age, education level, nationality and immunocompromised state. Additionally, the following travel characteristics and travel-related behaviour were also analysed: destination, travel distance, length of stay and purpose of travel. Pre-travel recommendations were compared with travel clinic visits, self-reported HAV vaccination, vaccination records and serological status with chi-square tests. Additionally, a logistic regression model was used to calculate whether travel distance could predict vaccination status. Data analyses were performed with IBM SPSS statistics 25 and RStudio. 95%- confidence intervals were maintained and a p-value of < 0.05 was considered significant.

2.7. Ethics

The study protocol was approved by the Medical Ethical Research Committee of the Erasmus Medical Centre (MEC-2015-538). Furthermore, the study was carried out in accordance with the declaration of Helsinki.

3. Results

Our study population consisted of 246 travellers from 188 families; 30% were children and 55% were females. The study participants were mainly from municipalities in the Netherlands that were highly populated in 2015 [24]. A relatively large proportion of the study population was highly educated with 49% of students attending VWO (the Dutch equivalent of pre-university education) [25].

As shown in Table 1, 63% of travellers fell into category PTA+. Their pre-travel advice would have included HAV vaccination, given their destination and date of travel. Of these travellers, 9% went to Croatia, where HAV vaccination was only recommended if they had travelled before February 2017, due to a subsequent update of the LCR guidelines. Furthermore, 7% of the study population were categorised as PTA+/- because they travelled to South Africa or Israel, two countries for which the pre-travel advice only included the HAV vaccination if travellers stayed under unhygienic circumstances. In category PTA- there were 73 travellers, representing 30% of the study population. Table 1 shows that the education level of both children and parents differs significantly between the categories of travellers, with higher education levels being more strongly represented in the PTA+ group.

Table 2
HAV vaccination status compared with HAV vaccination pre-travel advice in guidelines.

	Received pre-travel advice			Self-reported HAV vaccination			HAV protected according to vaccination records			DBS eluate anti-HAV positive[a]			TOTAL (%)
	No (%)	Yes (%)	? (%)	No (%)	Yes (%)	? (%)	No (booklet) (%)	Yes (%)	? (%)	No (%)	Yes (%)	? (%)	
PTA +	98 (63.2)	56 (36.1)	1 (0.7)	21 (13.5)	69 (44.5)	65 (41.9)	38 (24.5)	64 (41.3)	53 (34.2)	47 (30.3)	98 (63.2)	10 (6.5)	155 (100)
PTA-	69 (94.5)	2 (2.7)	2 (2.7)	1 (1.4)	1 (1.4)	71 (97.3)	26 (35.6)	12 (16.4)	35 (48.0)	44 (60.3)	22 (30.1)	7 (9.6)	73 (100)
PTA + /-	5 (41.7)	12 (70.6)	0 (0.0)	4 (23.5)	8 (47.1)	5 (29.4)	2 (11.8)	9 (52.9)	6 (35.3)	8 (47.1)	8 (47.1)	1 (5.9)	17 (100)
p-value	< 0.001			< 0.001			0.002			< 0.001			

[a] DBS eluate anti-HAV positive means a positive or equivocal result with the CLIA or ELISA. DBS eluate anti-HAV negative means a negative result with the CLIA and ELISA, or a negative result with the ELISA and not tested on CLIA.

P-values were comparable when PTA + /- travellers were excluded.

In Table 2, we compared the vaccination-related behaviour of the three categories of travellers. As you would expect, more PTA + than PTA- travellers said they received pre-travel advice prior to their last trip (36% as opposed to almost 3%). Similarly, according to their vaccination records, more PTA + than PTA- travellers were able to prove they were protected against HAV (41% as opposed to 16%). Despite the smaller numbers, according to their vaccination records, PTA + /- travellers showed higher percentages than PTA + travellers for both receiving pre-travel advice and HAV protection. However, it must be added here that many participants did not know their HAV vaccination status (29% for PTA + /- and 97% for PTA-) and vaccination records were often not available (34% for PTA + and 48% for PTA-).

