Table 4. The comparison between *P. vivax* malaria cases and *P. ovale* malaria cases

	P. vivax malaria	*P. ovale* malaria	P value
Number of patients	18	10	
Age (mean ± SD)	29.8 ± 12.0	27.8 ± 7.0	0.326
Sex (male)	13	7	0.900
Areas to travel			
Africa	1	10	
Asia, Oceania	13	0	< 0.001
South America	4	0	
Average parasitemia (%)	0.229	0.031	0.002
Positive by RDTs (%)	16/17 (94.1)	2/9 (22.2)	< 0.001
BN (%)	9/10 (90.0)	0/5 (0)	< 0.001
SDMA (%)	7/7 (100)	2/4 (50.0)	0.039

The data are presented as number of patients, unless otherwise specified.
P. vivax: *Plasmodium vivax*; *P. ovale*: *Plasmodium ovale*; RDT: rapid diagnostic test; BN: Binax NOW® malaria; SDMA: SD malaria antigen®

Discussion

RDTs are generally useful for diagnosing malaria infection [3–5]. However, the sensitivity of RDTs depends upon the species of malaria parasite. The highest sensitivity was observed for *P. falciparum* malaria (78.8–99.1%) [5, 11, 15–18], followed by *P. vivax* malaria (77.6–96%), *P. ovale* malaria (18.4–80.0%), and *P. malariae* malaria (21.4–47.0%) [3–5, 19, 20]. For non-falciparum malaria, RDT sensitivity was particularly low for *P. ovale* and *P. malariae*, a finding that may be attributable to the low parasitemia [3–5], the difference in targeted antigens [6, 9, 10], or the genetic variability between the infected parasites [21, 22].

Low parasitemia was associated with false-negative results from the RDTs regardless of malaria species [4, 5]. Moreover, since reinfection and semi-immune status generally cause low parasitemia [23], those influences need to be eliminated. Travellers who visiting families and relatives and expatriates living in malaria endemic areas were excluded from our study because they were at a higher risk of reinfection. The parasitemia in *P. ovale* malaria was consequently as low as that in immune patients and was significantly lower than that in *P. vivax* malaria. This finding, along with those in previous reports [23], suggests that *P. ovale* malaria presents with low parasitemia even in non-immune travellers, which may result in false-negative results from the RDTs.

As mentioned above, *P. malariae* and *P. ovale* malaria may be difficult to diagnose by RDTs due to the low parasitemia [7, 8, 11]. Recently, Houzé et al. [24] reported that the new RDT, Clearview, has improved sensitivity for *P. malariae* malaria but that the sensitivity for *P. ovale* malaria was not improved. Moreover, even a case of *P. ovale* malaria with relatively high parasitemia (21,150 parasites/μL) resulted in a false-negative RDT result in their study, implying some reason for false-negative results other than low parasitemia in *P. ovale* malaria. The difference in target antigens from parasites, such as HRP2 and PfLDH for *P. falciparum* or pLDH and aldolase for pan-malaria species, can also influence the sensitivity of RDTs [6]. Detecting *P. ovale* and *P. vivax*, two RDTs (BN for aldolase detection and SDMA for pLDH detection) were used in our study. SDMA showed relatively good sensitivity for both *P. vivax* and *P. ovale* as compared to BN, probably because pLDH-based RDTs generally perform better than aldolase-based RDTs [20]. Bigaillon et al. [6] also reported the ineffectiveness of BN in detecting *P. ovale* malaria, which they suggested was due to low aldolase production by *P. ovale* malaria [10]. Aldolase-based RDTs generally show low sensitivity not only for *P. ovale* malaria but also for other types of malaria [9], but low sensitivity was also observed for pLDH-based RDTs [10–12, 16, 17, 24].

Although the genetic variability of HRP2 was related to the low sensitivity of RDTs for *P. falciparum* malaria [21], it was reported that the genetic variability of pLDH [22] and aldolase [25, 26] did not explain the relatively poor performance of RDTs for the detection of *P. falciparum*, *P. vivax*, and *P. malariae*. Talman et al. [22] reported that *P. ovale* exhibited three different types of amino acid sequence (named O1, O2 and O3), which may contribute to the relatively poor detection of *P. ovale*. The sensitivity of RDTs is still insufficient for accurate diagnosis of *P. ovale* malaria regardless of the type of antigens. Therefore, microscopic examination is preferable for the definitive diagnosis of *P. ovale* malaria.

The sensitivity of RDTs was not high enough to accurately diagnose *P. ovale* malaria in Japanese travellers who were never infected with malaria previously. Thus, microscopic examination is required to ensure that *P. ovale* malaria is not overlooked.

Conflict of Interests

All the authors declare that they have no conflict of interests.

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References

1. WHO: Guidelines for the treatment of malaria. 2nd edition. Geneva: World Health Organization; 2010.
2. Kimura M, Miyake H, Kim HS, et al. Species-specific PCR detection of malaria parasites by microtiter plate hybridization: clinical study with malaria patients. J Clin Microbiol 1995; 33: 2342–2346.
3. Moody A. Rapid diagnostic tests for malaria parasites. Clin Microbiol Rev 2002; 15: 66–78.
4. McMorrow ML, Aidoo M, Kachur SP. Malaria rapid diagnostic tests in elimination settings—can they find the last parasite? Clin Microbiol Infect 2011; 17: 1624–1631.
5. Marx A, Pewsner D, Egger M, et al. Meta-analysis: accuracy of rapid tests for malaria in travelers returning from endemic areas. Ann Intern Med 2005; 142: 836–846.
6. Bigaillon C, Fontan E, Cavallo JD, et al. Ineffectiveness of the Binax NOW malaria test for diagnosis of Plasmodium ovale malaria. J Clin Microbiol 2005; 43: 1011.
7. Farcas GA, Zhong KJ, Lovegrove FE, et al. Evaluation of the Binax NOW ICT test versus polymerase chain reaction and microscopy for the detection of malaria in returned travelers. Am J Trop Med Hyg 2003; 69: 589–592.
8. Grobusch MP, Hanscheid T, Zoller T, et al. Rapid immunochromatographic malarial antigen detection unreliable for detecting Plasmodium malariae and Plasmodium ovale. Eur J Clin Microbiol Infect Dis 2002; 21: 818–820.
9. Nkrumah B, Acquah SE, Ibrahim L, et al. Comparative evaluation of two rapid field tests for malaria diagnosis: Partec Rapid Malaria Test® and Binax Now® Malaria Rapid Diagnostic Test. BMC Infect Dis 2011; 11: 143.
10. Mason DP, Kawamoto F, Lin K, et al. A comparison of two rapid field immunochromatographic tests to expert microscopy in the diagnosis of malaria. Acta Trop 2002; 82: 51–59.
11. Maltha J, Gillet P, Bottieau E, et al. Evaluation of a rapid diagnostic test (CareStart Malaria HRP-2/pLDH (Pf/pan) Combo Test) for the diagnosis of malaria in a reference setting. Malar J 2010; 9: 171.
12. Gillet P, van Dijk DP, Bottieau E, et al. Test characteristics of the SD FK80 Plasmodium falciparum/Plasmodium vivax malaria rapid diagnostic test in a non-endemic setting. Malar J 2009; 8: 262.
13. Kimura M, Kaneko O, Liu Q, et al. Identification of the four species of human malaria parasites by nested PCR that targets variant sequences in the small subunit rRNA gene. Parasitol Int 1997; 46: 91–95.
14. Tanizaki R, Ujiie M, Kato Y, et al. First case of *Plasmodium knowlesi* infection in a Japanese traveller returning from Malaysia. Malar J 2013; 12: 128.
15. Maltha J, Gillet P, Jacobs J. Malaria rapid diagnostic tests in endemic settings. Clin Microbiol Infect 2013; 19: 399–407.
16. Van der Palen M, Gillet P, Bottieau E, et al. Test characteristics of two rapid antigen detection tests (SD FK50 and SD FK60) for the diagnosis of malaria in returned travellers. Malar J 2009; 8: 90.
17. Maltha J, Gillet P, Cnops L, et al. Evaluation of the rapid diagnostic test SDFK40 (Pf-pLDH/pan-pLDH) for the diagnosis of malaria in a non-endemic setting. Malar J 2011; 10: 7.
18. Maltha J, Gillet P, Jacobs J. Malaria rapid diagnostic tests in travel medicine. Clin Microbiol Infect 2013; 19: 408–415.
19. Abba K, Deeks JJ, Olliaro P, et al. Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. Cochrane Database Syst Rev 2011: CD008122.
20. Barber BE, William T, Grigg MJ, et al. Evaluation of the sensitivity of a pLDH-based and an aldolase-based rapid diagnostic test for diagnosis of uncomplicated and severe malaria caused by PCR-confirmed Plasmodium knowlesi, Plasmodium falciparum, and Plasmodium vivax. J Clin Microbiol 2013; 51: 1118–1123.
21. Baker J, McCarthy J, Gatton M, et al. Genetic diversity of Plasmodium falciparum histidine-rich protein 2 (PfHRP2) and its effect on the performance of PfHRP2-based rapid diagnostic tests. J Infect Dis 2005; 192: 870–877.
22. Talman AM, Duval L, Legrand E, et al. Evaluation of the intra- and inter-specific genetic variability of Plasmodium lactate dehydrogenase. Malar J 2007; 6: 140.
23. Collins WE, Jeffery GM. Plasmodium ovale: parasite and disease. Clin Microbiol Rev 2005; 18: 570–581.
24. Houze S, Hubert V, Cohen DP, et al. Evaluation of the Clearview(R) Malaria pLDH Malaria Rapid Diagnostic Test in a non-endemic setting. Malar J 2011; 10: 284.
25. Lee N, Baker J, Bell D, et al. Assessing the genetic diversity of the aldolase genes of Plasmodium falciparum and Plasmodium vivax and its potential effect on performance of aldolase-detecting rapid diagnostic tests. J Clin Microbiol 2006; 44: 4547–4549.
26. Cho CH, Nam MH, Kim JS, et al. Genetic variability in Plasmodium vivax aldolase gene in Korean isolates and the sensitivity of the Binax Now malaria test. Trop Med Int Health 2011; 16: 223–226.

