る。熱帯熱マラリアでは、sequestration により、赤血球内サイクルの前半（約 24 時間）部分の原虫しか末梢血中に出現しない。このため、通常は 12～24 時間毎に 3 回連続の陰性確認がマラリアの否定には必要である。

補助的診断法として、迅速抗原検出キット（研究用試薬）がある。免疫クロマトグラフィー法により Histidine-rich protein 2（HRP2）や原虫の LDH、アルドラーゼを検出するもので、熱帯熱と非熱帯熱マラリア原虫を区別できるものもある。15 分程度で結果が判明するため、特に休日・夜間には利用価値が高いと考えられる。実験室レベルでは PCR 法が原虫種や混合感染の確認に役立つ。

治療薬

抗マラリア薬は、キナの樹皮から発見されたキニーネに始まる。最近では、耐性化を防ぐため、多剤併用療法が推奨されるようになってきた。中でも、中国でクソニンジン（キク科ヨモギ属）から開発されたアーテミシニン系薬の合剤（ACT）が治療の中心である。わが国では、1975 年にクロロキン、2010 年にファンシダールが販売中止となり、2013 年 12 月現在、わが国で承認販売されている抗マラリア薬は、塩酸キニーネ末、メフロキン塩酸錠、アトバコン・プログアニル配合錠の 3 種類である。この他に、アーテメター・ルメファントリン配合錠、グルコン酸キニーネ注射薬、アーテスネート座薬、リン酸クロロキン錠、塩酸プリマキン錠が必要時に速やかに使用できる体制が厚生労働科学研究費補助金（熱帯病治療薬研究班）によりとられている。なお、これらの未承認薬の使用は倫理承認を受けた全国 31 の医療機関において、臨床研究として行われている。

治療の効果判定は、原虫消失、および発熱などの臨床症状の改善をもって行う。原虫消失は、末梢血塗抹標本により判定する。治療開始後 24～36 時間以内では、原虫寄生率が一過性に増加することがあるため、この時期の治療効果判定は一般に困難である。

治療後に再び発熱が生じ、原虫を末梢血中に認めた場合には、その原因を検討する。三日熱、卵形マラリアでは、残存した赤血球内原虫の増殖による再燃（recrudescence）と休眠体からの再発（relapse）を区別するのは困難である。

わが国での重症マラリアの治療は、熱帯病治療薬研究班が保管するキニーネ注射薬が使用されるのが望ましい。薬剤使用機関に患者を転院させるのが難しい場合には、同研究班の最寄りの薬剤使用機関、またはデータセンターの独立行政法人国立国際医療研究センター国際感染症センター国際感染症対策室に相談する。マラリア常在地では、重症マラリアの治療において、アーテスネート静注薬がキニーネ注射薬より優れていることが明らかとなっている[3]。しかし、先進国 GMP 基準で製造されている製剤がないため、わが国を含めて一般に使用が困難である。支持療法として、輸液・輸血、血糖管理、血液浄化療法、人工呼吸などを適切に行うため、集中治療室で管理するのが原則である。

新興マラリア　ヒト *P. knowlesi* 感染症

症例：30 歳代　男性　日本人

主訴：発熱

病歴：2012 年 7～9 月、マレーシアに滞在し、森林地帯で植物や昆虫の調査を行った。9 月末、帰国当日夜から 38℃台の発熱を認め、24 時間ごとに繰り返すため、発熱 3 日目に受診した。

1965 年にマレー半島のジャングルに滞在した米国人でサルマラリア原虫の自然感染が初めて報告された。この原虫 *P. knowlesi* は、東南アジアのジャングルに生息するブタオザル等を宿主とし、森林地帯に生息するハマダラカにより媒介される。ヒト症例の報告は以後限られていたが、マレーシア・ボルネオで 2000～2002 年に診断されたマラリア 208 例中 120 例で PCR 法により *P. knowlesi* が陽性であったことが 2004 年に報告され、注目を集めるようになった。その後、マレーシアを中心に、ミャンマー、タイ、シンガポール、フィリピン、ベトナム、インドネシアなどから報告がみられる。最近では、東南アジアのジャングルに滞在歴のある旅行者の症例も少

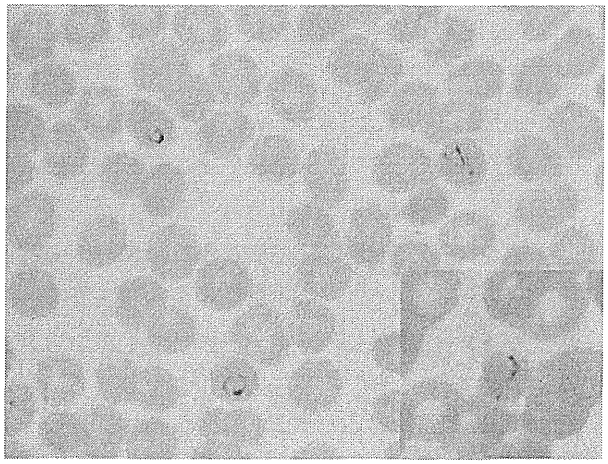

図2. 患者末梢血塗抹標本（ヒト *P. knowlesi* 感染症）

数ながら報告されており、我が国でも2例の報告がある[4),5)]。

2006～2008年にかけて、マレーシア・サラワク州の病院に入院した成人マラリア152症例の検討では、全体の70%にあたる107例が *P. knowlesi* によるものであった。発熱、頭痛、悪寒戦慄、倦怠感などの症状や血小板減少はあるが貧血を認めないといった血液検査所見は、ほかのヒトマラリア原虫による急性マラリアのそれと一致した。重症マラリアの基準を満たした10例において、合併症は呼吸不全が最も多く、熱帯熱マラリアに多い脳マラリアは認められなかった。重症度と原虫数が相関するのは熱帯熱マラリアと同様で、死亡した2例のそれは20万/μLを越えていた。

本症の潜伏期は2週間程度と考えられている。赤血球内サイクルは24時間であることが特徴であり、発熱は連日認められる。休眠体は存在しない。末梢血塗抹標本における本原虫は四日熱マラリア原虫のそれに似る。このため、鏡検法では原虫種の鑑別が難しいため、遺伝子診断が必要となる。