Therefore, we chose to compare compliance with guidelines of the PTA + group on the basis of the serological status of travellers. From the 155 PTA + travellers, 145 DBS eluates were available (Table 2). In these samples, we found that 98 of the 145 (67%) had anti-HAV antibodies (DBS +), compared to 22 of 66 (33%) in PTA- travellers and 8 of 16 (50%) of the PTA + /- travellers ($p < 0.001$).

Of the 47 PTA + DBS- travellers, 35 (74%) had not visited a travel clinic and 37 (79%) of them said that they were not aware that vaccinations were advised for their destination. Vaccination records of these 47 PTA + DBS- individuals showed that 20 travellers (43%) indeed had no proof that they were (still) protected against HAV, but according to their vaccination records 9 travellers (19%) were HAV protected during their trip. From the 18 cases in which DBS eluates were missing, 5 (28%) claimed to have been HAV vaccinated. In the PTA + category without DBS analysis, 2 out of 10 (20%) self-reported to be HAV vaccinated. Therefore, even in the most optimistic of scenarios, 23% of PTA + individuals travelled unprotected.

To distinguish the risk category of PTA + travellers lacking anti-HAV antibodies (DBS-), we compared baseline and travel characteristics of DBS + and DBS- travellers in this category (Table 3). Significantly more often children were DBS- than DBS + (37% as opposed to nearly 23%, respectively). However, when using age as a continuous variable, this significant difference disappears. However, the proportion of PTA + children who were DBS- was 45% (17/38 available DBS). Furthermore, the reason behind the journey for DBS- travellers was more often than not to visit friends or relatives (VFR), as opposed to regular holidays or business trips. Also, PTA + DBS- individuals travelled to closer destinations more frequently. A logistic regression model showed that travel distance can be a significantly predictor of serological status (DBS + or DBS-). PTA + travellers who covered a distance of more than 5000 km (as the crow flies) were more likely to be DBS + than those who travelled shorter distances to their destinations (OR = 2.89, $p = 0.00421$). In 45% of cases, PTA + DBS- participants travelled to destinations in Eastern Europe or North Africa. Although we had to take into account that the reported numbers are small, none of the travellers to Eastern Europe and the Middle East sought advice from a pre-travel clinic and neither did 86% of travellers to North Africa. Of the PTA + individuals travelling to these regions, 58, 50 and 33%, respectively, were DBS- (Fig. 1).

4. Discussion and conclusion

According to the serological data from this study, only 67% of Dutch travellers comply with travel health guidelines. Of all the travellers visiting a region for which a HAV vaccination was recommended (PTA +), only 36% received pre-travel advice prior to their trip, while only 41% had proof of valid HAV vaccination in their records. In line with these findings, in a third of all PTA + instances, we could not find HAV antibodies in dry blood spot analyses, suggesting a lack vaccination protection. Non-adherence to travel health guidelines was associated with being a child, visiting friends and relatives and/or only travelling a short distance.

As expected, in the surveys that we conducted and in the records that were available to us, there proved to be a relatively large amount of missing vaccination data. Recall bias will have played a role here, even though we tried to include travellers returning a maximum of one year after their journey. We therefore increased the reliability of our data by adding serological evidence of vaccination by analysing DBS eluates.

The fact that 9 out of 47 PTA + travellers who were DBS- could show proof of being HAV protected during travel but had no detectable antibodies, could be explained by the fact that their vaccination was up to 32 weeks prior to travel and the DBS sampling was up to 12 months after they returned. In other words, at the moment of DBS sampling their HAV antibody concentrations could have decreased (probably after the primary vaccination) and the vaccination was no longer valid, although it would have offered the necessary protection during their journey. Also, the cut-off used in this study (48 mIU/ml) is slightly higher than the commonly used correlates of protection (10–33 mIU/ml). This could also explain this inconsistency, if the antibody titre dropped just below our detection rate but was still above the correlate of protection. Finally, people could belong to the small group (approximately 5%) of non- or low-responders to the HAV primary vaccination [26,27].