原　著

アーテメター・ルメファントリン合剤の日本人における使用経験

[1] 国立国際医療研究センター国際感染症センター，[2] 国立国際医療研究センターエイズ治療開発センター，
[3] 東京医科大学病院感染制御部・感染症科，[4] 国立国際医療研究センター研究所熱帯医学・マラリア研究部

忽那　賢志[1]　小林泰一郎[1,2]　加藤　康幸[1]　藤谷　好弘[1]
馬渡　桃子[1]　氏家　無限[1]　竹下　　望[1]　早川佳代子[1]
金川　修造[1]　水野　泰孝[1,3]　狩野　繁之[4]　大曲　貴夫[1]

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要　旨

近年，合併症のない熱帯熱マラリアに対してはアーテミシニン誘導体と他剤を組み合わせた併用療法が第一選択となっている．本邦では熱帯病治療薬研究班が保管・供給しており薬剤使用機関にて使用可能である．

今回我々は2005年10月1日から2013年3月31日までに国立国際医療研究センターを受診しマラリアと診断され，治療薬としてアーテメター・ルメファントリン合剤（以下AL合剤とする）を用いた日本人症例19例（熱帯熱マラリア18例，三日熱マラリア1例）について診療録を用いて後方視的検討を行った．日本人症例19例のうちAL合剤のみで治療を行った熱帯熱マラリア症例は10例あり，原虫寄生率は0.02～4.4%（中央値0.28%），寄生原虫数は22～225,720/μL（中央値12,440/μL）に分布した．発熱消失時間は14～66時間（中央値25.0時間），原虫消失時間は16～62時間（中央値36.0時間）であった．原虫消失時間と初診時の原虫寄生率において正の相関が得られた．再燃群（n＝2）では非再燃群（n＝8）と比較して原虫寄生率が高く（再燃群4.05%vs非再燃群0.24%：p＝0.044），原虫消失時間（再燃群55.5時間vs非再燃群31.5時間：p＝0.044）が長かった．

本研究では19例中3例とこれまでに報告されている再燃率よりも高かったが，これは嘔吐・下痢などの消化器症状が強く吸収が不十分であったこと，同時に摂取すべき脂質量が不十分であったこと，原虫寄生率が他の非再燃群と比較して高い傾向にあったことなどが考えられた．これらの症例ではグルコン酸キニーネ注を選択することによって再燃は防げたかもしれない．その一方で，重症マラリアの定義を満たす症例であっても経口治療で治癒しうる症例も少なからず存在しており，どのような症例で経口治療が可能であるかは今後さらなる検討を要する．

〔感染症誌　88：833～839，2014〕

序　文

近年，本邦におけるマラリアは年間70例前後の比較的稀な疾患であるが，渡航者における発熱疾患として最も注意すべき感染症であることは論をまたない[1]．本邦で薬事承認を受けている抗マラリア薬として，塩酸メフロキン錠（メファキン「ヒサミツ」錠275），塩酸キニーネ末，アトバコン・プログアニル塩酸塩錠（マラロン配合錠）がある．しかし国外では，合併症のない熱帯熱マラリアに対しては，アーテミシニン誘導体と他剤を組み合わせた併用療法（Artemisinin-based combination therapy：ACT）が第一選択となっている国もある．アーテメター・ルメファントリン合剤（リアメット）（以下AL合剤とする）は1錠中にアーテミシニン誘導体であるアーテメター20mgとアリルアミノアルコール系抗マラリア薬であるルメファントリン120mgを含むACTを代表する抗マラリア薬である．1980年に厚生省研究事業として発足した「熱帯病治療薬研究班（現，厚生労働科学研究費補助金医療技術実用化総合研究事業「わが国における熱帯病・寄生虫症の最適な診断治療体制の構築」班）」は，AL合剤を2002年11月より導入し，マラリア症例に

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国立国際医療研究センター国際感染症センター
忽那　賢志

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使用してきた．これまで海外では多くの使用報告があるものの，日本人におけるAL合剤の使用成績についてはまとまったものは少ない．今回，国立国際医療研究センターにおいてAL合剤が使用された日本人症例について，既報告の13例[2]に6例を追加し，治療効果，再燃率，副反応を詳細に検討した．

対象と方法

2005年10月1日から2013年3月31日までに国立国際医療研究センターを受診し，マラリアと診断され，AL合剤が使用された日本人症例について診療録を用いて後方視的検討を行った．当院は東京都新宿区に位置する急性期医療を担う教育病院であり，トラベルクリニックを有する．1999年から「熱帯病治療薬研究班」の薬剤使用機関となっている．

マラリアの診断は，国立国際医療研究センター研究所熱帯医学・マラリア研究部において，末梢血薄層塗抹標本の鏡検により行われた．原虫種鑑別が困難な場合，臨床的に偽陰性が疑われる場合にはPCR法も行われた．

該当する症例について，年齢，性別，渡航先，渡航期間，渡航目的，発症から治療開始までの期間，マラリア予防内服の有無，感染マラリア原虫種，原虫寄生率，AL合剤投与回数，発熱消失期間(Fever Clearance Time：FCT)，原虫消失期間(Parasite Clearance Time：PCT)，再燃の有無，副反応を抽出した．統計解析はIBM-SPSS statistics 20 (2011)を使用した．再燃群と非再燃群における原虫寄生率，FCT，PCTの比較にはMann-Whitney U testを利用し，$p<0.05$を有意差ありとした．

なお，国内未承認であるAL合剤：Riamet (Novartis社)は，「熱帯病治療薬研究班」から入手し，患者本人に対する説明と文書による同意の取得後に使用した．

成　績

対象期間において当院でマラリアと診断された107症例のうち，抗マラリア薬による治療の対象となったのは86症例であり，残り21例は渡航先で治療がすでに完了している等の理由で治療対象から除外された．治療の対象となった86症例のうちAL合剤が使用されたのは23症例であった．このうち日本人以外の症例4例を除き，19症例を本研究の対象とした．

19症例の詳細をTable 1に示す．対象となった患者は全て入院し，体温は1日5回以上測定されていた．また，全ての症例でAL合剤4錠（アーテメター80 mg/ルメファントリン480mg）が計6回（1日2回）投与されていた．男性13例，女性6例，年齢は18歳から53歳（中央値29歳）であった．

感染マラリア原虫種は熱帯熱マラリアが18例，三日熱マラリアが1例であった．3例が予防内服（ドキシサイクリン1例，メフロキン1例，クロロキン/プログアニル1例）をしていたが，いずれも滞在中に内服を中断していた．原虫寄生率は0（PCR法でのみ陽性）～27.7%（中央値0.72%），寄生原虫数は0～1,263,100/μL（中央値33,500/μL）に分布した．なお，原虫寄生率0%・寄生原虫数0/μ/であった症例2は渡航先のパプアニューギニアで熱帯熱マラリアと診断され受診時にすでに現地で処方されたアーテスネート100mgを2回内服していたが，現地初診時の原虫寄生率・寄生原虫数は不明である．

渡航先はサハラ以南のアフリカ地域20例，オセアニア2例，東南アジア1例であった．発症から何らかの抗マラリア薬が開始されるまでの時間は0～12日（中央値4.0日）であった．

19例のうち8例（症例11～18）において，AL合剤投与前に他の抗マラリア薬が使用されていた．5例にアーテスネート坐薬（Plasmotrim Rectocaps；Mepha社），2例にアーテスネート静注製剤（中国桂林製薬社），1例にグルコン酸キニーネ注（Quinimax；Sanofi-Aventis社），1例にメフロキン錠（メファキン「ヒサミツ」錠275；久光製薬）が使用されており，1例は現地で処方されたアーテスネート錠を内服していた．また，このうち2例はAL合剤に加えてドキシサイクリン（ビブラマイシン；ファイザー）が併用されていた．三日熱マラリアの1例（症例19）ではAL合剤の投与後にプリマキンによる根治療法が行われた．

19例のうち，AL合剤のみが使用された熱帯熱マラリア10例(症例1～10)では，原虫寄生率は0.02～4.4%（中央値0.28%），寄生原虫数は22～225,720/μL（中央値12,440/μL）に分布した．FCTは14～66時間（中央値25.0時間）であり，PCTは16～62時間（中央値36.0時間）であった．PCTをY軸，初診時の寄生原虫数をX軸として，10症例をそれぞれプロットして線形単回帰分析をしたところ，$R^2=0.482$（B＝0.026，95%信頼区間：0.000018—0.000217）の正の相関が得られた（Fig.）．

AL合剤のみで治療した10症例のうち2例(症例9，10）が初期治療開始から28日以内に再燃した．2例ともに再燃時もAL合剤で治療が行われた．最終的に全ての症例が治癒した．再燃群（n＝2）では非再燃群（n＝8）と比較して原虫寄生率が高く（再燃群4.05% vs 非再燃群0.24%；p＝0.044），PCT（再燃群55.5時間 vs 非再燃群31.5時間；p＝0.044)が長かった．FCT（再燃群49.0時間 vs 非再燃群24.0時間；p＝0.267）については再燃群の方が長い傾向にあったが統計学的な有意差はなかった．

Table 1 Demographic features and clinical course of those treated with Artemether/lumefantrine (n = 19).

No.	Age	Gender	Contracted countries	Purpose	Time between onset to start of malaria therapy	Parasitemia (%)	Parasites /μL	Malaria species	Malaria prophylaxis	FCT	PCT	Adverse effect	Use of other antimalarial drug	Recrudescence
1	39	M	Burkina Faso	Leisure	2	0.45	21,375	*P. falciparum*	−	24	24	−	−	−
2	46	M	Benin	Leisure	2	0.28	12,656	*P. falciparum*	−	24	20	−	−	−
3	22	M	Republic of Congo Senegal Mali	Leisure	5	0.02	858	*P. falciparum*	−	22	27	−	−	−
4	26	F	Guinea	Business	7	0.06	22.2	*P. falciparum*	−	40	46	−	−	−
5	27	F	Benin	Business	1	0.72	33,552	*P. falciparum*	Chloroquine/ Proguanil (cessation)	25	39	−	−	−
6	26	F	Uganda	Business	10	0.33	12,441	*P. falciparum*	−	14	36	−	−	−
7	49	M	Ghana	Business	2	0.03	1,593	*P. falciparum*	doxycycline (cessation)	66	16	nausea	−	−
8	24	F	Mallawi	Leisure	3	0.2	6,440	*P. falciparum*	+	22	41	−	−	−
9	32	M	Benin	Business	3	4.4	225,720	*P. falciparum*	−	36	49	nausea, vomitting, elevation of LFTs	−	+
10	50	M	Nigeria	VFR	2	3.7	193,880	*P. falciparum*	−	62	62	−	−	+
11	20	M	Papua New Guinea	Leisure	6	0	0	*P. falciparum*	mefloquine (cessation)	18		−	artesunate tablets (foreign products)	−
12	53	M	Mallawi	Leisure	5	27.7	1,263,120	*P. falciparum*	−	48	89	−	intravenous artesunate, artesunate suppository, doxycycline	−
13	26	M	Sierra Leone	Business	5	22.7	760,450	*P. falciparum*	−	42	90	−	intravenous artesunate, doxycycline	−
14	29	F	Ghana	Business	3	12	289,200	*P. falciparum*	−	94	84	blackwater fever	artesunate suppository, intravenous quinine gluconate	−
15	33	M	South Sudan Kenya	Business	6	5	231,500	*P. falciparum*	−	120	32	−	artesunate suppository	−
16	51	M	Indonesia	Business	13	13	266500	*P. falciparum*	−	30	24	−	artesunate suppository	−
17	32	M	Uganda	Business	6	7.3	289,080	*P. falciparum*	−	360	48	−	artesunate suppository	+
18	18	F	Ghana	Volunteering	3	2.3	103,730	*P. falciparum*	−	144	72	−	mefloquine	−
19	25	M	Papua New Guinea	Leisure	5	0.1	4,980	*P. vivax*	−	48	24	−	primaquine	−

FCT: Fever Clearance Time
PCT: Parasites Clearance Time
VFR: Visiting friends and relatives

4例においてAL合剤との関連が否定できない有害事象が出現した（黒水熱1例，肝機能障害2例，全身倦怠感1例，嘔気2例，嘔吐1例）．症例11はグルコン酸キニーネ注射薬とアーテスネート坐薬の併用で治療が開始され，治療2日目にAL合剤に切り替えられたが，経過中に黒水熱が認められた．

考　察

AL合剤が使用された日本人マラリア患者19例を報告した．世界保健機関（WHO）は合併症のない熱帯熱マラリアに対する第一選択薬として，アーテミシニン誘導体と他剤を組み合わせた併用療法（ACT）を推奨している[3]．AL合剤は，あらゆる赤血球内ステージのマラリア原虫に活性を持ち，即効性のあるアーテメターと半減期の長いルメファントリンを組み合わせることによって再燃や薬剤耐性の出現を防ぐACTを代表する抗マラリア薬である[1]．このため，寄生原虫数が多い場合に，本邦承認薬（メフロキン，アトバコン・プログアニル合剤，キニーネ末）と比べて速効性が高いと考えられる．また，アーテミシニン誘導体はキニーネと比較して，キニーネ中毒（シンコニズム）や低血糖といった深刻な副作用がないという利点を持つ[5]．

今回の調査ではAL合剤が使用された19例のうち3例（15.8%），AL合剤のみが使用された10例のうち2例（20.0%）において再燃が認められた．これまでに報告されている合併症のない熱帯熱マラリアにおける再燃率1.0〜2.8%[6,7]と比較して高かった．再燃を認めた症例は，いずれも治療前寄生原虫数が高く，本研究における高い再燃率の原因は，重症マラリアの定義をみたす原虫寄生率が高い症例も治療対象となった

