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## Changes to country-specific hepatitis A travel vaccination recommendation for UK travellers in 2017—responding to a vaccine shortage in the national context

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## ABSTRACT

**Objectives:** A routine review of hepatitis A travel vaccination recommendations was brought forward in June 2017 due to hepatitis A vaccine shortages and a concurrent outbreak in men who have sex with men (MSM). There were three objectives: first, to document the review process for changing the recommendations for the UK travellers in June 2017. Second, to study the impact of these changes on prescribing in general practice in 2017 compared with the previous 5 years. Third, to study any changes in hepatitis A notifications in June–October 2017 compared with the previous 5 years.

**Study design:** This is an observational study.

**Methods:** Travel vaccination recommendations for countries with either low-risk (<20%) or high-risk (>90%) status according to child hepatitis A seroprevalence were not changed. A total of 67 intermediate-risk countries with existing recommendations for most travellers and with new data on rural sanitation levels were shortlisted for the analysis. Data on child hepatitis A seroprevalence, country income status, access to sanitation in rural areas and traveller volumes were obtained. Information about the vaccine supply was obtained from Public Health England. Changes to the existing classification were made through expert consensus, based on countries' hepatitis A seroprevalence, sanitation levels, level of income, volume of travel and hepatitis A traveller cases. Data on the number of combined and monovalent hepatitis A-containing vaccines prescribed in England, 2012–2017, were obtained from the National Health Service Business Service Authorities. The number of monthly prescriptions for January–September 2017 was compared with the mean number of prescriptions for the same month in the previous 5 years (*t*-test,  $\alpha = 5\%$ , *df* = 4). The

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number of hepatitis A cases notified in June–October 2017 not related to the MSM outbreak was compared with the number of notifications in the same months in previous years.

**Results:** A total of 36 countries were downgraded based on good access (80+% of population) to sanitation in rural areas and the intermediate-risk status in terms of child hepatitis A seroprevalence. For these countries, vaccination would only be recommended to travellers staying long term, visiting friends and relatives or staying in areas without good sanitation. There was a significant decline in hepatitis A vaccine prescriptions in June–September 2017, and there was no increase in the number of notifications.

**Conclusions:** Hepatitis A vaccination recommendations for travel were revised in 2017 following a systematic approach to maintain continuity of supply after a hepatitis A vaccine shortage and increased hepatitis A vaccine demand related to a large outbreak. Improved access to good sanitation in rural areas and low seroprevalence estimates among children have led to 36 countries to no longer require vaccination for most travellers. These changes do not seem to have impacted on hepatitis A notifications in England, although further research will be needed to quantify the impact more precisely.

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## Introduction

Hepatitis A is transmitted faeco-orally via contaminated food and drink, direct contact or sexual activity.<sup>1</sup> It typically leads to mild liver disease but in rare cases, can lead to fulminant hepatitis and death. There is no specific treatment for hepatitis A, and recovery can take weeks and months.<sup>1</sup> Globally, the World Health Organization (WHO) estimates that there are more than 120 million cases per year.<sup>2</sup> Most cases in England and Wales are travel associated, and nearly 250 cases in returning travellers were diagnosed in England and Wales in 2014.<sup>3</sup>

Hepatitis A vaccines are safe and effective. The duration of protection from a completed two-dose course of vaccine can be expected to be at least 25 years in immunocompetent individuals. After this primary course, a booster dose is recommended at 25 years for those at ongoing risk.<sup>1,4</sup>

An outbreak of hepatitis A among men who have sex with men (MSM) affecting England since July 2016 and other parts of the world<sup>5</sup> exacerbated an ongoing global shortage of hepatitis A vaccine. As the UK vaccine supply was severely impacted in Spring 2017, Public Health England (PHE) took a multipronged approach to mitigate supply constraints and respond to the outbreak in MSM. In June 2017, PHE, with the endorsement of the Joint Committee on Vaccination and Immunisation, issued temporary hepatitis A vaccine recommendations on risk-based prioritisation of patients, dose-sparing and alternative vaccine use to preserve the stock for those most likely to benefit from the vaccine.<sup>6</sup> A planned review of country-specific travel vaccination recommendations was brought forward and implemented alongside PHE's temporary vaccine recommendations. Hepatitis A vaccine was prioritised and offered opportunistically to all MSM attending sexual health services.<sup>7</sup>

This article describes the review approach and process for revising the country-specific travel vaccinations and examines evidence of the impact on prescribing in general practice during 2017 versus the previous 5 years and on the number of notified cases of hepatitis A before and during 2017.