Low adherence to travel health guidelines would seem to be mainly a matter of unawareness of the vaccination recommendations [14], particularly when it comes to travelling shorter distances. As destinations in Eastern Europe seem relatively close to home, travellers probably underestimate the risk of contracting an infectious disease [28]. Together with Asia, Eastern Europe is the travel region where the most morbidity attributable to vaccine-preventable diseases occurs [29]. However, the guidelines-compliance rate of travellers to Eastern Europe was only 37% - while for these travellers HAV is one of the most preventable VPDs [29,30]. Asia is the most visited region among the DiVeST population and 82% of travellers who go there comply with travel health guidelines. However, the number of people travelling to Turkey and other countries quite close to the Netherlands but outside Europe, such as Morocco and other North African countries, was relatively high. This is probably due the number of VFR travellers going to those countries. VFR travellers also seem to have a lower risk perception, as do travellers who travel for holiday or business purposes [14]. However, it must be added here that VFR travellers face certain limitations

Table 3
Characteristics of seronegative and seropositive PTA+ travellers.

	PTA+ DBS- travellers (%) n = 47	PTA+ DBS+ travellers (%) n = 98	Total PTA+ travellers (%) n = 145	Chi-square p-value
Age groups (in years)				0.042
11–18	17 (37.0)	22 (22.5)	39 (27.1)	
> 18-35	0 (0.0)	6 (6.1)	6 (4.2)	
> 35-65	28 (60.9)	70 (71.4)	98 (68.1)	
> 65	1 (2.2)	0 (0.0)	1 (0.7)	
Education level (child)[a]				0.942
VMBO	8 (17.8)	20 (21.1)	28 (20.0)	
HAVO	13 (28.9)	28 (29.5)	41 (29.3)	
VWO	24 (53.3)	47 (49.5)	71 (50.7)	
Duration of travel (in days)				0.488
0–7	10 (21.3)	12 (12.2)	22 (15.2)	
> 7-28	33 (70.2)	76 (77.6)	109 (75.2)	
> 28-56	4 (8.5)	9 (9.2)	13 (9.0)	
> 56	0 (0.0)	1 (1.0)	1 (0.7)	
Purpose of travel				0.011
Holiday	28 (60.9)	73 (74.5)	101 (70.1)	
VFR	10 (21.7)	13 (13.3)	23 (16.0)	
Business	4 (8.7)	12 (12.2)	16 (11.0)	
Other	4 (8.7)	0 (0.0)	4 (2.8)	
Destination				0.013
Eastern Europe	15 (31.9)	11 (11.2)	26 (17.9)	
South/Central America	8 (17.0)	14 (14.3)	22 (15.2)	
North Africa	6 (12.8)	12 (12.2)	18 (12.4)	
Central Africa	4 (8.5)	11 (11.2)	15 (10.3)	
Middle East	4 (8.5)	4 (4.1)	8 (5.5)	
Asia	10 (21.3)	46 (46.9)	56 (38.6)	

**Eastern Europe in this table includes the following PTA+ countries: Albania, Belarus, Bosnia, Bulgaria, Macedonia, Montenegro, Romania, Russia, Slovenia and Turkey.

[a] VMBO stands for pre-vocational secondary education, HAVO stands for secondary general education and VWO stands for pre-university education level.

when it comes to pre-travel precautions, such as the cost of consultations and vaccinations and a possible language barrier restricting their access to travel health advice [31]. It could be argued that VFR travellers might be protected by natural immunity. However, in our study population, anti-HAV seropositivity in VFR travellers was lower than in non-VFR travellers.