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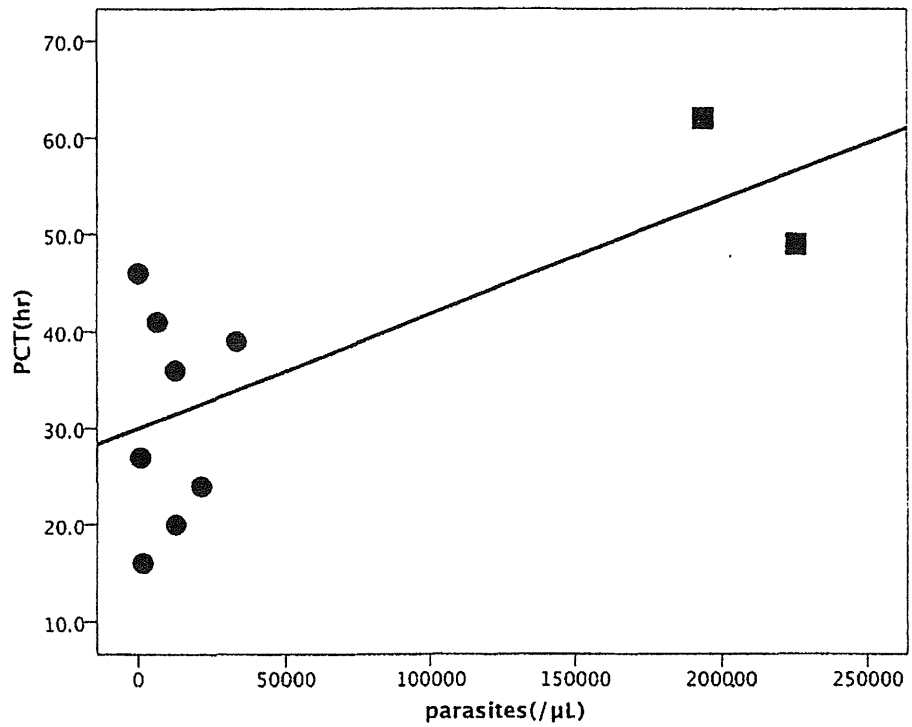
Fig. The correlation between parasitemia and time from start of therapy to disappearance of parasites (falciparum malaria patients without prior administration of antimalarial drugs, n = 10)



ためと考えられた．その他の再燃の原因として嘔吐・下痢などの消化器症状が強く吸収が不十分であったこと，同時に摂取すべき脂質の量が不十分であったことなどが考えられた．AL 合剤による治療ではルメファントリンの吸収不良が治療失敗の原因となることがあり，脂質を含む食物・飲料の摂取と同時に内服することで吸収が改善する[7]ことが知られている．再燃した3症例は消化器症状を呈していたため，ルメファントリンの血中濃度が十分に得られず治療失敗に繋がった可能性がある[8]．治療開始後7日目におけるルメファントリンの血中濃度が280ng/mL以上に保たれていれば，再燃率が低くなることが知られている[9,10]．本邦ではルメファントリンの血中濃度の測定は困難であり，本研究では検討が行えなかった．日本人症例において，再燃とルメファントリン血中濃度が関連しているかどうかについては今後検討すべき課題である．また，AL 合剤のみが使用された10例において，再燃群は非再燃群と比較して PCT が有意に長かった．PCT が長い症例では再燃する可能性を考慮して慎重に経過観察を行う必要があるかもしれない．

寄生原虫数が高い症例において，AL 合剤が選択された背景として，静注用アーテスネートは先進国の GMP 基準に適合した製剤がなく，本邦でも容易に使用できる状況にはないことがあげられる[11]．再燃がみられた2例では比較的全身状態が良く内服が可能であり，シンコニズムなどの副作用が多いグルコン酸キニーネ注（熱帯病治療薬研究班保管）の使用を避け AL 合剤が選択された．重症マラリアの定義を満たす場合には，内服が可能であっても，グルコン酸キニーネで治療を開始し，経口抗マラリア薬にスイッチした方が再燃は少ないと予想される．一方で，WHO ガイドラインにおける重症マラリアの症例定義は医療資源の不足した開発途上国での利用を考慮して，必ずしもマラリアの重症度と一致しない症状や所見も含まれており[12]，定義を満たしても経口治療で治癒しうる症例も少なからず存在すると考えられる[13]．どのような症例で経口治療が可能であるかは今後さらなる検討を要する．

合併症のない熱帯熱マラリアでは，AL 合剤の他にアトバコン・プログアニル合剤（AP 合剤）とメフロキンが選択肢となりうる．これらの薬剤は多くの場合において AL 合剤の代替薬となりうるが，タイ―ミャンマーおよびタイ―カンボジア国境付近ではメフロキン耐性熱帯熱マラリア原虫が存在しており，この地域

Table 2 Comparisons of treatment outcomes in malaria patients treated with Artemether/lumefantrine, Mefloquine and Atovaquone/proguanil

	Artemether/lumefantrine (n = 10)*	Mefloquine (n = 50)**	Atovaquone/proguanil (n = 20)**
mean age (years old)	34.1	38.3	32.4
mean parasites (/μL)	27,500	27,400	27,100
Mean FCT (day)	1.4	2.9	3.7
Mean PCT (day)	1.5	2.8	3.3

FCT: Fever Clearance Time
PCT: Parasites Clearance Time
*Patients reported in this study
** Patients reported in reference (J Infect Chemother. 2006 Oct; 12 (5): 277-82.)

での感染が疑われる場合にはメフロキンは使用すべきではない．また欧州臨床微生物感染症学会のマラリア診断・治療のポジションペーパーでは，AL 合剤耐性の熱帯熱マラリアが報告されている地域（カンボジア，タイ国境地域）では AP 合剤の使用を推奨している[11]．このように，近年薬剤耐性マラリアが問題となっており国内に使用できる抗マラリア薬が複数揃えられている状況にあることが望ましい．Hitani らは日本人の合併症のないマラリア症例に対してメフロキンと AP 合剤の治療成績を比較した研究を報告している[15]．この研究におけるメフロキンと AL 合剤による治療成績と，本研究における AL 合剤による治療成績を比較して表にまとめた（Table 2）．各治療群は同等の患者平均年齢および原虫寄生率であったが，AL 合剤治療群では FCT および PCT が短い傾向にあった．ACT は他の抗マラリア薬よりも PCT が短いとされており[16]，この点は AL 合剤のメリットと考えられる．

本研究では 1 例の三日熱マラリア症例に対して AL 合剤が使用されていた（症例 19）．国際的に三日熱マラリアの第一選択薬はクロロキンであるが，近年はクロロキン耐性三日熱マラリアも増加している．例えば，パプアニューギニアにおける三日熱マラリアに対しクロロキンを投与した場合 95% の症例で治療失敗したと報告されている[17]．AL 合剤は熱帯熱マラリアだけでなく，全ての原虫種に活性を持ち，またクロロキンよりも PCT・FCT が短かったと報告されている[18]ことから，薬剤耐性が報告されている地域の三日熱マラリアの症例でも AL 合剤は良い適応であると考えられた．

今回の調査では，4 例において AL 合剤との関連が否定できない有害事象が出現した．2 例において認められた嘔気・嘔吐については，AL 合剤の副作用としては頻度が高いことが知られている．Bakshi らによる合併症のない熱帯熱マラリアの治療として 1,869 人に AL 合剤を投与し副作用の頻度について調査した研究では，嘔気（6.3%），腹痛（12%），嘔吐（2.4%），食欲不振（12%）など消化器症状と，頭痛（21%），めまい（16%）などの中枢神経症状が主な副作用であった[19]．今回の我々の調査では 1 例において AL 合剤投与後に黒水熱を発症した症例がみられた．黒水熱は熱帯熱マラリア患者において主にキニーネの投与によって誘発される急性の血管内溶血であり，ヘモグロビン尿，黄疸などの症状を特徴とする．前述の Bakshi らの研究においても，AL 合剤の関与が否定できない溶血性貧血の症例が 1 例認められている．

マラリアは本邦でも時に遭遇しうる輸入感染症である．熱帯熱マラリアは免疫のない渡航者では致死的な疾患であり，適切な診断，治療が重要である．メフロキンや新たに薬事承認されたアトバコン・プログアニル合剤がマラリア予防に今後広く使用されるようになると，交叉耐性の生じにくいもう一つの経口抗マラリア薬を準備しておくべきであろう．国際的な標準となっている AL 合剤などの ACT はその重要な選択肢である．

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利益相反自己申告：申告すべきものなし

文　献

1) Spira AM : Assessment of travellers who return home ill. Lancet 2003 ; 26 : 361 : 1459—69.
2) Mizuno Y, Kato Y, Kano S, Takasaki T : Imported malaria and dengue fever in returned travelers in Japan from 2005 to 2010. Travel Med Infect Dis 2012 : 10 : 86—91.
3) WHO guidelines for the treatment of malaria. 2010. World Health Organization.
4) Wernsdorfer WH : Coartemether (artemether

平成26年11月20日

and lumefantrine): an oral antimalarial drug. Expert Rev Anti Infect Ther 2004 : 2 : 181—96.
5) Newton P, White N : Malaria : new developments in treatment and prevention. Annu Rev Med 1999 : 50 : 179—92.
6) Dorsey G, Staedke S, Clark TD, Njama-Meya D, Nzarubara B, Maiteki-Sebuguzi C, *et al.* : Combination therapy for uncomplicated falciparum malaria in Ugandan children : a randomized trial. JAMA 2007 ; 23 : 297 : 2210—9.
7) Mutabingwa TK, Anthony D, Heller A, Hallett R, Ahmed J, Drakeley C, *et al.* : Amodiaquine alone, amodiaquine+sulfadoxine-pyrimethamine, amodiaquine + artesunate, and artemether-lumefantrine for outpatient treatment of malaria in Tanzanian children : a four-arm randomised effectiveness trial. Lancet 2005 : 365 : 23—9. 1474—80.
8) Mizuno Y, Kato Y, Kudo K, Kano S : First case of treatment failure of artemether-lumefantrine in a Japanese traveler with imported falciparum malaria. Jpn J Infect Dis 2009 : 62 : 139—41.
9) Ezzet F, Mull R, Karbwang J : Population pharmacokinetics and therapeutic response of CGP 56697 (artemether + benflumetol) in malaria patients. Br J Clin Pharmacol 1998 : 46 : 553—61.
10) Ezzet F, van Vugt M, Nosten F, Looareesuwan S, White NJ : Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. Antimicrob Agents Chemother 2000 : 44 : 697—704.
11) 水野泰孝, 藤元 瞳, 横田恭子, 加藤康幸, 源河いくみ, 金川修造, 他 : アーテスネート静注と血液透析による支持療法で救命しえた重症熱帯熱マラリアの1例. 感染症誌 2006 : 80 : 706—10.
12) Anstey NM, Price RN : Improving case definitions for severe malaria. PLoS Med 2007 : 4 : e267.
13) Kopel E, Marhoom E, Sidi Y, Schwartz E : Successful oral therapy for severe falciparum malaria : the World Health Organization criteria revisited. Am J Trop Med Hyg 2012 : 86 : 409—11.
14) Askling HH, Bruneel F, Burchard G, Castelli F, Chiodini PL, Grobusch MP, *et al.* : Management of imported malaria in Europe. Malar J 2012 : 11 : 328.
15) Hitani A, Nakamura T, Ohtomo H, Nawa Y, Kimura M : Efficacy and safety of atovaquone-proguanil compared with mefloquine in the treatment of nonimmune patients with uncomplicated P. falciparum malaria in Japan. J Infect Chemother 2006 : 12 : 277—82.
16) Mayxay M, Khanthavong M, Lindegårdh N, Keola S, Barends M, Pongvongsa T, *et al.* : Randomized comparison of chloroquine plus sulfadoxine-pyrimethamine versus artesunate plus mefloquine versus artemether-lumefantrine in the treatment of uncomplicated falciparum malaria in the Lao People's Democratic Republic. Clin Infect Dis 2004 : 39 : 1139—47.
17) Sumawinata IW, Bernadeta, Leksana B, Sutamihardja A, Purnomo, Subianto B, *et al.* : Very high risk of therapeutic failure with chloroquine for uncomplicated Plasmodium falciparum and P. vivax malaria in Indonesian Papua. Am J Trop Med Hyg 2003 : 68 : 416—20.
18) Bassat Q : The use of artemether-lumefantrine for the treatment of uncomplicated Plasmodium vivax malaria. PLoS Negl Trop Dis 2011 : 5 : e 1325.
19) Bakshi R, Hermeling-Fritz I, Gathmann I, Alteri E : An integrated assessment of the clinical safety of artemether-lumefantrine : a new oral fixed-dose combination antimalarial drug. Trans R Soc Trop Med Hyg 2000 : 94 : 419—24.