## Methods

The existing country-specific hepatitis A vaccination recommendations for UK travellers before June 2017 were based on the WHO data on child hepatitis A virus seroprevalence,<sup>8</sup> country income status (high-income status versus any lower status)<sup>9</sup> and access to sanitation in rural areas (90+% of population).<sup>10</sup>

Travel vaccination recommendations for countries with either low-risk (<20%) or high-risk (>90%) status according to child hepatitis A seroprevalence were not changed. Vaccination continues to be recommended for 'most' travellers to high-risk countries, whereas vaccination is not recommended for travellers to low-risk countries.

As a cautious approach, vaccination was recommended for 'most' travellers to intermediate-risk countries in the existing recommendations, except for the countries with high-income status and where 90+% of the rural population had access to good sanitation. For these countries, vaccination would only be recommended for 'some' travellers.

The terminology, 'most' versus 'some' travellers, is routinely used for travel vaccination advice in the UK. For countries with a 'most' recommendation, vaccine is recommended for all travellers, unless there is a specific reason not to. Several factors will determine whether travellers visiting countries with a 'some' recommendation should be vaccinated; these include the following: individual health status, duration and purpose of travel and planned activities associated with higher risk. In the case of hepatitis A, vaccination is recommended for those planning a long-term stay, visiting friends and relatives or visiting areas with poor sanitation.

For the updated classification, the analyses included the most recent WHO and the United Nations International Children's Emergency Fund data on rural sanitation levels.<sup>11</sup> At the time of the review, no new comprehensive data set was available on child seroprevalence.

The review of the country-specific recommendation was carried out in two stages. First, a modification of the existing criteria was considered, such as lowering the threshold for

access to sanitation in rural areas from 90% to either 80% or 70% and removing the existing high-income country criterion. The previous review incorporated the World Bank income status. The income status is correlated with access to good sanitation and therefore, not strictly needed in this particular construct. Incorporating the income status at the same time meant that a number of countries with significant improvement in access to good sanitation would unnecessarily be excluded from consideration in the full review process. Second, the results were discussed by an expert panel taking additional factors into account such as available data on foreign travel-associated hepatitis A cases, volumes and purpose of travel.

The total number of intermediate-risk countries under review was 67; of these, 25 had figures for the proportion of rural population with access to good sanitation between 90% and 100%, 15 between 80% and 89% and eight between 70% and 79%. The remaining countries had figures below 70%. Data on the volume of travel to specific destinations were obtained from the International Passenger Survey on visits abroad undertaken by residents in England, 2013–2016, and averaged over the 4 years.<sup>12</sup>

Information about vaccine supply issues was obtained from PHE's Vaccine Update newsletters, March–September 2017.<sup>13</sup> The shortage was first mentioned in March 2017.

Data on the number of hepatitis A-containing vaccines (monovalent hepatitis A, combined hepatitis A/hepatitis B and hepatitis A/typhoid) prescribed in general practice in England between January 2012 and September 2017 were obtained from the National Health Service (NHS) Business Service Authorities.<sup>14</sup> The number of monthly prescriptions between January and September 2017 was compared with the mean number of prescriptions for the same month in the previous 5 years as a reference period with no known incidences of vaccine shortage using t-tests (single versus multiple observation two-group equivalence of means,  $\alpha = 5\%$ ,  $df = 4$ ).<sup>15</sup>

To estimate the combined impact of the revised recommendations and vaccine supply issues on disease incidence, we compared the number of hepatitis A cases (excluding cases associated with the MSM outbreak) notified to PHE between June and October 2017, with the number of notifications in the same time period in the previous 4 years (excluding those associated with the MSM outbreak in 2016), using a test for trends. These cases are not exclusively travel associated, but as most cases in England are travel related, these numbers can be used as a crude way to evaluate whether the aforementioned factors have had a major impact on disease notifications.