Rates of non-compliance with travel health guidelines obtained from the DiVeST were surprisingly consistent with the results of Dutch survey-only studies. One third of travellers were unaware of the risks of contracting infectious diseases while travelling to endemic regions worldwide, while the same could be said for 64% of those travelling to closer risk destinations [4,5]. Survey-only research from seven other Western countries was also in line with our results, with 67% reporting that they have been vaccinated. However, 70% of travellers sought pre-travel advice, which was much higher than in our study population [14]. Given that we had a relatively high rate of fully vaccinated people (of all vaccination records showing any form of HAV vaccination, 80% of them showed proof of having received the complete vaccination

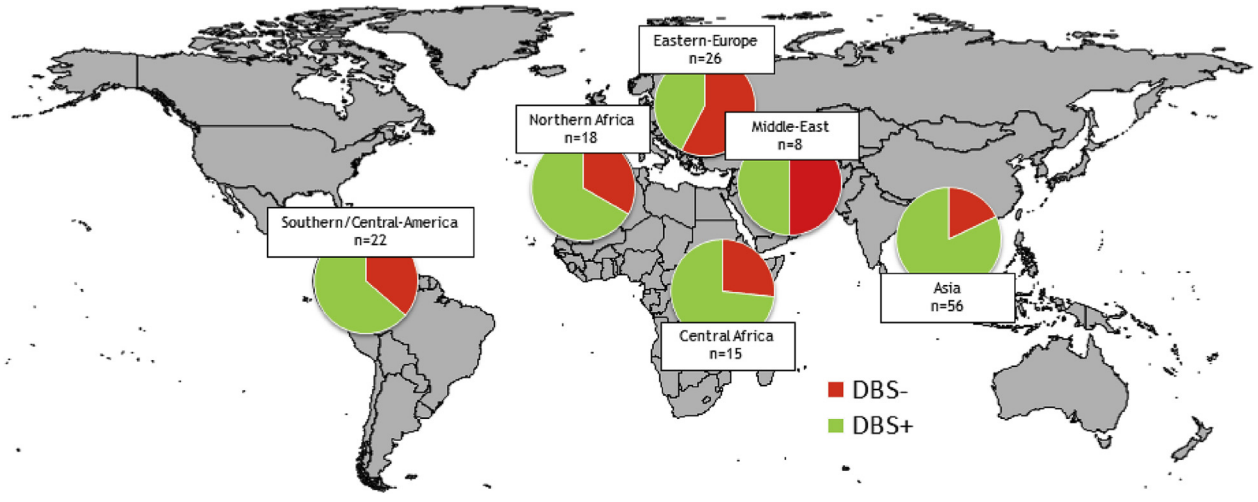

Fig. 1. Adherence to travel health guidelines per PTA+ region*
Missing data was excluded
Eastern Europe includes the following PTA+ countries: Albania, Belarus, Bosnia, Bulgaria, Macedonia, Montenegro, Romania, Russia, Slovenia and Turkey. South/Central America includes Brazil, Colombia, Costa Rica, Cuba, Mexico, Nicaragua, Panama and Suriname. North Africa includes Egypt, Morocco, Gambia and Senegal. Central Africa includes Ghana, Kenya, Mauritius, Namibia, Uganda and Tanzania. The Middle East includes Armenia, Georgia, UAE, Iran, Israel, Jordan and Kazakhstan. Asia includes Cambodia, Hong Kong, India, Indonesia, Japan, Korea, Laos, Mongolia, Myanmar, Nepal, New Caledonia, Sri Lanka, Thailand and Vietnam.

series), it might be the case that our population comprised more experienced travellers [14]. A survey study from nine European airports, reported a rate of non-compliance in travellers to developing countries of at least 44% for HAV vaccination. This higher rate might be explained by a higher rate of VFR (22%) than in our study (16%) [32].

The HAV seroprevalence rate of 27% reported in the general Dutch population aged 15–61, largely corresponds with the 30% seropositivity in our PTA- group [33]. However, this pre-existing immunity also implies that the seroprevalence rate of 67% in the PTA+ population might be an overestimation of the adherence to travel health guidelines.