Malaria Cases Treated with Artemether/Lumefantrine in Japanese Travelers

Satoshi KUTSUNA[1], Taiichiro KOBAYASHI[1,2], Yasuyuki KATO[1], Yoshihiro FUJIYA[1], Momoko MAWATARI[1], Mugen UJIIE[1], Nozomi TAKESHITA[1], Kayoko HAYAKAWA[1], Shuzo KANAGAWA[1], Yasutaka MIZUNO[1,3], Shigeyuki KANO[4] & Norio OHMAGARI[1]

[1]Disease Control and Prevention Center, National Center for Global Health and Medicine, [2]Division of AIDS Clinical Center, National Center for Global Health and Medicine, [3]Department of Infection Control and Prevention, Tokyo Medical University Hospital, [4]Department of Tropical Medicine and Malaria, Research Institute, National Center for Global Health and Medicine,

Artemisinin-based combination therapy (ACT) has been the standard treatment for uncomplicated malaria. Although not licensed in Japan, artemether/lumefantrine (AL), one type of ACT, has been administered to patients with malaria since 2002 by the Research Group on Chemotherapy of Tropical Diseases. Herein, we reviewed malaria cases treated with AL in Japanese travelers.

A retrospective study was conducted at the National Center for Global Health and Medicine from October 2005 to March 2013. There were 19 malaria patients treated with AL, and 10 falciparum malaria patients treated with AL only. In these 10 patients treated with AL only, the median time of fever clearance was 25.0 hours (range : 14-66 hours), and the median time of parasite clearance was 36.0 hours (range : 16-62 hours). There was a positive correlation between parasitemia and time from the start of therapy to the disappearance of the parasites. Parasitemia was higher (4.05% vs. 0.24% ; $p=0.044$) and parasite clearance time was longer (55.5 hours vs. 31.5 hours ; $p=0.044$) in the cases of recrudescence than non-recrudescence, respectively.

Three of the 19 malaria patients showed recrudescence of malaria after treatment with AL. The reason that treatment failure was more frequently observed in this study than in previous reports may be related to poor absorption of lumefantrine owing to gastrointestinal symptoms, insufficiently ingested fatty foods, or high parasitemia on admission. The World Health Organization recommends that intravenous antimalarials should be administered in cases of severe malaria ; however, this is not applicable in Japan. Further studies are needed to distinguish patients with malaria who are treatable with ACT from those who should be treated initially with other intravenous antimalarials.

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REVIEW

Prioritising immunisations for travel: International and Japanese perspectives

Mikio Kimura [a,*], Tatsuya Fujii [b], Bernadette Carroll [c]

[a] *Shin-Yamanote Hospital, Japan Anti-Tuberculosis Association, Tokyo, Japan*
[b] *Kawakita General Hospital, Tokyo, Japan*
[c] *Travel Clinic, Hospital for Tropical Diseases, London, United Kingdom*

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Summary Immunisation has traditionally played an important role in travel medicine practice and unlike routine immunisations, vaccines for travel are sought by and often paid for by the traveller. A convenient way of looking at vaccines for travel is by grouping them into those that are: Required, Routine, or Recommended, although this classification is not always consistent. Prioritising the use of vaccines classed as "Recommended" has proved the most controversial. There are a number of factors that influence both the traveller and health professional in this decision making process. The incidence rate and impact of a disease are thought by many to be the two most important factors to consider when prioritising vaccines. For travellers, the efficacy and adverse events associated with vaccines may also be important. This article reviews the role of immunisation in travel health with the aim of assisting travel health professionals prioritise their use of vaccines. It also highlights the need for travel medicine advisors worldwide to be aware of the differences between Japan and other nations with regard to national immunisation programmes, vaccine availability and vaccine uptake.

Global travel from industrialised countries to developing countries is growing rapidly [1]. This is due mainly to increased demand for tourism, business and other professional purposes, visits to friends and relatives by a rising immigrant population and religious pilgrimages. Larger aircraft carrying capacity and the expansion of travel routes has increased travel by making it more affordable and accessible. Japan is no exception, and the annual number of Japanese citizens departing to foreign countries increased from 270 thousand in 1965 to over 18 million in 2012 [2], with many of those destined for developing

* Corresponding author. Shin-Yamanote Hospital, Japan Anti-Tuberculosis Association, Suwa-cho 3-6-1, Higashi-Murayama, Tokyo 189-0021, Japan. Tel.: +81 42 391 1425; fax: +81 42 391 5760.
E-mail address: kimumiki@abox3.so-net.ne.jp (M. Kimura).

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countries. In such a large population of travellers, infectious disease risks, including rare, life-threatening diseases, are becoming an important clinical and public health issue.

Over the last two decades, travel medicine has grown as an independent medical specialty, and the importance of informing travellers about health risks and advising on preventive measures before departure is increasingly recognised. As with other travel-related risks, the behaviour of the traveller while abroad impacts upon his/her risk of contracting an infectious disease, and advice on behaviour modification is an important part of the travel health consultation. Immunisation has traditionally played an important role in travel medicine practice [3] and, where appropriate, vaccines provide a highly effective, largely safe, and usually long-lasting means of preventing infectious disease. This article reviews the role of immunisation in travel health, with the aim of helping travel medicine practitioners recognise when immunisations are appropriate, enabling them to prioritise their use effectively. Issues pertinent to travellers from Japan are discussed and the differences between Japan and Western countries in their approach to immunisation are outlined. While influenza is increasingly recognised as an important cause of travel associated morbidity [4], this will not be reviewed here.

Routine and travel immunisations

Routine immunisations are administered according to the national policy of a country in order to protect not just individuals, but also the community, against infectious disease threats. For this reason, vaccines may continue to be routinely recommended to maintain herd immunity, despite their associated costs and adverse events (AEs). A good example of this is the poliomyelitis vaccine which remains part of the childhood immunisation programme worldwide, including in industrialised countries. The costs of routine immunisations are paid for by the government of a country. Compensation for individuals who experience severe AEs after routine vaccines can usually be claimed through a Government scheme, for example, in Japan, compensation is covered under the Protective Vaccinations Act. Several routine immunisations have been shown to be cost effective, e.g., measles, mumps, and rubella vaccines, particularly when the incidence of disease is high in the community [5].

In contrast, travel immunisations are sought by travellers who wish to reduce their own health risks and disruption to their travel plans, the cost of which is usually borne by the traveller. Travel immunisations can also help prevent diseases being imported to a country. Outbreaks of meningococcal disease in 2000 due to the serogroup W135 in British, French and other European visitors to the Hajj [6], and of hepatitis A in German and other European travellers to Egypt in 2004 [7] resulted in secondary outbreaks after travellers returned home. Travellers tend to be unaware of, or indifferent to, the importance of this public health concern and are often reluctant to have vaccines solely for this reason. In Japan, compensation for AEs associated with travel vaccines is covered by the Pharmaceuticals and Medical Devices Agency (i.e., by pharmaceutical companies, rather than through a Government scheme) if the vaccine is used within its licensed indication. However, the compensation granted is lower than that provided through the Government. Travel immunisations are not usually cost effective [3] as evidenced by a British study on hepatitis A and typhoid vaccines (injectable Vi polysaccharide and oral Ty21a) [8], and a more recent study on typhoid vaccines [9]. An exception to this may be the whole-cell-recombinant B subunit (WC/rBS) oral cholera vaccine which is cross-reactive to the heat-labile enterotoxin (LT) released from enterotoxigenic *Escherichia coli* (ETEC), thus providing cross-protection against ETEC-induced travellers' diarrhoea. This vaccine may prove cost effective where the illness occurs in $\geq$1 per 10 travellers [10]. Despite the generally poor cost-effectiveness of travel immunisations, travellers may be willing to pay for these to reduce their own risk of an illness which may affect their travel plans or prevent them returning to work post travel.

Vaccines for travellers: the three Rs

A convenient way of categorising travel vaccines is to group them as: Required, Routine, or Recommended [3]. This classification, however, is not always clear-cut as some vaccines belong to more than one group, and these categories may differ between countries.

Required vaccines

Yellow fever vaccine is mandatory for entering many sub-Saharan African countries and is required for entry to many Middle Eastern, Asian, and Latin American countries when travelling from a country with yellow fever transmission risk. This requirement is based on the International Health Regulations (IHR) of the World Health Organization (WHO) [11]. Since yellow fever vaccine requirements change intermittently, updated information should be sought from official reference sources such as the WHO International Travel and Health [12] and Travelers' Health, Centers for Disease Control and Prevention (CDC), the United States (U.S.) [13]. Where the yellow fever vaccination is contraindicated on medical grounds, a letter of medical exemption can be issued by the physician; however, its acceptance is at the discretion of the authorities of the destination country. Since May 2001, quadrivalent meningococcal vaccination has become a requirement for entry to Saudi Arabia for pilgrims, and some polio-free countries may require travellers from countries, or areas, reporting wild poliovirus to be vaccinated against the disease before an entry visa is granted. However, neither of these two vaccines is required under the IHR. Currently, no country formally requires cholera vaccine as a condition of entry.

Measles vaccination, as well as other routine vaccinations, may be required for entry into schools in some countries, especially the U.S. Even when not required, measles vaccination should be updated, especially in travellers from high prevalence countries travelling to countries where local transmission has been eradicated. In the U.S.,

Table 1 Licensed and unlicensed vaccines in Japan as of November 2013.

Classification		Vaccines
Licensed vaccines	Routine vaccines	Diphtheria-pertussis-tetanus-inactivated polio (DTP-IPV), diphtheria-pertussis-tetanus, diphtheria-tetanus, inactivated polio
		Measles-rubella (MR), measles, rubella
		BCG (Bacillus Calmette–Guérin)
		Japanese encephalitis (Vero cell-derived, Beijing strain)
		Pneumococcal conjugate (PCV13)[a]
		Haemophilus influenzae type b conjugate (Hib)[a]
		Human papillomavirus (bivalent, quadrivalent)[a]
	Voluntary vaccines	Mumps
		Varicella
		Hepatitis B[b]
		Hepatitis A
		Influenza (injectable, A/H1N1, A/H3N2, and B)[c]
		Pneumococcal polysaccharide (PPV23)
		Rotavirus (monovalent, pentavalent)
		Oral polio
		Rabies
		Yellow fever
Unlicensed vaccines		Typhoid (injectable or oral)
		Meningococcal
		Cholera (oral)
		Tick-borne encephalitis

[a] These have only become routine vaccines since April 2013. PCV13 has been in use since November 2013, replacing PCV7.
[b] Vaccine use in infants born to a hepatitis B virus-positive mother is covered by health insurance.
[c] Vaccines are routinely administered to those aged 65 years and above and from age 60 in individuals with cardiac, renal, or respiratory impairment, or immune deficiency due to human immunodeficiency virus.

of the 222 measles cases reported in 2011, as many as 200 (90%) were imported from other countries [14].