## Results

### Review of country recommendations review

A total of 67 intermediate-risk countries with existing recommendations for most travellers and with new data on rural sanitation levels were shortlisted for the analysis. Jamaica had previously been assigned to the lower risk, 'some' travellers status based on the expert consensus, but was included in the analysis for a comparison of the effect of different criteria (Table

1). Removing the high-income criterion, while keeping the 90+% threshold for rural sanitation, would 'release' 25 lower income countries with good rural sanitation for consideration in a downgrading exercise. Lowering the rural sanitation threshold from 90+% to 80+% would include a further 15 countries. Lowering the threshold still further from 80+% to 70+% would only increase the list of countries with another eight countries. Based on the expert consensus taking into account the number of travel-associated cases of hepatitis A against the traveller flows and types of traveller to those countries, and any other factors (such as the rates of other gastro-intestinal illness), Egypt, Syria and Tunisia were re-assigned to the stricter 'most' travellers category. In some instances, the political stability and infrastructure of a country were taken into consideration. Therefore, the total number of countries that were downgraded from 'most' to 'some' as a result of this exercise was 36 (Table 1; as indicated in column K).

### Hepatitis A vaccine prescribing

Compared with the mean number of prescriptions of hepatitis A-containing vaccines for the same month in the previous 5 years, prescription numbers dropped by 23% in June 2017, 33% in July, 47% in August and 56% in September ( $P < 0.05$  for all, Fig. 1). Hepatitis A/hepatitis B vaccine prescriptions were also significantly lower in February and April of 2017 compared with those months in the previous 5 years (–24% and –33%, respectively).

There were no or only limited supply of most adult vaccines from manufacturers during March–September 2017 (end of the study period), although supply constraints for hepatitis A/hepatitis B combination vaccine were only reported from July 2017 onwards (Table 2). The vaccine shortage was less severe for child/adolescent vaccines early in the year, but only limited stock was available from July onwards. There was a limited supply of one of the hepatitis A typhoid vaccine products in March and April for both adults and adolescents, after which there were no supply of either product for the rest of the study period.

The number of visits abroad to countries where 'most' travellers would be recommended hepatitis A vaccination (assuming that they either had not been vaccinated previously or a booster was due) is estimated, as a result of the revised recommendations, to have fallen from 7.4 million (2013–2016 average) to 2.5 million visits (2017) per year, i.e. a 66% decrease.

### Hepatitis A notifications

Between June and October 2017, 244 hepatitis cases were notified to PHE, excluding those associated with the MSM outbreak, compared with an average of 230 in 2013–2016 (Table 3). No trend in notification was detected between 2013 and 2017 ( $P = 0.17$ ).

## Discussion

June–July are the peak months for hepatitis A vaccination in the lead up the main UK holiday period in August. In 2017,

**Table 1 – Hepatitis A country classification revisited—with and without high-income status, latest rural sanitation data and variable sanitation threshold.**