我が国で承認販売されている抗マラリア薬はいずれも有効である。

おわりに

マラリアはサハラ以南アフリカへの渡航者を中心に、頻度の高い輸入感染症である。とくに熱帯熱マラリアは緊急性の高い疾患であり、迅速な検査診断と治療が重要である。わが国では、予防にも使えるアトバコン・プログアニル配合錠が承認されるなどしているが、マラリアの診療体制という面では、未だ改善の余地があると思われる。迅速診断キットや重症マラリアに使用する注射薬が必要な患者に迅速に使えるような体制の構築されることが望ましい。また、海外渡航者への啓発も重要である。黄熱予防接種の際などには、流行地の重なるマラリアの予防に関しても十分な情報提供がなされるよう関係者の取り組みが望まれる。

参考文献

1) Leder K, Torresi J, Libman MD, et al. GeoSentinel Surveillance of illness in returned travelers, 2007-2011. Ann Intern Med. 158:456-468. 2013.
2) Taylor SM, Molyneux ME, Simel DL, et al. Does this patient have malaria? JAMA. 304:2048-2056. 2010.
3) World Health Organization. Guidelines for the treatment of malaria. 2nd edition. 2010.
4) Kantele A, Jokiranta TS. Review of cases with the emerging fifth human malaria parasite, *Plasmodium knowlesi*. Clin Infect Dis. 52:1356-1362. 2011.
5) Tanizaki R, Ujiie M, Kato Y, et al. First case of *Plasmodium knowlesi* infection in a Japanese traveller returning from Malaysia. Malaria J. 12:128. 2013.

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学会報告1

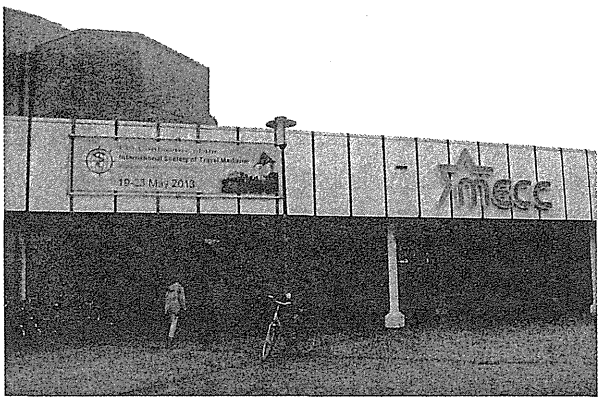
第13回国際旅行医学会議におけるトピックス（1）
—マラリア—

木村幹男[1)]　清水少一[2)]

1）結核予防会新山手病院内科　2）三菱電機株式会社鎌倉製作所健康増進センター

国際旅行医学会（International Society of Travel Medicine：ISTM）は1991年に設立され，旅行医学における知識や実践のスタンダードを確立して提供し，学際的な専門分野としてのさらなる発展を目指すものである．ISTMは2年に1度国際会議を開いてきたが，最近では間の年にもRegional Meetingを開催しており，毎年1回開いていることになる．筆者（木村）は現在，ISTMの機関誌であるJournal of Travel Medicineの編集査読委員，およびISTMが実施する国際的認定試験（CTH™）の委員を務めている．会員数は90ヵ国から3,000名以上で，日本からの会員数は5番目にまで増えた．会議における日本人参加者も増えつつあり，前述の認定試験にでは英語での出題にもかかわらず，高い合格率である．

今回，第13回会議が開かれたのはオランダの南端に位置するマーストリヒトであり，ベルギーおよびドイツとの国境に近接する．古代ローマ人によって築かれた古い歴史を有し，昔から種々の地域から人が集まる交易の要所で，フランス，スペインに帰属したこともある．そのため，オランダでありながら独立性も保っていると言われる．まさに，旅行医学の会議が開かれるに相応しいこの地において，2013年5月19〜23日の5日間，第13回会議が開かれたが，会場は，1992年に欧州連合（EU）発足の調印式が行われたMaastricht Exhibition and Congress Centreである．旅行医学の守備範囲は広く，一人の関係者がすべての分野に精通するのは不可能である．これから3回にわたり，同会議におけるトピックス的な演題を紹介するが，1回目はマラリア，2回目はマラリアを除く感染症，3回目は航空機内医療，長期滞在者や小児の問題を扱う予定である．



会議場の正面玄関
オランダらしく自転車が多数並んでいる

▶ マラリア

1 治療薬剤

わが国では欧米先進国に15年も遅れたが，2013年2月よりアトバコン・プログアニル合剤（AP，マラロン®）が承認薬としてマラリアの治療および予防に使用可能となった．今回，non-immuneイスラエル人旅行者における合併症のない熱帯熱マラリアで（ほとんどがアフリカでの感染），APとアーテメター・ルメファントリン合剤（AL）との効果を比べた（Grynberg他）．治療失敗率はAPで13%（6/45），ALで0%（0/18）で，発熱消失時間も後者

0913-7963/2013/¥800/論文/JCOPY

のほうが短かった．過去にAPでこれほど高い治療失敗率はなかったと思われ，今後，他のデータの検討が必要である．

マラリア治療におけるアーテミシニン系薬の役割が取り上げられた（Bassat）．なかでも，アーテミシニン系薬と他の薬剤とを組み合わせるACT（artemisinin-based combination therapy）が注目されており，上記ALもその一種である．本来，薬剤耐性熱帯熱マラリアの治療薬として開発されてきたが，三日熱マラリアでも耐性が出現し始めており，重症例もあること，熱帯熱マラリアとの混合感染が見逃される可能性もあること，また*P. knowlesi*でも重症化する例がありうるので，すべてのマラリアでACTの使用が提案されている．ただし，三日熱/卵形マラリアにおける再発予防にはプリマキンが必要である．

2 溶血性貧血の副作用

アーテミシニン誘導体の一種であるアーテスネート，特にその注射薬は即効性のゆえに，重症熱帯熱マラリアの治療における評価が高い．しかし，それが奏効したころに出現する溶血性貧血（delayed hemolysis）が問題となっている．フランスからは，そのような重症熱帯熱マラリア1例の報告があった（Rapp他）．アーテスネート注射薬による治療を行い，72時間後にマラリア原虫は消失し，血小板数も正常化したが，網赤血球数が増え始め，第7病日にはHb 7 g/dLの最低値を示した．クームス試験は陰性で異常ヘモグロビン，G6PD（グルコース6リン酸脱水素酵素）やPK（ピルビン酸キナーゼ）などの赤血球酵素の欠損は見られなかった．また，貧血は自然に改善した．ドイツからの報告では，これについての治療薬剤の影響を検討した（Rolling他）．Delayed hemolysisはアーテスネート注射薬を受けた症例，キニーネ注射薬とアーテスネート坐薬の併用症例にみられ，キニーネ注射薬単独症例ではみられず，アーテスネートとの関連が深いと思われた．逆に，キニーネ注射薬では他の副作用，すなわち低血糖，聴力障害，腎機能悪化，心毒性などがみられた．