Routine vaccines

Travel provides an excellent opportunity to review and, if necessary, update routine immunisations. Measles immunisation should be recommended if the traveller has not been immunised or has not received two doses of vaccination. The latter is often the case among Japanese travellers where, until mid-2006, only a single dose of measles vaccine was given under the national immunisation programme.

There seems to be no evidence that travellers are at greater risk of tetanus infection when visiting developing countries [3], however, this may be at least partly because most travellers are immunised through their national immunisation programmes. A booster dose may be recommended for travel to areas where appropriate medical attention may not be accessible in the event of a tetanus-prone wound. An American surveillance study between 2001 and 2008 revealed a 13.2% case fatality rate overall from tetanus, and a rate as high as 31.3% in older people (aged $\geq$ 65 years) [15]. In Japan, around 100 cases of tetanus are reported every year, most of which are due to domestic transmission [16]. Serologic surveys in Japan have shown that protective anti-tetanus antibodies begin to wane 10 years after the last dose of the childhood vaccinations, and a booster dose is thus recommended every 10 years even if the individual is not travelling [17]. In Western countries, following the large diphtheria outbreaks which occurred in the 1990s in the Russian Federation and the New Independent States of the former Soviet Union, boosters were recommended routinely and in travellers to the region [18]. This booster dose is often given as diphtheria-tetanus bivalent vaccine, or as a trivalent (diphtheria, tetanus and polio) vaccine, containing lower doses of diphtheria toxoid suitable for older children and adults [19].

The Japanese encephalitis vaccine is administered routinely in Japan (Table 1), while in the West, it is only recommended for travellers at risk. For many years, the vaccine produced by Biken, Japan, had been the sole vaccine in use worldwide. As a mouse brain-derived vaccine, there were theoretical concerns about AEs. Urticaria, angioedema, and even respiratory distress have been reported from Western countries, mainly clustering in the period 1989 to 1992 [20], which limited its use to those at very high risk of the disease. In Japan, cases of acute disseminating encephalomyelitis after vaccination led to its suspension as a routine immunisation in 2005. New cell culture vaccines have recently become available in both the West and Japan, and in a recent review, the Ixiaro vaccine was shown to be effective and well tolerated [21]. Vaccination coverage with the new Japanese encephalitis vaccine in Japan is anticipated to be high enough to allay concerns about a possible resurgence of disease particularly among inhabitants of parts of western Japan and in travellers to areas where the virus is actively circulating among pigs [22].

The live oral polio vaccine (OPV) has been used until recently in Japan. However, rarely reported vaccine-associated paralytic poliomyelitis in children and their

Table 2 Factors to consider when prioritising immunisations for travel (adapted from Zuckerman et al. [23]).

Travel-related considerations
Country (ies) of destination
Purpose of travel
Duration and type of travel
Mandatory or recommended requirements
Host-related considerations
Personal immune status
Health status
Age and specific contraindications for vaccination
Lifestyle and perception of infection risk
Disease-related considerations
Associated morbidity/mortality
Available treatments, including antibiotic resistance
Vaccine-related considerations
Efficacy
Tolerability
Schedule
Compliance/acceptance
Cost

carers led to a fall in vaccination coverage and since September 2012, OPV has been replaced by the inactivated parental polio vaccine (IPV) (Table 1). It is not yet clear whether IPV use will reverse the downward trend in vaccine coverage.

Mumps, varicella, hepatitis B, or meningococcal vaccines are not administered routinely in Japan although they are given routinely in many other developed countries.

Recommended vaccines

Recommendations on immunisation can vary between countries depending on which vaccines are considered routine. Yellow fever vaccine is often viewed as a required vaccine but may be considered a recommended vaccine for travellers to a country where a vaccine certificate is not required but where disease transmission occurs.

There are many factors that influence the travellers' decision when having vaccines (Table 2). This is one of the most frequently discussed issues among travel medicine practitioners. It makes sense to immunise travellers against a disease that is common and has a high case fatality rate, and not immunise against a disease that occurs infrequently and has a low case fatality rate. However, it is not always that straightforward as some diseases have a low case fatality rate but are common, e.g., influenza, while others are uncommon but have a high case fatality rate, e.g., rabies. Obviously travellers will differ in regards to the priority they give to each of the items listed in Table 2. For some travellers, the benefits of preventing disease will outweigh any disadvantages associated with immunisation, i.e., vaccine AEs or the cost, but for others cost and risk of AEs will be more important. Travel medicine practitioners should be knowledgeable about the impact that each of the factors listed in Table 2 has on the risk of illness during travel, and ultimately be able to guide travellers to a decision they feel is appropriate and acceptable.

The incidence rate and disease impact are considered by many to be key factors influencing immunisation and these have been discussed previously by Steffen and Connor [3] (Fig. 1) and will be reviewed here. The disease impact includes the case fatality rate, as well as the possibility of a worse clinical outcome if treated in a developing country, long-term sequelae, and absence from work or school after returning home. Travellers may also consider the efficacy of a vaccine and any associated AEs to be very important in their decision, and these will be focused on in this article. Cost or time constraints may be more important considerations for some travellers, particularly backpackers and business travellers, respectively; however these issues will not be addressed here.

Factors to be considered

Incidence rates of disease

Data on the incidence of a disease among the local population of the travel destination can be useful, however, data on health problems affecting travellers visiting the area is more relevant. Travellers tend to eat, drink, sleep, and behave differently from the indigenous population, affording them better or worse protection depending on their environment, and their lack of immunity from prior exposure may make them more vulnerable to some disease risks. Incidence data on travellers is often limited, it may not be current and may not be applicable to those travelling under extreme conditions or the very adventurous traveller, but it is essential in order to provide more precise information on risk and preventive measures.

Pioneering work on non-immune Swiss travellers to developing countries by Steffen's group between 1981 and 1984 showed an incidence rate of hepatitis A of 3(−6) per 1000 person months [24]. The seroconversion rate of French volunteers staying long-term in Africa around 1980 was found to be 19 per 1000 person months, most of which presented with jaundice [25]. Recently, however, decreasing incidence rates of hepatitis A have been reported. The incidence rate was 33 cases per 100,000 person months in unprotected Canadian travellers between 1996 and 2001 [26], and 10 to 15 cases per 100,000 visits between 1998 and 2002 in Swiss travellers [27]. A recent Swedish study between 1997 and 2005 also showed a lower incidence rate of hepatitis A in unprotected travellers; 2 cases per 100,000 person months in travellers to southeast Asia, 12 in North Africa, and 18 in the Middle East [28]. Improvements in socioeconomic and hygiene conditions in the developing world may have contributed significantly to these decreasing rates [29]. Nevertheless, it should not be forgotten that even luxury hotels can be a source of infection for tourists as illustrated by the Egyptian outbreak of 2004 [7].

Nearly all reports of typhoid fever in travellers show that the highest incidence is in India or its neighbouring countries. A study of U.S. travellers between 1985 and 1994 reported incidence rates of 11−41 per 100,000 travellers to the Indian subcontinent, 0.5 to 1.2 in southeast Asia, 0.4 to 1.4 in Africa, and 0.5 to 0.6 in Central America [30]. A Swedish study between 1997 and 2003 showed a rate of 41.7 cases per 100,000 visits in travellers to India and

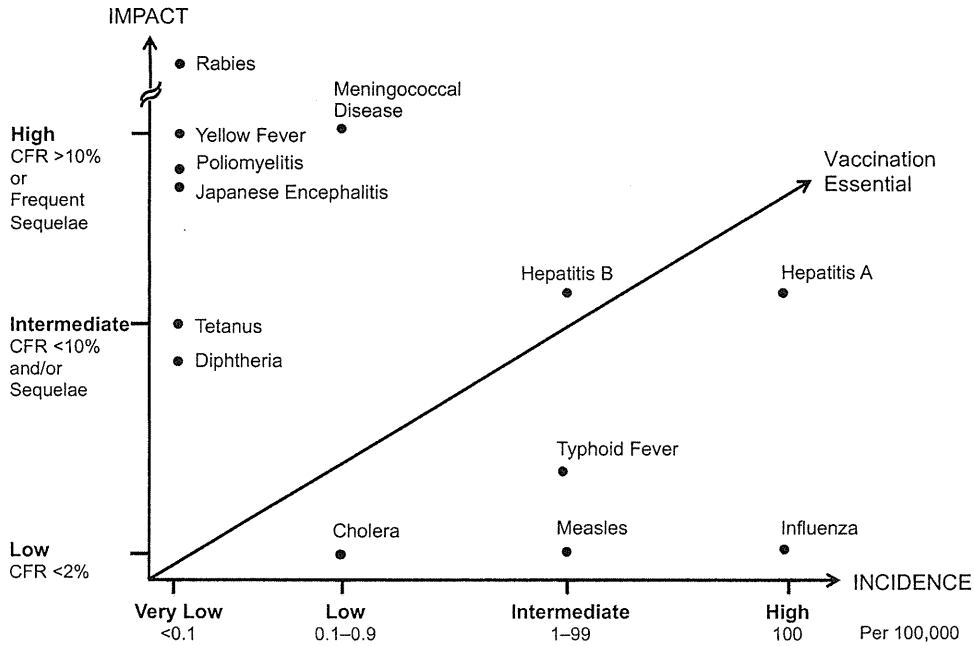

Fig. 1 Incidence and impact of vaccine-preventable diseases in travellers to developing countries. CFR = case fatality rate (reproduced with kind permission from Steffen et al. [3]). This figure differs from the original in that the incidence and impact of rabies acquisition in travellers rather than the risk of potential rabies exposure are now given.

neighbouring countries, 5.9 in the Middle East, 3.3 in Central Africa, and 0.2 in southeast/east Asia [31]. The incidence rate per 100,000 Israeli travellers was 24 in the Indian subcontinent between 1995 and 1999 (where the oral Ty21a vaccine was used) but fell to 14 between 2000 and 2003 (where the parenteral Vi polysaccharide vaccine used) [32]. A second U.S. study between 1999 and 2006 revealed a rate of 8.9 cases per 100,000 travellers returning from India, ranging from 5.5 cases in 1999 to 12.2 cases in 2003 [33].

The data on hepatitis B acquired by travellers and expatriates is conflicting. This may be partly because the risk of infection is very much influenced by the traveller's behaviour abroad and also by the study method used for disease detection; official disease surveillance systems often detect symptomatic cases only but seroconversion studies detect both symptomatic and asymptomatic infections. Serological surveys detected higher rates of 10.5% and 5.5% seroconversion against hepatitis B virus among French volunteers leaving France in 1979 and 1980 and working in Africa for an average of 25.2 months [25], and North American missionaries deployed in various regions, 78% of whom were in Africa for an average of 7.3 years between 1967 and 1984, respectively [34]. These figures correspond to 417 and 63 per 100,000 person months, respectively. In contrast, a Dutch group (using official surveillance data) identified 27 cases of hepatitis B contracted while travelling to endemic countries between 1992 and 2003, yielding a low incidence rate of 4.5 per 100,000 travellers [35]. Given that more than half of the 27 cases were immigrants from hepatitis B-endemic countries, they concluded that hepatitis B vaccination was unnecessary for Dutch short-term travellers. A Danish study focused on infections acquired by Danes in non-Western countries from 2000 to 2010, and estimated the overall incidence rate to be 10.2 per 100,000 person months [36]. It also demonstrated that, contrary to general opinion, rates of newly acquired hepatitis B infection did not increase with longer stays.

The incidence of cholera is low but greatly influenced by outbreaks. The incidence in U.S. Embassy employees in Peru between 1991 and 1993 during an outbreak reached 44 cases per 100,000 person months [37]. A study by Wittlinger, Steffen and colleagues showed that during 1991, the cholera incidence rate was 0.2 per 100,000 European and North American travellers but was 13.0 in Japanese travellers returning from Indonesia, mainly Bali [38]. The increased rate in Japanese travellers was attributed to the more intensive surveillance conducted in Japan rather than to a true higher incidence.