Children, VFR and short-distance travellers were mentioned as risk groups before, among solo travellers and last-minute travellers [34–37]. These groups must be addressed with clear, bespoke information to increase their adherence to travel health guidelines and thus decrease travel-related morbidity [29]. Moreover, solutions must be found to solve barriers faced by VFR travellers. In our opinion, awareness could best be created via public channels shortly before the start of holiday seasons and, to trigger the awareness of the relevant target groups, specific (short-distance) destinations, travel purposes and age groups should be mentioned [38,39]. The fact that adherence to travel health guidelines in children is lower than in adults, can be related to insufficient knowledge about the recommendations and availability of preventive measures for these age groups or fear for side-effects [36]. Some argue that in very young children hepatitis A is a very mild disease and therefore vaccination is not needed. However, Dutch travel health guidelines recommend to vaccinate children older than 5 (all participants in this study), because even if they are asymptomatic, they will be infectious, putting naïve contacts at risk upon their return [40,41].

While in this study we only focused on the vaccination status and seroprevalence of HAV, it should only be seen as a representation of adherence to guidelines. Travel health advice provided in guidelines is not restricted to vaccination recommendations; it also includes recommendations regarding chemoprophylaxis and risk behaviour related to other travel-related aspects, such as food and water consumption, sexual behaviour and protection against mosquito bites. An extensive study by EuroTravNet has shown that pre-travel consultations were associated with reduced morbidity when it comes to travel-related infectious diseases [42]. The long-term protection afforded by vaccinations can explain why travellers often do not visit a travel clinic prior to their next trip. However, as travellers do not visit a travel clinic prior to each journey, prevention other than vaccination, like pre-travel health advices, hygiene and advice regarding risk behaviour, might also be forgotten in the long run. Another point of attention is making general healthcare providers aware of risks of travel-related infections for travellers to destinations on short-distance, as short-distance travellers in particular are likely to consult their general practice instead of a specialized travel clinic for pre-travel health advice [28,43].

Covering travellers from all over the Netherlands, including all people who did and did not consult a travel clinic, the DiVeST represents a broad travelling population. Although the study excluded elderly and childless couples, it includes people who travelled with all modes of transportation, in contrast with airport surveys. This is highly relevant because air travel comprises only 57% of all international travel [1]. Shorter-distance travellers are not only more likely to travel by land, they are also more likely to be unvaccinated. In this study, members of the same family were included, so as to recruit a larger number of travellers. Although most participants were single-family members, this might still have induced some selection bias. However, the vaccination status of parents and children of the same family can differ, due to natural immunity and misperceptions of protection induced by the NIP.

Furthermore, the study population had a greater proportion of highly educated people than the general population. However, as there is no significant difference in education level between the PTA+ DBS- and PTA+ DBS+ (Table 3), there is no reason to expect the adherence rate to be different. Seen in the context of all international travellers, the study population comprised relatively few VFR travellers - 16% as opposed to 27% of international travellers [1]. Furthermore, non-NIP vaccinated individuals were less willing to participate and were thus underrepresented. This implies that 67% adherence to travel health guidelines is more likely to be an overestimation than an underestimation.

In conclusion it can be said that only two-thirds of Dutch travellers adhere to travel health guidelines. Because their protection is suboptimal, during international travel children, VFR and short-distance travellers are particularly vulnerable to contracting travel-related infectious diseases like hepatitis A. According to our results, these subgroups constitute excellent target groups on which to focus in raising the necessary awareness and thereby reducing travel-related morbidity.

CRediT authorship contribution statement

Laura Doornekamp: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Project administration, Writing - original draft, Visualization. **Corine GeurtsvanKessel:** Resources, Writing - review & editing. **Lennert Slobbe:** Writing - review & editing. **Merel R. te Marvelde:** Validation, Investigation, Data curation. **Sandra M.J. Scherbeijn:** Methodology, Resources. **Perry J.J. van Genderen:** Writing - review & editing. **Eric C.M. van Gorp:** Conceptualization, Supervision. **Marco Goeijenbier:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of competing interest

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

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