3 プリマキンの有効性・安全性

筆者らのグループは熱帯病治療薬研究班のデータで，日本人三日熱マラリア症例で急性期治療の後の再発予防にプリマキンを使用した症例を調べた（Shimizu他）．高用量（30 mg/日・14日間）では再発例がなく，標準療法（15 mg/日・14日間）では再発例がみられたが，標準療法での再発例は非再発例と比べて体重当たり総投与量が低かった．このことから逆に，体重が少ない症例では必ずしも高用量を使う必要がないと思われた．また，副作用の出現については両群で有意差は見られなかった．フランスのグループもプリマキン高用量投与を受けた三日熱マラリア症例の解析を行った（ほとんどが仏領ギアナでの感染）（Rapp他）．有効率は初発例で96%，再発例で94.5%で，効果は高いと考えられ，副作用の問題もみられなかった．上記Shimizu他のデータと異なり，再発例で体重当たり総量が少なくはなかった．

4 顕微鏡法以外の診断法

海外では，マラリア原虫抗原を迅速に検査するキット（RDT）が数種類市販されており，主に熱帯熱マラリア原虫特異的なHRP2（histidine rich protein2）検出を主とするものと，マラリア原虫由来pLDHを検出するものとに大別できる．前者の場合，特に熱帯熱マラリア原虫の検出感度に優れている．今回，ローザンヌのグループが顕微鏡法以外のマラリア診断について述べた（D'Acremont）．同病院においてマラリアを疑う症例については，初めにRDTを行い，陽性であれば直ちに抗マラリア薬を投与する．その後3時間以内に顕微鏡法の結果を出し，陽性であれば，状況によっては経口薬から静注薬に変更し，顕微鏡法が陰性であっても，初期の抗マラリア薬を継続する．一方，RDTが陰性の場合，やはり3時間以内に顕微鏡法の結果を出し，陽性であれば抗マラリア薬の投与を開始し，陰性であれば，発熱が続く限り毎日RDTを繰り返す．すなわち，RDTの併用で多少のoverdiagnosisが生じても，マラリアの見逃しを避けることを重視している．

さらに，HRP2検出系ではprozone現象がありうるが，pLDH測定系ではみられず，両者を組み合わせたキットが望ましいこと，RDTと顕微鏡法とは同等のperformanceを有し，両者を併用するのが望ましく，必要に応じて繰り返すべきであること，PCR法（ポリメラーゼ連鎖反応法）は，繰り返すあるいは長期の発熱症例，原虫種の確定，精度管理などを除けば，輸入マラリアの診断には有用でないと述べた．

5 臨床症状

ドイツからは，SIADH（抗利尿ホルモン不適合分泌症候群）が疑われる低ナトリウム血症（115 mEq/L）および神経症状を呈した熱帯熱マラリアで，水分制限や高張食塩液の投与でも改善せず，ADH受容体拮抗薬のトルバプタン（わが国での適応は心不全）により低ナトリウム血症が改善した1例が報告された（Schmiedel他）．ただし，神経症状の改善はみられなかった．サハラ以南アフリカの生まれ育ちでフランスに住んでいる人が故国を訪ねて（VFRs），熱帯熱マラリアに罹患したとき，重症化や死亡が少なく，血小板減少も軽度で，原虫数は少ない傾向がみられ，長期間経っていても部分的免疫が持続していることが示された（Pistone他）．WHOの重症マラリアの基準として黄疸が挙げられるが，輸入熱帯熱マラリア成人症例で，①溶血性黄疸（間接ビリルビン上昇），②直接ビリルビン上昇，③間接および直接ビリルビン上昇の群に分けて検討したところ，②群において重症化する例が多かった（Rapp他）．

6 その他

APは熱帯熱マラリアの治療のみならず，予防においての評価が高い．毎日の服用であるが，流行地を去ってからの服用は7日間と短い利点があり，最近では，流行地を去ってから3日間程度の服用でも有効と言われている．さらに，ヒトでのマラリア原虫チャレンジ試験の結果から，1回のみの服用で予防可能とのデータも出されている．そこで，2006～2010年に米国のマラリアサーベイランスに報告された症例の解析が報告された（Arguin他）．予防にAPを使用していた症例で，三日熱や卵形マラリアの再発例を除いた“急性マラリア”が62例みられたが，完璧に本薬剤を服用した者，滞在中に服薬忘れがあった者，流行地を去ってから7日間経たないで服薬を中止した者などが見られた．したがって，従来より少ないAPの服用で効果的なマラリア予防が可能であるとは言えなかった．

カナダ・ケベックからの旅行者のマラリア症例では，半数以上がVFRsであったが，サハラ以南アフリカへの旅行692回につき1例の発生頻度であった（Bui他）．このような疫学データは貴重である．

コンゴ民主共和国に派遣されたベルギー軍人のマラリア予防薬としては，メフロキンが76.5%で，APは2%のみであったが（Soentjens他），米国ボストン地区のトラベルクリニックでマラリア流行地への旅行者について調べたところ，処方された抗マラリア薬ではAPが82%と多くを占め，メフロキンは3%に過ぎなかった（Stoney他）．予防的抗マラリア薬の選択において，軍人と一般人旅行者との違いを考えるべきかも知れない．

謝辞　本会議への出席は，厚生労働省科学研究費補助金・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（H25-医療技術-指定-012）」の研究活動の一環として行われた．

学会報告2

第13回国際旅行医学会議におけるトピックス（2）
―マラリアを除く感染症―

清水少一[1)]　木村幹男[2)]

1）三菱電機株式会社鎌倉製作所健康増進センター　2）結核予防会新山手病院内科

今回は，表記会議におけるマラリア以外の感染症，ワクチンなどに関する話題を取り上げる．

▶ マラリアを除く感染症

1 旅行者下痢症（Travelers diarrhea：TD）

タイの空港で，東南アジアへの旅行者のTD罹患率や危険因子を解析した（Kittitrakulら）．オセアニアからの旅行者における罹患率がもっとも高く32.9%（100人/月），東アジアからの旅行者がもっとも低く2.6%であった（国ごとの報告ではない点に注意）．行き先別TD罹患率ではインドネシア，ベトナムがもっとも高く，共に19.3%であった．他の危険因子として，若年，長期滞在，教育や研究目的，渡航国数，氷入りの飲み物が有意であった．90%の症例が軽症で，6%が外来受診し，4%が入院を必要とした．