An initial study on meningococcal disease by Koch and Steffen between 1986 and 1989 showed that the incidence rate among 100,000 travellers to developing countries was <0.1 overall, but rose to 200 cases in pilgrims to Mecca [39]. A study of Hajj pilgrims in 2000 reported incidence rates of 41 and 21 per 100,000 in British and French travellers, respectively, due to serogroup W135 [6]. The incidence rates of meningococcal disease are very much influenced by outbreaks, and those who have close contract with the local population are at higher risk. Residence in dormitories, military institutions and refugee camps as well as attendance at sporting events are regarded to be particularly high risk factors.

With 11 U.S. residents reported to have been infected with Japanese encephalitis while in Asia between 1981 and 1992, the incidence rate in U.S. travellers to Asia was

calculated as <0.1 per million person months [40]. A more recent study of 55 cases between 1973 and 2008 showed the risk was <1 per million travellers to endemic countries [41]. However, higher incidence rates have been reported in Finnish and Swedish travellers to Thailand, i.e., 1 per 257,000 and 400,000, respectively [41]. This study also suggests that longer stays, rural travel, residence on or near a farm, or in unscreened accommodation, trekking or other outdoor activities increased the risk of infection in travellers.

Yellow fever incidence rates among travellers are difficult to determine, probably due to variations in the ecological determinants of virus transmission. Based on the risk in indigenous populations, crude estimates of the risk to travellers were made, such that if 100,000 unvaccinated travellers stayed for 2 weeks during the peak transmission season in West Africa, 50 would become ill and 10 would die, while in South America, 5 would become ill and one would die [42]. Between 1970 and 2009, 9 cases of yellow fever were reported in unvaccinated travellers from the U.S. and Europe to West Africa (5 cases) or South America (4 cases), and 8 of the 9 cases were fatal [42].

Rabies infection among travellers is very rare with an estimated incidence of <1 case per million travellers. A recent survey of travel-related rabies infection identified 42 cases in travellers returning to Europe, the U.S., and Japan between 1990 and 2010, with cases infected in India ($n = 6$), the Philippines ($n = 6$), Mexico ($n = 5$), Morocco ($n = 3$), and Algeria ($n = 3$) [43]. Among the 39 cases for whom an animal exposure was known, 37 (95%) had contact with a dog, and of the remaining 2 cases, one had contact with a fox in Ukraine and the other with a bat in Kenya. Although no cases were reported in travellers to Bali, the increasing number of rabies cases in locals remains a serious concern for the large number of travellers visiting there [44].

The incidence rate of tick-borne encephalitis in travellers is difficult to estimate due to the variation in season of travel (the risk period for infection ranges from April to November), the environment visited (the risk is high in forested areas), and the behaviour of travellers. Based on epidemiological data from Austria, the incidence rate was estimated to be 10 per 100,000 person months in non-immune travellers to a highly endemic province, e.g., Styria, southern Austria [45]. Between 2000 and 2009, 5 cases were reported among U.S. travellers to Europe and Asia, one of which was in a traveller to China (Tianjin Province), but incidence rates were not reported in the study [46].

Disease impact

Although most cases of hepatitis A resolve without significant sequelae, some 10% have prolonged elevation of serum aminotransferase levels, sometimes persisting for up to 6 months [47]. Patients with hepatitis A are often incapacitated for a lengthy period, with the average time off work being one month [24]. Of greater concern is the increased mortality associated with advancing age. During an urban epidemic in the U.S., 5.7% of hospitalised patients aged ≥40 died [48], and in a British study, up to 12.8% of cases aged ≥70 were fatal [49].

The case-fatality rate of typhoid fever is reported to be ≥ 10% if left untreated [31]. With the initiation of early and appropriate antimicrobial therapy, the case fatality rate in travellers can be as low as 0.3% [3]; however, 10–15% may develop severe illness including intestinal bleeding/perforation, disseminated intravascular coagulation, encephalitis/meningitis, and severe pneumonia [50]. Emergent multidrug-resistant *Salmonella typhi* strains, i.e., those resistant to chloramphenicol, ampicillin, and sulfamethoxazole/trimethoprim, and strains with reduced susceptibility to fluoroquinolone drugs, which are frequently found in the Indian subcontinent and southeast Asia, are making curative treatment more difficult [51]. Data obtained in the U.S. between 1999 and 2006 showed that 85% of patients infected with multidrug-resistant *S. typhi* and 94% of those infected with nalidixic acid-resistant *S. typhi* had travelled to the Indian subcontinent, while 44% of those infected with susceptible strains had visited the region [33].

Hepatitis B may develop into fulminant hepatitis, and, even with current treatment, around half of these cases will be fatal. In a Japanese study of 890 cases of acute hepatitis B between 2007 and 2008, 53 (6.0%) developed fulminant hepatitis and 36 (4.0% of the total, 68% of the 53 cases) died [52]. Five to 10% of adult cases of acute hepatitis B will follow a chronic course [53], and this is more likely to occur with genotypes A and D which are less frequent in Japan. Between 3% and 23% of cases due to genotype A were reported to progress to chronic disease [53]. Genotype A used to be rare in Japan but has recently increased in newly infected cases; accounting for 52% of acute hepatitis B cases acquired in Japan in 2008 [54].

The case-fatality rate of cholera can be as high as 20–50% if untreated or poorly treated in epidemic settings, but with proper rehydration therapy, the rate can be as low as <1% [55].

Meningococcal meningitis has a case fatality rate of 5–10% even with appropriate antimicrobial treatment [56], and up to 40% once septicaemia develops [57]. The case-fatality rates in the U.S. between 1994 and 2002 were reported to be 21% and 11% in outbreak-associated and sporadic cases, respectively [58]. Furthermore, 11–19% of individuals who survive can suffer long-term neurological sequelae or disability [57].

Japanese encephalitis has a 30–40% case fatality rate and up to 50% of the children that survive have permanent neuropsychiatric impairment [20]. These children develop motor paresis, spasticity, movement disorders, chronic seizures, and developmental delay [22]. Fifty five cases of travel-related Japanese encephalitis were identified in citizens between 1973 and 2008, and of those, 10 (18%) died and 24 (44%) had mild-to-severe sequelae [41].

Case-fatality rates of yellow fever are reported to be between 20 and 50% among local populations in disease endemic areas, and according to recent data obtained between 2008 and 2009 in Brazil, there were 10 deaths among 29 cases, yielding a 34% case-fatality rate [59]. Case-fatality rates among travellers are difficult to ascertain with the low number of cases identified. As described above, 8 (89%) deaths occurred in 9 cases of travel-related infections [42]. This rate could of course be overestimated, due to a significant number of undiagnosed cases, where milder forms of the illness occur, or where medical

personnel are unfamiliar with the symptoms. Nevertheless, the case fatality rate associated with yellow fever should be assumed to be high as there is no specific antiviral drug available to treat the infection.

There have been 5 cases worldwide known to have recovered from clinical rabies until 2004, all of whom had received either pre- or post-exposure vaccination previously [60]. In the U.S. a 15-year-old unvaccinated female developed rabies after a bat bite and eventually recovered after a drug-induced coma and ribavirin. This was the first documented case of recovery from rabies without pre- or post-exposure vaccination [60]. Therapeutic coma also appeared successful in an 8-year-old previously unvaccinated girl in California in 2011 who became ill after contact with cats at her school [61]. Recovery from rabies without therapeutic coma has also been reported in a 17-year-old female in 2009 (presumptive abortive rabies) [62]. At present, the effectiveness of treatment with therapeutic coma has not been confirmed worldwide and rabies should continue to be regarded as a fatal disease.

With the European- and Siberian-subtype tick-borne encephalitis, the case-fatality rate is 0.5–2%, but up to 31–58% of cases may suffer permanent central nervous system sequelae [63,64]. Illness due to the Far Eastern-subtype may lead to a 20% case-fatality, with neurological sequelae developing in 30–80% of children who survive. In 2001, a Japanese traveller who visited his daughter living in Austria died of this infection [65].

Vaccine efficacy

Hepatitis A vaccines confer ≥95% seroprotection in adults and children [47]. There are some anecdotal reports of clinical hepatitis A despite previous vaccination but immunisation was incomplete in most cases. The latest case report, in which the traveller left for Africa 11 days after receiving a single dose of Havrix 1440, may be explained by failure to seroconvert due to the short interval between vaccination and exposure [66]. Seroconversion rates of 79% at day 13 and 100% at day 19 have been shown after one dose of Havrix 1440 [67], with similar findings obtained with other Western vaccines. Thus, the CDC notes "one dose of single-antigen hepatitis A vaccine administered at any time before departure provides adequate protection for most healthy individuals" [68]. Hepatitis A immunisation may prove cost effective for the traveller since in immunocompetent individuals, a booster dose of hepatitis A may be unnecessary for life-long protection after a full primary course [69].

The immunogenicity of hepatitis B vaccine has been shown to be ≥90%, sometimes up to ≥95%. A recent study on Japanese nursing school students showed a 97.8% seroprotection (≥10 mIU/mL) rate 10 or 17 weeks after the last dose of the 3-dose primary immunisation series [70]. Another study on Canadian children aged 8–10 years showed 98.9% seroprotection 28–60 days after the 3rd dose [71]. According to the European Consensus Group on Hepatitis B Immunity, there are no data to suggest the need for a booster dose in immunocompetent individuals [72].

Not all vaccines have been shown to be highly effective or confer long-term immunity, particularly the polysaccharide vaccines and orally administered vaccines. For example, the Vi polysaccharide vaccine against typhoid fever conferred only 77% protection at 21 months follow-up in children vaccinated at 2–5 years of age, and this fell to 55% after 3 years [73]. The recently developed Vi polysaccharide conjugate vaccines may have a higher protective efficacy in terms of immunogenicity in young children and booster responses. A field study in Vietnam showed that a conjugate vaccine in which Vi was bound to recombinant *Pseudomonas aeruginosa* exotoxin A was 91.5% protective 27 months after the first of two injections in children aged 2–5 years [74]. The live oral Ty21a typhoid vaccine demonstrated a protective efficacy of 69% persisting for at least 4 years in schoolchildren in Chile, when three doses of an enteric-coated formulation were administered over a period of one week [75].

The efficacy of the WC-rBS oral cholera vaccine with two doses is approximately 80–85% for 6 months and 51% for 36 months against *Vibrio cholerae* O1, but the vaccine does not provide protection against *V. cholerae* O139 [55]. The advantage of this cholera vaccine is provision of short-term protection against ETEC-causing diarrhoea, i.e., 67% efficacy at 3 months and 21% at 12 months [55].

There are two types of meningococcal vaccine, polysaccharide and conjugate vaccines. Polysaccharide vaccines are safe and highly immunogenic in older children and adults, but the duration of protection is limited and they are poorly immunogenic in young children (<2 years of age) [57]. The advantages of the newer conjugate vaccines are that they are T-cell dependent, which enables them to induce an immunological memory and a booster effect, they confer long-term protection, and can be used in children under 2 years of age [57]. They also have the advantage of reducing nasopharyngeal carriage of the pathogen, and thus may be of public health importance by decreasing human-to-human transmission. In Western countries, three quadrivalent (A, C, W-135, and Y) conjugate vaccines are commercially available. The ACWY-CRM vaccine is reported to be comparable or superior to the earlier licensed ACWY-D vaccine with a greater proportion of individuals achieving a protective immune response [hSBA (serum bactericidal assay using human complement) titre ≥1:8] against the four serogroups [57]. The ACWY-CRM proved highly immunogenic in all age groups, including children aged 2–10 and infants ≥ 2 months of age.

Data has recently been published on the new cell-culture vaccine against Japanese encephalitis approved in 2009 in Europe (IC51, Ixiaro®) [21]. In subjects given two doses of vaccine four weeks apart, the seroconversion rate was 98% 4 weeks after the 2nd dose, compared with 95% after 3 doses of mouse brain-derived, inactivated vaccine given on days 0, 7, and 28, and the geometric mean neutralising antibody titres were 2.3-fold higher in the IC51 group. Although seroprotection achieved by primary immunisation with IC51 wanes over time, i.e., 83%, 58%, 48% at months 6, 12, 24, respectively, a booster dose at month 11 and/or month 23 in individuals with neutralising antibody titres below the detection limit led to 100% seroprotection. Moreover, a single dose of IC51 could potentially boost immunity in individuals primed with the mouse brain-derived vaccine [76].