Country	Travellers per year 2013–2016	VFR%	Economic status	Sanitation% Rural (previous review)	Sanitation% Rural (new)	2015 Review decision	Predicted based on high-income and 90+% rural sanitation (previous)	Predicted based on 90+% rural sanitation (new)	Predicted based on 80+% rural sanitation (new)	Predicted based on 70+% rural sanitation (new)
A	B	C	D	E	F	G	I	J	K	L
Albania	35,423	54.2	Low	86	90	Most	Most	Some	Some	Some
Argentina	25,607	28.9	Low	99	98	Most	Most	Some	Some	Some
Belarus	8563	52.4	Low	95	95	Most	Most	Some	Some	Some
Bosnia and Hz.	10,624	47.3	Low	92	92	Most	Most	Some	Some	Some
Chile	12,143	22.3	High	89	91	Most	Most	Some	Some	Some
Egypt <sup>a</sup>	248,480	14.9	Low	94	93	Most	Most	Some	Some	Some
Jordan	28,327	37.8	Low	98	99	Most	Most	Some	Some	Some
Kazakhstan	11,284	35.9	Low	98	98	Most	Most	Some	Some	Some
Kyrgyzstan	2628	40.9	Low	92	96	Most	Most	Some	Some	Some
Libya	16,278	48.2	Low	96	96	Most	Most	Some	Some	Some
Malaysia	102,963	39.8	Low	95	96	Most	Most	Some	Some	Some
The Maldives	48,799	1.1	Low	100	98	Most	Most	Some	Some	Some
Mauritius	114,408	16.5	Low	90	93	Most	Most	Some	Some	Some
Montenegro	25,330	11.3	Low	87	92	Most	Most	Some	Some	Some
Palau	–	–	Low	100	100	Most	Most	Some	Some	Some
Samoa	–	–	Low	91	91	Most	Most	Some	Some	Some
Serbia	47,014	61.0	Low	96	94	Most	Most	Some	Some	Some
Sri Lanka	112,580	41.5	Low	94	97	Most	Most	Some	Some	Some
Syria <sup>a</sup>	810	100	Low	95	95	Most	Most	Some	Some	Some
Tajikistan	1204	0	Low	95	95	Most	Most	Some	Some	Some
Thailand	372,618	18.0	Low	96	96	Most	Most	Some	Some	Some
Ukraine	48,176	50.3	Low	89	93	Most	Most	Some	Some	Some
Uzbekistan	5154	33.1	Low	100	100	Most	Most	Some	Some	Some
Poland	1,729,136	70.7	High	–	97	Most	–	Some	Some	Some
Réunion	–	–	–	–	95	Most	–	Some	Some	Some
Algeria	55,106	77.0	Low	88	82	Most	Most	Most	Some	Some
Azerbaijan	7997	32.0	Low	78	87	Most	Most	Most	Some	Some
Belize	2044	14.5	Low	88	88	Most	Most	Most	Some	Some
Bulgaria	289,211	33.3	Low	100	84	Most	Most	Most	Some	Some
Cuba	134,466	3.4	Low	88	89	Most	Most	Most	Some	Some
Fiji	2371	40.7	Low	82	88	Most	Most	Most	Some	Some
Guyana	2607	0	Low	82	82	Most	Most	Most	Some	Some
Iran	48,330	80.2	Low	82	82	Most	Most	Most	Some	Some
Iraq	41,403	63.8	Low	82	84	Most	Most	Most	Some	Some
Jamaica <sup>b</sup>	190,532	35.8	Low	82	84	Some	Most	Most	Some	Some
Lithuania	238,799	77.2	High	85	83	Most	Most	Most	Some	Some
Tonga	–	–	Low	89	89	Most	Most	Most	Some	Some
Tunisia <sup>a</sup>	253,878	5.9	Low	77	80	Most	Most	Most	Some	Some
Turkey	1,172,756	6.0	Low	75	86	Most	Most	Most	Some	Some
Latvia	152,340	68.6	High	–	82	Most	–	Most	Some	Some

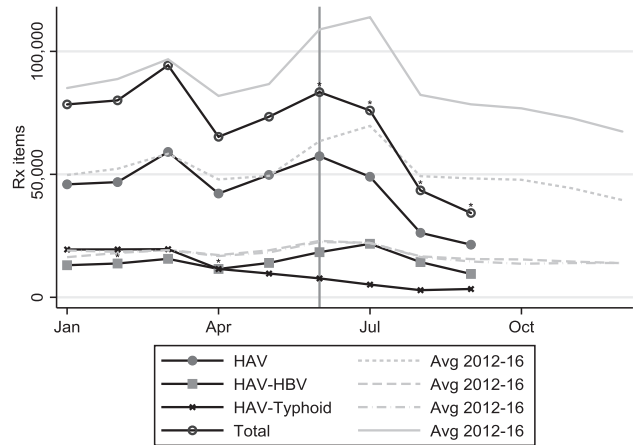
Armenia	3898	37.4	Low	81	78	Most	Most	Most	Most	Some
Myanmar	–	23.8	Low	74	77	Most	Most	Most	Most	Some
Georgia	4595	45.9	Low	91	76	Most	Most	Most	Most	Some
North Korea	1579	0	Low	73	73	Most	Most	Most	Most	Some
Paraguay	832	18.5	Low	53	78	Most	Most	Most	Most	Some
The Philippines	97,192	65.5	Low	69	71	Most	Most	Most	Most	Some
Vietnam	79,381	23.3	Low	67	70	Most	Most	Most	Most	Some
Dominican Republic	73,176	8.2	Low	–	76	Most	Most	Most	Most	Some

VFR, visiting friends and relatives.

Previous review was based on column D and E resulting in I. The current review was based on column F resulting in K.

<sup>a</sup> Egypt, Syria and Tunisia retained the 'most' traveller status based on return traveller cases and other particulars.

<sup>b</sup> Jamaica had already been reassigned to the more lenient 'some' traveller status in the previous review, i.e. no change in the status as result of the current review.