米国ではメキシコ，グアテマラ，インドへの旅行者でETECによるTDを調べたが，その検出にはDNAプローブを用いた（Jiangら）．インドでの下痢症例の61%，メキシコ＋グアテマラでの下痢症例の45%にETECが検出された．それら菌株につきST，LT，CFA産生を調べたが，全体としてST単独産生株が多く，LTを対象としたワクチンなどは効果的でないと思われた．ただしSTの免疫原性は低いことから，ワクチンで効果が期待されるのはLT＋CFA（CS6を含む）を含むものである．

フランスの渡航者診療所で，便17,536検体の寄生虫感染を解析した報告では，18.3%が何らかの寄生虫に感染していた（Mlisson-Saunéら）．陽性者のうち80%がアフリカ帰りであった．上位は大腸アメーバや小型アメーバとほぼ無害なもので，病原性の寄生虫は4%に見られた（赤痢アメーバ0.84%，ジアルジア1.1%）．また，メタ解析の結果からノロウイルスがTDの原因の10～15%を占めていたと報告された（Verstraeten）．対象者の年齢や流行時期などに大きく左右されるが，TDの原因としてノロウイルスを認識する必要がある．

2 ワクチン接種

欧米で使われている狂犬病ワクチンRabipur®（PCECV）を用いた報告があった（Lauら）．皮内注射法としては従来，day 0，7，21あるいは28の3回受診時にそれぞれ0.1 mLずつの接種が行われてきたが，今回，day 0，7の2回受診時に，それぞれ0.1 mLの皮内注射を2ヵ所ずつ，すなわち合計で0.1 mLを4回接種する方法を検討した．以前にはSanofi Pasteur SA社製のHDCVを用いて優れた成績が得られている．今回44人に接種した結果，抗体陽性化率は94.4%で，HDCVとほぼ同じ効果が得られた．特に若年層で免疫付与率が高く，バックパッカーや子ど

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も連れの家族において期待される．

日本脳炎ワクチン Ixiaro®（ベロ細胞由来）の市販後 36ヵ月間の調査結果が報告された（Müller ら）．10 万接種当たりの副作用報告は 13.0 例であり，主に頭痛，めまい，インフルエンザ様症状，局所症状などであった．入院を要する重症例は 1.6 例であり，神経炎，けいれん，脳炎などであったが，ADEM やアナフィラキシーショックはなかった．副作用頻度は以前のマウス脳由来の JE-VAX®に比べて半分程度と少なかった．

毒素原性大腸菌（ETEC）の易熱性毒素（LT）を抗原とするパッチワクチンの開発が行われている．今回，世界 20ヵ所（ドイツおよび英国）のサイトにおいて，メキシコ/グアテマラへの旅行者を対象にランダム化プラセボ対照二重盲検試験が行われた（Behrens ら）．対照群での ETEC による中等度～重度下痢は 5.6%と低かったが，それに対するワクチンの効果は 35%，LT 単独陽性 ETEC による下痢に対する効果は 61%であったが，残念ながらすべての下痢に対する効果は算出されなかった．また，長期間持続する局所の皮膚症状が目立った．

欧米では血液透析者を含む腎不全患者を対象に B 型肝炎ワクチン Fendrix®（immune enhancer 含有）が用いられているが，今回，通常の B 型肝炎ワクチンでの non-responder を対象に効果を検討した（Wieten ら）．対象者の半分近くは HIV 感染者であったが，本ワクチン 1 回の接種で少なくとも 3 分の 1 に抗体陽転がみられ，さらに 2 回目の接種で陽転する例もみられ，期待が持てる結果であった．

3 感染症の診断

タイからは，デングウイルス非構造タンパク（NS1）に対する抗体の報告がなされた（Kositanon ら）．リコンビナント NS1（43 kDa）に対するデング熱患者血清 36 例の反応をみたが，36 例は 4 種の血清型それぞれにつき 9 例ずつ，しかも初感染と二次感染の症例が含まれていた．IgM 抗体の感度と特異度は共に 100%で，IgG 抗体の感度と特異度は 100%と 88.2%であり，診断上有意義と思われた．ただし，感染後に陽性となる時期については明らかでない．一方，イスラエル人でのデング熱患者血清を用いて，市販のキット（Panbio 社）で NS1 抗原そのものを測定したところ，発症 1～3 日での感度は 87%で，4～7 日には 70%に低下し，特異度は 92%で，西ナイルウイルスの影響はほとんど受けなかった（Fuchs ら）．

アフリカに滞在し，淡水との接触後 6～12 週して最終的に住血吸虫症と診断された旅行者の血清を用い，PCR 法（マンソン住血吸虫により特異的なものと，ビルハルツ住血吸虫に特異的なものの 2 種類）の検討を行った（Cnops ら）．計 34 例が対象となったが，訪問国はルワンダ（13 例），マリ（9 例），マラウイ（5 例），ケニア（7 例）であった．顕微鏡的虫卵検査，血清抗体，血清 PCR での陽性率はそれぞれ 50.0%，67.6%，82.4%であり，PCR 法がもっとも高かった．

パプアニューギニアから帰国した旅行者が頭痛と発熱を生じ，第 3 病日の検査で肝酵素の上昇がみられたが IgM-HAV 抗体は陰性であった（Sugihara ら）．その後肝酵素はさらなる上昇を示し，第 10 病日に再度 IgM 抗体を検査したところ陽性を示した．そこで，経時的に保存された血清を調べたところ，第 6 から第 7 病日の間で抗体陽転したことが示された．A 型肝炎の診断には IgM 抗体が重要視されるが，特に発病早期では注意が必要である．

4 薬剤耐性菌

インドを中心とするアジアにおいて，ESBL（Extended-Spectrum Beta-Lactamases）産生菌が多くなっており，インドや中国からの帰国者や入院患者に対して，スクリーニングが推奨される（Andremont）．渡航者の感染危険因子としては，高齢，下痢が挙げられるが，バックパッカーは危険因子からは除外された．また，プロバイオティクスによる予防効果は認められなかった．実際に，日本で帰国後旅行者から得られた糞便中大腸菌につき，ESBL 産生菌（18 例）と非産生菌（50 例）保有者に分け，症例対照研究を行った（Yaita ら）．その結果，ESBL 産生大腸菌保有の