The protective efficacy of the tick-borne encephalitis vaccine was estimated to be between 95.6% and 100% as

assessed from cases among vaccinated and unvaccinated individuals in Austria, and regardless of the vaccines used, seroconversion rates of >95% were obtained after the 2nd dose [45].

Rabies vaccines induce long-lasting memory cells giving rise to an accelerated immune response when a booster dose is administered. In Western countries, the post-exposure course in individuals who have been fully immunised consists of only two doses two days apart without the need for immune globulin [77]. Appropriate post-exposure rabies vaccination together with thorough wound cleansing and the administration of immune globulin, with infiltration in and around the wound, if indicated, appears to be highly effective in preventing clinical rabies. Most of the fatalities reported were due to a failure to comply fully with all three of the recommendations above or delay in implementing treatment [43,78]. Extremely rare cases of human rabies attributed to genuine post-exposure prophylaxis failure have been documented [79].

Yellow fever vaccine induces neutralising antibodies in 90% of vaccinees within 10 days of injection and in 99% within 30 days [80]. Although under the IHR, a single dose of vaccine should be administered at 10 yearly intervals if required for entry to a country, 80% of vaccine recipients remained seropositive 30 years after a single dose [80]. In another study, protective antibody levels were reported in 95.2% of individuals who had received the vaccine ≥10 years (median 14 years) previously, including one case where vaccine was administered 60 years previously [81].

Yellow fever vaccine – vaccine safety

Most AEs associated with travel vaccines are minor and well tolerated by travellers. However, rare but potentially serious AEs caused by yellow fever vaccine should be recognised and discussed fully with the traveller. Neurological and viscerotropic disease are of particular importance with the latter (YEL-AVD) associated with a high fatality rate. Since 1990, 31 cases and 12 deaths due to YEL-AVD were reported in travellers while 6 travellers acquired natural infection (all fatal) which raised concern that the risk of vaccination may outweigh its benefit in travellers [59]. This review reported the rate of vaccine-related serious AEs as 0.4–0.8 per 100,000 travellers, which is higher than other live vaccines, and with a greater risk in individuals aged >60 years. Geographically, the risk of serious vaccine-related AEs may exceed the risk of wild-type virus infection in travellers to tropical America, but the reverse may be true for travel to Africa. Thus, a careful assessment of the risk factors both for naturally acquired infection and YEL-AVD is needed. The vaccine is contraindicated in those with a history of a thymus disorder, with or without thymectomy, and should be withheld or given with caution to those aged ≥60 and breastfeeding women [77].

Immunising travellers from Japan

Differences between Japan and Western countries in the national immunisation programmes, production and availability of vaccines merit discussion. Firstly, several vaccines in routine use in many developed countries are not yet routinely given in Japan. These include mumps, varicella, rotavirus, and hepatitis B vaccine (Table 1), which are licensed but have to be paid for by the vaccine recipient. An exception to this is the hepatitis B vaccine where the cost will be covered by health insurance when given to infants born to a hepatitis B virus-positive mother. Since April 2013, the pneumococcal conjugate vaccine (for children), *Haemophilus influenzae* type b, and the human papillomavirus vaccines have been included in the national immunisation programme; however, of course, most Japanese travellers will not have been immunised with any of these vaccines. These vaccines may therefore be viewed as a priority for Japanese travellers, reducing the time and money available for other vaccines that are recommended for travel. Secondly, several travel vaccines are not licensed in Japan; they are the typhoid fever vaccine (the parenteral Vi polysaccharide and the oral Ty21a), the oral cholera, meningococcal, and tick-borne encephalitis vaccines. This narrows the spectrum of travel-related diseases that can be prevented by immunisation in travellers from Japan. Since, exceptionally, the yellow fever vaccine has been licensed without official national data from Japan, its availability is restricted to a limited number of facilities, most of which are quarantine offices and related facilities. This makes the vaccine less easily accessible for many Japanese travellers in need of it. Thirdly, some vaccines are developed and produced nationally, and are not used outside Japan, i.e., the hepatitis A vaccine, one of two available hepatitis B vaccines, and rabies vaccine. This makes it difficult to apply the large volume of data available from studies on vaccines licensed in Western countries to those manufactured in Japan, e.g., data on the simultaneous administration of vaccines, accelerated schedules and interchangeability of vaccines. In recent years, these issues prompted many travel clinics in Japan to import vaccines from abroad, and therefore, the licensing of such Western vaccines in Japan may be viewed as a matter of priority.

In the meantime, studies on nationally produced Japanese vaccines are ongoing. Takayama et al. [82] examined rabies antibody levels in travellers who were given post-exposure prophylaxis, with initial doses of vaccine manufactured outside Japan and subsequent doses of Japanese manufactured vaccine (interchangeability study). After a total of 5 doses, protective antibody levels were noted in all travellers (n = 56), but in one combination of the foreign- and locally-manufactured (Japanese) vaccines, lower titres (<0.5 EU/mL) were noted in some recipients after a third dose of vaccine; however, the clinical significance of this is unknown. Another study revealed that approximately one in four travellers who received two doses of the Japanese-manufactured rabies vaccine as pre-exposure prophylaxis (days 0 and 28) failed to mount protective levels of antibodies [83]. This is a concern since many travellers are unable to complete the full pre-exposure course (days 0, 28, 180 in Japan) before departure. This data, together with other work by Takayama's group showing an excellent response (seroconversion in all subjects) to the accelerated schedule (days 0, 7, 28) with the Japanese rabies vaccine [84], supports the need to introduce an accelerated rabies vaccination schedule in Japan. Studies have also been carried out on the

tolerability of multiple vaccines administered simultaneously, using Japanese vaccines [85]. A critical evaluation of these Japanese studies would be required to establish whether there can be a change to the current immunisation practice in Japan or whether further data is needed beforehand. This role may be better served by a newly formed Japanese organisation equivalent to the Advisory Committee on Immunization Practices in the U.S., a proposal which is currently being promoted in Japan.

A study on vaccine uptake by Japanese travellers was conducted to compare the knowledge, attitudes and practices (KAP) of Japanese travellers and travellers from a number of other nations worldwide. It is clear from this study that vaccine uptake among Japanese travellers is low and their attitude towards vaccination is somewhat unenthusiastic [86]. Travellers may have been influenced by unsubstantiated media reports of vaccine-associated AEs [86]. The attitude towards immunisation is also reflected in the use of prophylactic measures in general. In fact, another KAP study conducted by one of the current authors (M.K.) showed poor use of malaria chemoprophylaxis among Japanese travellers [87].

Travel medicine advisors worldwide should be aware of the differences between Japan and other nations with regard to vaccine availability and vaccine uptake, while in Japan these differences should be discussed openly by professionals, incorporating the views and perceptions of travellers, trying to ultimately bridge those gaps.

Conflict of interest

The authors declare no conflicts of interest.

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References

[1] UNWTO (World Tourism Organization). Tourism Highlights, 2013 edition. Available at: http://mkt.unwto.org/en/publication/unwto-tourism-highlights-2013-edition [accessed 19.08.13].
[2] Ministry of Justice, Japan. [in Japanese]. Available at: http://www.moj.go.jp/content/000099305.pdf [accessed 19.08.13].
[3] Steffen R, Connor BA. Vaccines in travel health: from risk assessment to priorities. J Travel Med 2005;12:26–35.
[4] Mutsch M, Tavernini M, Marx A, Gregory V, Lin YP, Hay AJ, et al. Influenza virus infection in travelers to tropical and subtropical countries. Clin Infect Dis 2005;40:1282–7.
[5] Miller MA, Hinman AR. Economic analyses of vaccine policies. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th ed. Philadelphia: Saunders; 2004. pp. 1463–90. Chapter 57.
[6] Aguilera J-F, Perrocheau A, Meffre C, Hahné S, the W135 Working Group. Outbreak of serogroup W135 meningococcal disease after the Hajj pilgrimage, Europe, 2000. Emerg Infect Dis 2002;8:761–7.
[7] Frank C, Walter J, Muehlen M, Jansen A, van Treeck U, Hauri AM, et al. Large outbreak of hepatitis A in tourists staying at a hotel in Hurghada, Egypt, 2004 – orange juice implicated. Euro Surveill 2005;10(6):E050609.2.
[8] Behrens RH, Roberts JA. Is travel prophylaxis worth while? Economic appraisal of prophylactic measures against malaria, hepatitis A, and typhoid in travellers. BMJ 1994;309:918–22.
[9] Papadimitropoulos V, Vergidis PI, Bliziotis I, Falagas ME. Vaccination against typhoid fever in travellers: a cost-effectiveness approach. Clin Microbiol Infect 2004;10:681–3.
[10] Lundkvist J, Steffen R, Jönsson B. Cost-benefit of WC/rBS oral cholera vaccine for vaccination against ETEC-caused travelers' diarrhea. J Travel Med 2009;16:28–34.
[11] World Health Organization, International health regulations (2005). Available at: http://www.who.int/ihr/en/ [accessed 19.08.13].
[12] World Health Organization. International travel and health (edition 2012). Available at: http://www.who.int/ith/en/ [accessed 19.08.13].
[13] Centers for Disease Control and Prevention. Travelers' health. Available at: http://wwwnc.cdc.gov/travel/page/yellowbook-home-2014 [accessed 14.11.13].
[14] Centers for Disease Control and Prevention. Measles – United States, 2011. MMWR 2012;61:253–7.
[15] Centers for Disease Control and Prevention. Tetanus surveillance – United States, 2001–2008. MMWR 2011;60:365–9.
[16] Infectious Disease Surveillance Center (Japan). Tetanus in Japan as of December 2008. Infect Agents Surveill Rep 2009;30:65–6. Available at: http://idsc.nih.go.jp/iasr/30/349/tpc349.html [accessed 19.08.13].
[17] Infectious Disease Surveillance Center (Japan). Tetanus in Japan as of 2001. Infect Agents Surveill Rep 2002;23:1–2. Available at: http://idsc.nih.go.jp/iasr/23/263/tpc263.html [accessed 19.08.13].
[18] Anonymous. Diphtheria epidemic – new independent states of the former Soviet Union, 1990–1994. J Travel Med 1995;2:269–71.
[19] Wiedermann U. Routine adult vaccines and boosters. In: Keystone JS, Freedman DO, Kozarsky PE, Connor BA, Nothdurft HD, editors. Travel medicine. 3rd ed. Elsevier (Saunders); 2013. pp. 77–86.
[20] Shlim DR, Solomon T. Japanese encephalitis vaccine for travelers: exploring the limits of risk. Clin Infect Dis 2002;35:183–8.
[21] Jelinek T. IXIARO® updated: overview of clinical trials and developments with the inactivated vaccine against Japanese encephalitis. Expert Rev Vaccines 2013;12:859–69.
[22] Burchard GD, Caumes E, Connor BA, Freedman DO, Jelinek T, Jong EC, et al. Expert opinion on vaccination of travelers against Japanese encephalitis. J Travel Med 2009;16:204–16.
[23] Zuckerman JN, Van Damme P, Van Herck K, Löscher T. Vaccination options for last-minute travellers in need of travel-related prophylaxis against hepatitis A and B and typhoid fever: a practical guide. Travel Med Infect Dis 2003;1:219–26.
[24] Steffen R. Hepatitis A and hepatitis B: risks compared with other vaccine preventable diseases and immunization recommendations. Vaccine 1993;11:518–20.
[25] Larouze B, Gaudebout C, Mercier E, Lionsquy G, Dazza MC, Elias M, et al. Infection with hepatitis A and B viruses in French volunteers working in tropical Africa. Am J Epidemiol 1987;126:31–7.
[26] Teitelbaum P. An estimate of the incidence of hepatitis A in unimmunized Canadian travelers to developing countries. J Travel Med 2004;11:102–6.