**Fig. 1 – Prescribing of HAV-containing vaccines in 2017 versus monthly averages from 2012 to 2016. Observations significantly different from the 2012–2016 mean at 5% level marked with \* (t-test,  $df = 4$ ). The vertical line indicates the month where changes to country-specific travel vaccination and dose-sparing recommendations were implemented. HAV, hepatitis A; HBV, hepatitis B.**

however, there was a decrease of 23% in vaccinations in June, the month of the change in recommendations, and of 33%, 47% and 56% in July, August and September, respectively. The fact that the total number of hepatitis A and hepatitis A combination vaccine prescriptions had already begun to decrease in June suggests that the vaccine supply constraints also played a role in the overall decline as ordering restrictions were imposed by manufacturers. The estimated decline in vaccinations required for 'most' travellers was 66% assuming the prior unvaccinated status. These data are consistent with the observed decrease in vaccine prescriptions. Limited data on hepatitis A notifications suggest that the changes in recommendations, taken together with the concurrent vaccine supply issues, have not led to a large increase in hepatitis A importation to England. The supply situation is expected to improve in 2018, and only a longer time series will be able to reveal the overall impact on disease incidence, if any, of the changes to the country-specific recommendations.

### Limitations

Data on hepatitis A vaccinations were only available from NHS general practice (GP), where the vaccine can be obtained for free both in response to outbreaks and for overseas travel.<sup>16</sup> In practice, hepatitis A travel vaccinations are also administered in private travel clinics and private GP practices. There is no centralised database for private travel clinics and private prescriptions.<sup>17</sup> Hypothetically, some of the bigger, private chains of travel clinics may be more resilient to shortages compared with the smaller GP practices as the stock is likely to be purchased centrally in bulk and distributed within the organisation. So, even though the vaccine is available for free in general practice (NHS), it is possible that some travellers will have been able to obtain vaccination in the private sector during the shortage. The analysis of hepatitis A notifications is limited as it is not possible to differentiate travel-associated



**Table 2 – The UK hepatitis A travel vaccine supply constraints information (current situation), March–September 2017.**

Age group	Adult					Children/adolescents								
	Havrix Single	Havrix ×10	Avaxim	VAQTA	Twinrix	Hepatyrix	ViATIM	Havrix Single	Havrix ×10	VAQTA	Ambirix	Twinrix Paed	Hepatyrix	ViATIM
Hepatitis Month	A	A	A	A	A/B	A/T	A/T	A	A	A	A/B	A/B	A/T	A/T
March	Lim	None	Lim	None	None	None	Lim	None	None	None	None	None	None	Lim
April		None	Lim	None	None	None	Lim	None	None	None	None	None	None	Lim
May		None	Lim	None	None	None	None	None	None	None	None	None	None	None
June		None	Lim	None	None	None	None	None	None	None	None	None	None	None
July		None	Lim	None	None	None	None	None	None	None	None	Lim	None	None
August		None	Lim	None	None	None	None	None	None	None	None	Lim	None	None
September		None	None	None	None	None	Lim	None	None	Lim	None	Lim	None	Lim

T, typhoid; Lim, limited supply.  
 Market authorisation holder/products include GSK: Ambirix, Havrix, Hepatyrix, Twinrix; MSD: VAQTA; Sanofi Pasteur: Avaxim, ViATIM.  
 A = Hepatitis A; B = Hepatitis B; A/B = Hepatitis A and B combined; A/T = Hepatitis A and typhoid combined.  
 Source: PHE (2017).<sup>13</sup>

**Table 3 – Hepatitis A notifications, 2013–2016.<sup>a</sup>**

Time period	Notifications
June–October 2013	159
June–October 2014	232
June–October 2015	276
June–October 2016	251
June–October 2017	244

MSM, men who have sex with men.  
<sup>a</sup> Excludes cases associated with the MSM outbreak ongoing since July 2016.

cases from others in the current data. While most cases in England are travel associated, the data provide reassurance that the travel hepatitis A vaccination changes have not led to a large increase in hepatitis A incidence. Restricting the analysis to travel-associated cases, including the country of travel will enable a more precise estimation of the impact of the changes on recommendations. There is often a lag of several months in these data becoming available.

### Conclusions

Hepatitis A vaccination recommendations for travel were revised in 2017 following a systematic approach to maintain continuity of supply after a hepatitis A vaccine shortage and increased hepatitis A vaccine demand related to a large outbreak. Improved access to good sanitation in rural areas and low seroprevalence estimates among children have led to 36 countries to no longer require vaccination for most travellers. These changes do not seem to have impacted on hepatitis A notifications in England, although further research will be needed to quantify the impact more precisely.

### Author statements

#### Ethical approval

None sought. This is a database study.

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#### Competing interests

None declared.

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