危険因子としてインドへの旅行が挙げられたが，バックパッカーか否か，旅行目的，滞在期間などとの関係はみられなかった．

5 中東呼吸器症候群（MERS）

サウジアラビアを中心に発生し，高い致死率の呼吸器感染症であり，2013年5月の会議当時は，旅行者によってヨーロッパ各地に広がっているときであった．そのため，プログラムを変更して，中東呼吸器症候群コロナウィルスMERS-CoVに関する最新の研究成果が取り上げられた（Cletonら）．このウイルスは，ヒトに感染するコロナウイルスとしては6番目に発見されたものであり，betacoronavirus lineage Cに分類される初のヒトコロナウイルスであることが報告された．この分類はオランダで発見されたコウモリコロナウイルスと同じものであり，近縁種である可能性が示されたが，コウモリの他に単数または複数の中間宿主の存在も疑われていた．また，2ヵ所における集団感染事例が報告されるも，感染者が限られていたことから，ヒト-ヒト感染は限定的と推測された．なお，会議開催時点ではMERS-CoVという用語は使われておらず，発見した研究施設の名前を冠してHCoV-EMC（Human Coronavirus for Erasmus Medical Center）の用語が使われていた．

6 他の感染症

1990～2012年の世界における輸入狂犬病60症例の解析が行われた（Gautretら）．特徴として，滞在期間の長短は余り関係なく，7割が成人男性であり，インドとフィリピンの症例が多く，半数の症例で死後に診断されていた．診断遅延の因子として，当該地で狂犬病が根絶されているか近年報告がほとんどないこと，動物咬傷が明らかでないこと，症状が非典型的であること，などが挙げられた．

コンゴ民主共和国に派遣され，2ヵ月間，水や土に曝露されたベルギー兵士184名の解析が行われた（Soentiensら）．33例（18%）に好酸球増多を認め，そのうち11例が糞線虫，5例が赤痢アメーバ，5例が幼虫移行症，4例が住血吸虫，3例がズビニ鉤虫に感染していた．住血吸虫感染者は以前に比べて少なくなっていたが，マラリア予防薬による効果も推察された．

37歳イタリア人がビジネスでシンガポールに出張後，発熱，全身倦怠，乾性咳嗽，広汎な筋肉痛を生じた．WBC 10,920/μL，CRP 16.7 mg/dLで軽度の脾腫，両側性肺結節影がみられ，血液培養で*Burkholderia pseudomallei*が陽性となり，メリオイドーシスの診断が確定した（Amadasiら）．セフタジジム大量投与を開始したが，間もなくメロペネム1 gの6時間ごと静注，ST合剤の1日3回経口投与（スルファメトキサゾール2,400 mg/日，トリメトプリム480 mg/日）の併用に変更した．その後の画像検査で，脾膿瘍，骨病変（上腕骨）を疑う所見もみられた．上記治療を約2週間行い，骨髄炎疑いに対してST合剤経口投与を6ヵ月間継続した．

7 終わりに

本会議においては種々の感染症がさまざまな観点から取り上げられ，改めて旅行医学の学際的特徴を感じるものであった．また，わが国からは会員数の増加のみならず，優れた演題も徐々に増えつつあることに印象づけられた．

さらに旅行医学の対象には単に旅行者のみならず，海外派遣労働者も多く含まれてきており，近年はその派遣先が多様化し，労働環境に合わせた専門的なサポートが必要となってきている．今後は企業の産業医もこの分野の研究を担い，発展させていくことが望ましいと考えられる．

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Efficacy and safety of paromomycin for treating amebiasis in Japan

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ABSTRACT

The clinical management of amebiasis is a growing concern, particularly among human immunodeficiency virus (HIV)-infected individuals who are predisposed to severe illness. Treatment with a luminal amebicide is strongly recommended following acute-stage treatment with a nitroimidazole. In 2004, the Japanese Research Group on Chemotherapy of Tropical Diseases introduced paromomycin, which was not nationally licensed, and offered it to a number of patients. From 2004 to 2011, 143 case records of amebiasis (123 with amebic colitis, 16 with amebic liver abscess, and 4 with both) in which patients were treated with paromomycin, mainly 1500 mg/day for 9 or 10 days following metronidazole treatment, were submitted. Among 123 evaluable cases, 23 (18.7%) experienced possible adverse effects, the most common being diarrhea (17/123, 13.8%) and other gastrointestinal problems that were resolved after the completion or discontinuation of treatment. In addition, single cases of bloody stools associated with *Clostridium difficile* colitis, skin rash, and the elevation of liver enzymes were also reported, although the causal relationship was not clear. HIV infection did not appear to increase the incidence of adverse drug effects. Each of the 11 asymptomatic or mildly symptomatic amebic colitis cases became negative for stool cysts after paromomycin treatment. Paromomycin was shown to be safe and well tolerated, as well as effective in a special subset of amebic colitis cases.

1. Introduction

Amebiasis is a protozoan infection caused by *Entamoeba histolytica* that consists of two types, intestinal amebiasis (i.e., amebic colitis) and extraintestinal amebiasis, the latter including amebic liver abscess and rare manifestations such as pulmonary, cardiac, or brain involvement [1]. Both types can cause severe complications such as intestinal hemorrhage, ileus, intestinal perforation, or peritonitis in cases of amebic colitis, and rupture to the peritoneal, pleural, or pericardial cavity in cases of amebic liver abscess [2,3]. In developed countries, most amebiasis cases used to occur in travelers returning from developing countries [4,5]; however, recently, domestically infected cases among males who have sex with men (MSM) are increasing [6–8]. This is a concern given that MSM also constitute a risk group for human immunodeficiency virus (HIV) infection and amebiasis may develop into severe disease in HIV-infected individuals [9,10].

Currently, acute-stage treatment with a nitroimidazole (metronidazole or tinidazole) is followed by a luminal amebicide (paromomycin, diloxanide furoate, or iodoquinol), which is strongly recommended to eradicate the possibility of residual protozoan parasites [11,12]. This is because even after nitroimidazole treatment relieves acute symptoms and leads to negative stool tests for *E. histolytica*, a very small number of protozoa may survive in the intestine and can cause a relapse [1]. Luminal agents are poorly absorbed through the intestinal mucosa, thus attaining high intra-luminal drug concentrations. Apart from their use as anti-relapse therapy, luminal agents can be used as a monotherapy for treating asymptomatic (i.e., cyst passer) or mildly symptomatic amebic colitis [13].