[27] Steffen R. Changing travel-related global epidemiology of hepatitis A. Am J Med 2005;118(Suppl. 10A):46S–9S.
[28] Askling HH, Rombo L, Andersson Y, Martin S, Ekdahl K. Hepatitis A risk in travelers. J Travel Med 2009;16:233–8.
[29] Nelson KE. Global changes in the epidemiology of hepatitis A virus infections. Clin Infect Dis 2006;42:1151–2.
[30] Mermin JH, Townes JM, Gerber M, Dolan N, Mintz ED, Tauxe RV. Typhoid fever in the United States, 1985–1994: changing risks of international travel and increasing antimicrobial resistance. Arch Intern Med 1998;158:633–8.
[31] Ekdahl K, de Jong B, Andersson Y. Risk of travel-associated typhoid and paratyphoid fevers in various regions. J Travel Med 2005;12:197–204.
[32] Meltzer E, Sadik C, Schwartz E. Enteric fever in Israeli travelers: a nationwide study. J Travel Med 2005;12: 275–81.
[33] Lynch MF, Blanton EM, Bulens S, Polyak C, Vojdani J, Stevenson J, et al. Typhoid fever in the United States, 1999–2006. J Am Med Assoc 2009;302:859–65.
[34] Smalligan RD, Lange WR, Frame JD, Yarbough PO, Frankenfield DL, Hyams KC. The risk of viral hepatitis A, B, C, and E among North American missionaries. Am J Trop Med Hyg 1995;53:233–6.
[35] Sonder GJB, van Rijckevorsel GGC, van den Hoek A. Risk of hepatitis B for travelers: is vaccination for all travelers really necessary? J Travel Med 2009;16:18–22.
[36] Nielsen US, Thomsen RW, Cowan S, Larsen CS, Petersen E. Predictors of travel-related hepatitis A and B among native adult Danes: a nationwide case-control study. J Infect 2012; 64:399–408.
[37] Taylor DN, Rizzo J, Meza R, Perez J, Watts D. Cholera among Americans living in Peru. Clin Infect Dis 1996;22:1108–9.
[38] Wittlinger F, Steffen R, Watanabe H, Handszuh H. Risk of cholera among Western and Japanese travelers. J Travel Med 1995;2:154–8.
[39] Koch S, Steffen R. Meningococcal disease in travelers: vaccination recommendations. J Travel Med 1994;1:4–7.
[40] Centers for Disease Control and Prevention. Inactivated Japanese encephalitis virus vaccine. Recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep 1993;42(RR-1):1–15.
[41] Hills SL, Griggs AC, Fischer M. Japanese encephalitis in travelers from non-endemic countries, 1973–2008. Am J Trop Med Hyg 2010;82:930–6.
[42] Centers for Disease Control and Prevention. Yellow fever vaccine. Recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep 2010; 59(RR-7):1–27.
[43] Malerczyk C, DeTora L, Gniel D. Imported human rabies cases in Europe, the United States, and Japan, 1990 to 2010. J Travel Med 2011;18:402–7.
[44] Susilawathi NM, Darwinata AE, Dwija IB, Budayanti NS, Wirasandhi GA, Subrata K, et al. Epidemiological and clinical features of human rabies cases in Bali 2008–2010. BMC Infect Dis 2012;12:81.
[45] Rendi-Wagner P. Risk and prevention of tick-borne encephalitis in travelers. J Travel Med 2004;11:307–12.
[46] Centers for Disease Control and Prevention. Tick-borne encephalitis among U.S. travelers to Europe and Asia – 2000–2009. MMWR 2010;59:335–8.
[47] Fiore AE. Hepatitis A transmitted by food. Clin Infect Dis 2004;38:705–15.
[48] Willner IR, Uhl MD, Howard SC, Williams EQ, Riely CA, Waters B. Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States. Ann Intern Med 1998;128:111–4.
[49] Crowcroft NS, Walsh B, Davison KL. Gungabissoon U on behalf of PHLS Advisory Committee on Vaccination and Immunisation. Guidelines for the control of hepatitis A virus infection. Commun Dis Public Health 2001;4:213–27.
[50] Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. Lancet 2005;366:749–62.
[51] Cooke FJ, Wain J. The emergence of antibiotic resistance in typhoid fever. Travel Med Infect Dis 2004;2:67–74.
[52] Sako A, Yasunaga H, Horiguchi H, Hashimoto H, Masaki N, Matsuda S. Acute hepatitis B in Japan: incidence, clinical practices and health policy. Hepatol Res 2011;41:39–45.
[53] Miyoshi T, Hiraoka A, Hidaka S, Shimizu Y, Ninomiya K, Utsunomiya H, et al. An adult patient with acute infection with hepatitis B virus genotype C that progressed to chronic infection. Intern Med 2012;51:173–6.
[54] Yano K, Tamada Y, Yatsuhashi H, Komori A, Abiru S, Ito K, et al. Japan national Hospital acute hepatitis study group. Dynamic epidemiology of acute viral hepatitis in Japan. Intervirology 2010;53:70–5.
[55] Ryan ET, Calderwood SB. Cholera vaccines. J Travel Med 2001;8:82–91.
[56] Al-Tawfiq JA, Clark TA, Memish ZA. Meningococcal disease: the organism, clinical presentation, and worldwide epidemiology. J Travel Med 2010;17(S1):3–8.
[57] Black S. Travelers' protection against meningococcal disease: a new vaccine option. J Travel Med 2010;17(S1): 18–25.
[58] Brooks R, Woods CW, Benjamin Jr DK, Rosenstein NE. Increased case-fatality rate associated with outbreaks of *Neisseria meningitidis* infection, compared with sporadic meningococcal disease, in the United States, 1994–2002. Clin Infect Dis 2006;43:49–54.
[59] Monath TP. Review of the risks and benefits of yellow fever vaccination including some new analyses. Expert Rev Vaccines 2012;11:427–48.
[60] Willoughby Jr RE, Tieves KS, Hoffman GM, Ghanayem NS, Ammlie-Lefond CM, Schwabe MJ, et al. Survival after treatment of rabies with induction of coma. N Engl J Med 2005;352:2508–14.
[61] Centers for Disease Control and Prevention. Recovery of a patient from clinical rabies – California, 2011. MMWR 2012; 61:61–5.
[62] Centers for Disease Control and Prevention. Presumptive abortive human rabies – Texas, 2009. MMWR 2010;59: 185–90.
[63] Barrett PN, Dorner F, Ehrlich H, Plotkin SA. Tick-borne encephalitis vaccine. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th ed. Philadelphia: Saunders; 2004. pp. 1039–55.
[64] Haditsch M, Kunze U. Tick-borne encephalitis: a disease neglected by travel medicine. Travel Med Infect Dis 2013; 11:295–300.
[65] Infectious Disease Surveillance Center (Japan). A fatal case of tick-borne encephalitis in a Japanese (authors' translation). Infect Dis Wkly Rep (Japan) 2002;4(3):11 [in Japanese]. Available at: http://idsc.nih.go.jp/idwr/kanja/idwr/idwr2002-03.pdf [accessed 19.08.13].
[66] Senn N, Genton B. Acute hepatitis A in a young returning traveler from Kenya despite immunization before departure. J Travel Med 2009;16:72–3.
[67] Connor BA, Van Herck K, Van Damme P. Rapid protection and vaccination against hepatitis A for travellers. Biodrugs 2003;17(Suppl. 1):19–21.
[68] Centers for Disease Control and Prevention. Update: prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007;56:1080–4.
[69] Van Damme P, Banatvada J, Fay O, Iwarson S, McMahon B, Van Herck K, et al., The International Consensus Group on

Hepatitis A Virus Immunity. Hepatitis A booster vaccination: is there a need? Lancet 2003;362:1065–71.
[70] Aono J, Yotsuyanagi H, Moriya K, Koike K. Evaluation of hepatitis B vaccination in nursing school students. Jpn J Environ Infect 2012;27:253–8 [in Japanese].
[71] Gilca V, De Serres G, Boulianne N, Murphy D, De Wals P, Ouakki M, et al. Antibody persistence and the effect of a booster dose given 5, 10 or 15 years after vaccinating pre-adolescents with a recombinant hepatitis B vaccine. Vaccine 2013;31:448–51.
[72] European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? Lancet 2000;355:561–5.
[73] von Seidlein L. The need for another typhoid fever vaccine. J Infect Dis 2005;192:357–9.
[74] Lin FYC, Ho VA, Khiem HB, Trach DD, Bay PV, Thanh TC, et al. The efficacy of a *Salmonella typhi* Vi conjugate vaccine in two-to-five-year-old children. N Engl J Med 2001; 344:1263–9.
[75] Levine MM, Ferreccio C, Black RE, Tacket CO, Germanier R, the Chilean Typhoid Committee. Progress in vaccines against typhoid fever. Rev Infect Dis 1989;11(Suppl. 3): S552–67.
[76] Erra EO, Askling HH, Rombo L, Riutta J, Vene S, Yoksan S, et al. A single dose of Vero cell-derived Japanese encephalitis (JE) vaccine (Ixiaro) effectively boosts immunity in travelers primed with mouse brain-derived JE vaccines. Clin Infect Dis 2012;55:825–34.
[77] Chen LH, Hill DR, Wilder-Smith A. Vaccination of travelers: how far have we come and where are we going? Expert Rev Vaccines 2011;10:1609–20.
[78] Wilde H, Briggs DJ, Meslin F-X, Hemachudha T, Sitprija V. Rabies update for travel medicine advisors. Clin Infect Dis 2003;37:96–100.
[79] Wilde H. Failures of post-exposure rabies prophylaxis. Vaccine 2007;25:7605–9.
[80] Torresi J, Kollaritsch H. Special adult travel vaccines: yellow fever, meningococcal, Japanese encephalitis, TBE, rabies, polio, cholera. In: Keystone JS, Freedman DO, Kozarsky PE, Connor BA, Nothdurft HD, editors. Travel medicine. 3rd ed. Elsevier (Saunders); 2013. pp. 101–23.
[81] Coulange Bodilis H, Benabdelmoumen G, Gergely A, Goujon C, Pelicot M, Poujol P, et al. Long term persistence of yellow fever neutralising antibodies in elderly persons (Articles in French). Bull Soc Pathol Exot 2011;104:260–5.
[82] Takayama N, Suganuma A, Kasai D, Kurai D. Anti-rabies antibody titers among subjects who received rabies post-exposure prophylaxis with foreign-made rabies vaccines at the beginning and followed with Japanese rabies vaccine. Kansenshogaku Zasshi 2002;76:882–7 [in Japanese with an English abstract].
[83] Arai YT, Kimura M, Sakaue Y, Hamada A, Yamada K, Nakayama M, et al. Antibody responses induced by immunization with a Japanese rabies vaccine determined by neutralization test and enzyme-linked immunosorbent assay. Vaccine 2002;20:2448–53.
[84] Yanagisawa N, Takayama N, Nakayama E, Mannen K, Suganuma A. Pre-exposure immunization against rabies using Japanese rabies vaccine following the WHO recommended schedule. J Infect Chemother 2010;16:38–41.
[85] Mizuno Y, Kano S, Urashima M, Genka I, Kanagawa S, Kudo K. Simultaneous vaccination in Japanese travelers. Travel Med Infect Dis 2007;5:85–9.
[86] Namikawa K, Iida T, Ouchi K, Kimura M. Knowledge, attitudes, and practices of Japanese travelers on infectious disease risks and immunization uptake. J Travel Med 2010; 17:171–5.
[87] Namikawa K, Kikuchi H, Kato S, Takizawa Y, Konta A, Iida T, et al. Knowledge, attitudes and practices of Japanese travelers towards malaria prevention during overseas travel. Travel Med Infect Dis 2008;6:137–41.