The Japanese Research Group on Chemotherapy of Tropical Diseases, of which the authors are the principal members, imports nationally unlicensed medicines for tropical and parasitic diseases, and enables their use in patients in Japan when it is considered necessary and appropriate. This system is indispensable for the appropriate treatment of Japanese patients who contract exotic diseases against which there are only a limited number of nationally licensed medicines [14,15]. Previously, the research group had imported diloxanide furoate as a luminal agent and offered it to a number of patients with amebiasis. However, because diloxanide furoate became unavailable, the research group initiated the importation of paromomycin instead in 2004.

With the increased number of cases treated with this agent, we aimed to clarify the safety profile of paromomycin when used in Japan mainly as an anti-relapse amebicide, and also to evaluate its efficacy in asymptomatic or mildly symptomatic amebic colitis, although the

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cases might be few. These data have been obtained outside of Japan; however, the available Japanese data are very limited. Although this study was not a formal clinical trial, it could contribute to the delineation of how this agent could be utilized in Japan.

2. Patients and methods

2.1. The research group

The research group was established in 1980, and is currently funded by the Japanese Ministry of Health, Labour and Welfare. At present, the research group imports more than 15 nationally unlicensed medicines, among which 6 are antimalarial drugs. Imported drugs are stocked at the central storage facility, the Institute of Medical Science, University of Tokyo, Tokyo, and provided to 25 registered medical facilities upon request. Members of the registered medical facilities have obtained approval for participating in this program from the research ethics committee of each facility based on the approval obtained at the chief investigator's institution (M. Kimura, No. 09002). The drugs are used at those registered facilities after obtaining the patient's informed consent, which clearly states that the drugs are not licensed in Japan. In exceptional cases in which the patients cannot be referred to one of these medical facilities (e.g., due to severity of the disease), drugs are used outside the registered medical facilities on a humanitarian basis. Following treatments, physicians in charge fill in the patient records that were formulated by the research group and send them to us.

2.2. Treatments and analyses

Paromomycin in 250 mg capsules (Humatin®, manufactured by Parke-Davis, Germany) was purchased from the German pharmacy Paesel & Lorei. All of the moderately to severely symptomatic amebiasis cases were first treated with a nitroimidazole at the acute stage, followed by paromomycin for the prevention of relapse. The daily dose and duration of paromomycin administration were primarily determined by the physicians in charge, although in some cases advice was given from one of the authors.

Analysis was conducted using the patient records submitted by the physicians in charge. When necessary, direct contact with the physicians was made in order to gain more detailed information. Adverse effects (AEs) were evaluated by the physicians' descriptions, as well as by our own judgments on the laboratory data shown in the patient records. Cases that could not be followed up after treatment were excluded from the drug safety analysis.

2.3. Efficacy study

Asymptomatic or mildly symptomatic colitis cases were enrolled for the efficacy analysis if they seemed to be due to *E. histolytica*, but not due to *Entamoeba dispar*, which is morphologically undistinguishable from *E. histolytica* in the cyst form, but a non-pathogenic protozoan, and if they were treated with paromomycin, but no other amebicides, at least within 1 month. Specifically, cases were presumed to be amebic colitis if stool microscopy had previously shown typical features of *E. histolytica* trophozoites (e.g., ingestion of red blood cells), a colonoscopy had shown characteristic features with or without histology compatible with the disease, a stool had tested positive with a species-specific PCR, or serum antibodies had been raised [16]. Treatment success was defined mostly as the disappearance of cysts from the stool.

3. Results

3.1. Patients and treatments

From 2004 to 2011, 199 cases were treated with paromomycin, with 145 patient records being submitted and enrolled in this study.

Table 1
Characteristics of patients ($n = 145$).

Age[a]	Median: 45 (IQR: 37–57)		
Sex	Male	124	(85.5%)
	Female	19	(13.1%)
	Unknown	2	(1.4%)
Nationality	Japanese	141	(97.2%)
	Other	3	(2.1%)
	Unknown	1	(0.7%)
Illness	Amebic colitis alone	123	(84.8%)
	Amebic liver abscess alone	16	(11.0%)
	Both amebic colitis and liver abscess	4	(2.8%)
	Giardiasis	2	(1.4%)
HIV status	Reported to be positive	31	(21.4%)
	Not reported to be positive (i.e., negative or unknown)	114	(78.4%)

[a] Age was not reported in 2 cases. HIV, human immunodeficiency virus; IQR, inter-quartile range.

As shown in Table 1, the median age of the patients was 45 years, with 2 of them being under 20 years old (2 and 6 years old). The majority of patients were male, and most were of Japanese nationality. The majority were treated for amebic colitis alone, and a few received treatment for amebic liver abscess alone or for both diseases. Exceptionally, 2 cases were treated for giardiasis. Although the HIV status of the patients was not requested in the patient records, approximately 1 in 5 cases were reported to be HIV positive.

The majority (90/145, 62.1%) of patients were treated with a daily dose of 1500 mg for 8–10 days, 20 cases (20/145, 13.8%) with 1500 mg for 5–7 days, 4 cases (4/145, 2.8%) with 1500 mg for 1–4 days, 5 cases (5/145, 3.4%) with 1500 mg for unknown period, and 3 (3/145, 2.1%) cases with 750 mg for 3 days. In 11 cases, each received individually different combination of the daily dosage and the period (including cases treated for unknown period), and in the remaining 12 cases (12/145, 8.2%), daily dosages were not described. Among them, the 2-year-old child was treated with 360 mg/day for 10 days, and the 6-year-old child received 600 mg/day for an unknown period.

3.2. Safety of paromomycin

A total of 123 cases could be assessed for drug safety, among which 23 cases (23/123, 18.7%) were reported to have AEs (Table 2). Most of the reported AEs were gastrointestinal symptoms, mainly diarrhea (17/123, 13.8%), which were relieved after the completion or discontinuation of paromomycin administration (Table 3). Paromomycin was discontinued due to AEs in 7 cases (5.6%), including the 3 cases described below and another 4 diarrheal cases in which the diarrhea resolved soon after the discontinuation of the drug. No AEs were reported in either the 2- or 6-year-old child.

The first discontinued case involved a 51-year-old HIV-positive male with amebic liver abscess who first received metronidazole, followed by 1500 mg/day of paromomycin. On day 5 of drug administration, he developed diarrhea and bloody stools. His stools tested positive for *Clostridium difficile* toxin A and a colonofiberscopy revealed features of pseudomembranous colitis. However, the patient had received other antibiotics including cefepime, ciprofloxacin, clindamycin, aztreonam, and cefmetazole in 1 month before the onset of the symptoms, and the physician in charge suggested that the illness might be due to those antibiotics. He was lost to follow-up. Second, a 59-year-old male with amebic

Table 2
Reported presence or absence of adverse effects ($n = 123$).

Adverse effects	*n*	%
+	23	18.7
−	100	81.3

Evaluation could not be performed in 22 cases.

Table 3
Reported adverse effects ($n = 123$).

	n	%
Diarrhea	17	13.8
Nausea	2	1.6
Anorexia	1	0.8
Abdominal bloating	1	0.8
Excessive flatulence	1	0.8
Heartburn	1	0.8
Bloody stools (*Clostridium difficile* colitis)	1	0.8
Headache	1	0.8
Drowsiness	1	0.8
Skin rash	1	0.8
Elevation of liver enzymes	1	0.8

Evaluation could not be performed in 22 cases.

colitis first received metronidazole, followed by 1500 mg/day of paromomycin. Before paromomycin treatment, abnormal liver function levels of 62 IU/L γ-GTP and 2.7 mg/dL total bilirubin were noted; on day 5 of paromomycin treatment, AST, ALT, and LDH levels were found to be 88 IU/L, 115 IU/L, and 263 IU/L, respectively. Paromomycin was discontinued and the liver enzymes became normalized after 10 days. Lastly, a 47-year-old male with amebic colitis first received metronidazole, followed by 1500 mg/day of paromomycin. On day 2 of paromomycin treatment, he developed erythema and uriticaria on the trunk and limbs, and was treated with a single injection of glycyrrhizin, followed by oral betamethasone and *d*-chlorpheniramine for 3 days, after which the rash resolved.

Among the evaluable 22 cases with AE, the daily dosages were 1500 mg in 21 cases and 750 mg in one case, while among the evaluable 88 cases without any AE, they were 1500 mg in 80 cases, 750–1250 mg in 4 cases, and 1750–2250 mg in 4 cases. The median daily dosages were not significantly different between individuals with and without AE ($p = 0.56$, Mann–Whitney's *U*-test).

Among the 22 evaluable cases that were reported to be HIV positive, 4 (4/22, 18.2%) patients had AEs. Among the 101 evaluable cases that were not reported to be HIV positive (i.e., the HIV status was negative or unknown), 19 (19/101, 18.8%) had AEs.

3.3. Efficacy of paromomycin

A total of 11 asymptomatic or mildly symptomatic cases of amebic colitis were analyzed for the efficacy of paromomycin when given alone (Table 4). Most cases were treated with 1500 mg/day for 9–10 days, and parasite clearance was achieved in all cases. The 6-year-old boy was also found to be negative for cysts in the stool after paromomycin treatment.

Exceptionally, 2 patients with giardiasis received paromomycin, with one of them being evaluable. The patient had previously received metronidazole twice unsuccessfully (500 mg/day for 10 days and 2250 mg/day for 21 days), and was reported to be cured with 750 mg/day of paromomycin given for 5 days.

4. Discussion

Since 2009, the Japanese Ministry of Health, Labour and Welfare has been taking action to dissolve the so-called "drug lag," and data obtained from studies other than formal clinical trials have become useful in making a previously unlicensed medicine licensed in Japan. This move prompted us to analyze the safety (and if possible the efficacy) of paromomycin, in an effort to contribute to licensing the medicine in Japan where the clinical management of amebiasis is increasingly recognized as important. From the 1960s to 1982 and 1998, this agent was licensed in Japan as 2 different brands for treating certain cases of bacterial enterocolitis, respectively. In fact, it was used most frequently for treating tapeworm infestations and most reports supported the safety of paromomycin when used for this purpose [17–19], although this may not guarantee the safety of the drug when used for the treatment of amebiasis for longer periods. Thus, in a Japanese multicenter case series, 118 cases of fish tapeworm received 50 mg/kg paromomycin either as a single dose or divided into 2 doses 30 minutes apart [19]. Four patients reported a total of 5 AEs, i.e., nausea in 2 patients, anorexia in one patient, and transient/slight tinnitus plus speech disturbance appearing in one patient. These patients were given almost concomitantly magnesium sulfate as a laxative to facilitate purging the tapeworm, and therefore drug-induced diarrhea could not be assessed properly in this study.

The current study was not conducted as a formal clinical trial and is, therefore, subject to some limits in interpretation. First, the evaluation of AEs and of the effectiveness of the drug may have not been conducted uniformly by the physicians in charge. Second, post-treatment follow-up periods may have varied between cases; for example, foreign visitors to Japan may have been observed only for a short period of time prior to returning to their original country. However, it is also plausible that the physicians established close relationships with their patients due to the unique nature of this trial, resulting in most of the unusual events, such as delayed AEs, being reported even after the patient record was completed and submitted. Thus, despite these limitations, the data seem to contribute to the efficacy and safety evaluation of paromomycin in Japan.

Studies on the efficacy and safety of paromomycin were reported mostly in the 1960s, with almost all reports showing mild and acceptable symptoms. These older studies may have included *E. dispar* infections, and thus, may not be adequate for analyzing drug efficacy; however, drug safety could be assessed. In an Ethiopian study, 96 patients with amebiasis aged 1–75 years received paromomycin, mostly either 30, 15, or 7.5 mg/kg/day for 5 days. Diarrhea occurred on days 2–3 of treatment, but most cases improved on day 5 [20]. In the US, 79 patients with amebiasis or *Dientamoeba fragilis* received paromomycin, 1,750 mg/day for 2, 3, 4, or 5 days, or 4 doses of 1,000 mg each for one day. Totally, diarrhea

Table 4
Asymptomatic or mildly symptomatic amebic colitis cases treated with paromomycin.

Age	Sex	Evidence of *E. histolytica* infection	Treatment	Findings	
				Before treatment	After treatment
53	M	Trophozoites in stool	1500 mg/day, 10 days	Stool cyst (+)	Stool cyst (−)
49	M	Colonoscopy	1500 mg/day, 10 days	Stool cyst (+)	Stool cyst (−)
42	M	Colonoscopy	1500 mg/day, 10 days	Trophozoites in colonic mucosa	Stool trophozoite (−), cyst (−), improved histology
32	M	Colonoscopy	1500 mg/day, 10 days	Stool cyst (+)	Stool cyst (−)
37	F	Trophozoites in stool	1500 mg/day, 9 days	Stool cyst (+)	Stool cyst (−)
65	M	Colonoscopy	1500 mg/day, 10 days	Stool cyst (+)	Stool cyst (−)
47	M	Colonoscopy, serum antibodies	1500 mg/day, 10 days	Stool cyst (+)	Stool cyst (−)
61	F	Colonoscopy	1500 mg/day, 9 days	Stool cyst (+)	Stool cyst (−)
ND	M	Colonoscopy	1500 mg/day, 9 days	Stool cyst (+)	Stool cyst (−)
47	M	Trophozoites in stool	1500 mg/day, 9 days	Stool cyst (+)	Stool cyst (−)
6	M	Stool PCR	600 mg/day, for unknown period	Stool cyst (+)	Stool cyst (−)

ND, not described.

was noted in 13 cases (16.4%), nausea in 5 cases (6.3%), headache in 3 cases (3.8%), dizziness or abdominal cramps/bloating each in 2 cases (2.5%), and itching, urticaria, heartburn, or insomnia each in 1 case (1.3%), and except for a lower frequency in the one-day treatment arm, frequencies of the AEs did not correlate with duration of the treatments [21]. Another US study on 114 MSM patients with amebic colitis, receiving 25–35 mg/kg daily in 3 divided doses for 7 days, reported a high incidence of soft stools/diarrhea (67%), with most of the cases being mild, as well as nausea in 2 cases and constipation or dizziness each in 1 case [22]. The symptoms were reported to disappear after the completion of paromomycin treatment. A Kenyan study randomly allocated 417 amebic colitis patients aged 6–80 years to several treatment groups, including a paromomycin group in which adults and children received daily doses of 1,000 mg and 30 mg/kg, respectively, in 2 divided doses for 5 days [23]. The overall tolerability was reported to be excellent in the paromomycin group, with poor tolerability found only in 1% of cases.

Our data were largely consistent with previous reports in that most of the AEs consisted of mild gastrointestinal symptoms, and were mainly diarrhea that was resolved after completion or discontinuation of the agent. The case of *C. difficile* colitis might be due to the multiple antibiotics that had been given before paromomycin. The patient with liver function disturbance might have had an underlying liver disorder, and to our knowledge, there are no other reports on drug-induced hepatotoxicity with paromomycin. We found only 1 report on skin eruption, which was urticaria, and thus the dermatological AE does not seem to be unacceptable [21]. It is reassuring that HIV infection did not appear to increase the risk of drug-related AEs, although this issue was not formally addressed in this study.

The excellent efficacy of paromomycin monotherapy observed in our asymptomatic or mildly symptomatic cases deserves mentioning. This is consistent with the study results comparing paromomycin and diloxanide furoate given randomly to patients with PCR-confirmed asymptomatic *E. histolytica* infections in Vietnam (both 500 mg t.i.d. for 10 days) that showed the superiority of paromomycin over diloxanide furoate, with cure rates of 85% and 51%, respectively [24]. Most of our patients received paromomycin for preventing a relapse after successful acute-stage treatment; however, such efficacy of the agent could not be addressed in our study due to lack of the adequate control subjects. In addition, there have been no other reports with conclusive results on the relapse-preventing effect of the drug. A recent study of Japanese HIV-positive men with amebiasis showed that the recurrence rates of amebiasis were not different between those who took a luminal amebicide (paromomycin or diloxanide furoate) and those who did not [25]. However, this may be influenced by reinfections occurring more frequently among MSM. Apart from its use in the treatment of amebiasis, paromomycin has been suggested to be effective in patients with giardiasis or cryptosporidiosis that are refractory to the first-line treatment, as shown in the giardiasis case in this study [26,27].

Just recently, in December 2012, paromomycin was licensed for the treatment of amebiasis in Japan and is expected to be commercially available in mid-2013. As this licensing was decided without a formal clinical trial and based exclusively on the data shown here, we must remain vigilant as to whether a very rare, but potentially serious AE may occur with wider use of the agent. We will also attempt to determine its efficacy in protozoan diseases other than amebiasis in an effort to have it approved for the treatment of such diseases in the near future.

In conclusion, paromomycin was shown to be safe and well tolerated, as well as effective when used in the treatment of asymptomatic or mildly symptomatic amebic colitis in Japan. This agent was licensed just recently, and we will continue to further monitor its efficacy and safety.

Conflict of interest

T.M. is currently affiliated with ViiV Healthcare K.K., which was established by GlaxoSmithKline and Pfizer. Others have no potential conflicts of interest.

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References

[1] Haque R, Huston CD, Hughes M, Houpt E, Petri Jr WA. Amebiasis. The New England Journal of Medicine 2003;348:1565–73.
[2] Mandell GL, Bennett JE, Dolin R. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone/Elsevier; 2010.
[3] Longo DL, Harrison TR. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill; 2012.
[4] Freedman DO, Weld LH, Kozarsky PE, Fisk T, Robins R, von Sonnenburg F, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. The New England Journal of Medicine 2006;354:119–30.
[5] Taniguchi K, Yoshida M, Sunagawa T, Tada Y, Okabe N. Imported infectious diseases and surveillance in Japan. Travel Medicine and Infectious Disease 2008;6: 349–54.
[6] Takeuchi T, Okuzawa E, Nozaki T, Kobayashi S, Mizokami M, Minoshima N, et al. High seropositivity of Japanese homosexual men for amebic infection. Journal of Infectious Diseases 1989;159:808.
[7] Ohnishi K, Murata M, Okuzawa E. Symptomatic amebic colitis in a Japanese homosexual AIDS patient. Internal Medicine 1994;33:120–2.
[8] Nagata N, Shimbo T, Akiyama J, Nakashima R, Nishimura S, Yada T, et al. Risk factors for intestinal invasive amebiasis in Japan, 2003–2009. Emerging Infectious Diseases 2012;18:717–24.
[9] Ishioka H, Umezawa M, Hatakeyama S. Fulminant amebic colitis in an HIV-infected homosexual man. Internal Medicine 2011;50:2851–4.
[10] Ohnishi K, Uchiyama-Nakamura F. Metronidazole treatment for acute phase amoebic liver abscess in patients co-infected with HIV. International Journal of STD and AIDS 2012;23:e1–3.
[11] Gonzales ML, Dans LF, Martinez EG. Antiamoebic drugs for treating amoebic colitis. Cochrane Database of Systematic Reviews 2009:CD006085.
[12] World Health Organization. WHO model prescribing information: drugs used in parasitic diseases. 2nd ed. Geneva: World Health Organization; 1995.
[13] Stanley Jr SL. Amoebiasis. Lancet 2003;361:1025–34.
[14] 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. Journal of Infection and Chemotherapy 2006;12:277–82.

[15] Kimura M, Koga M, Kikuchi T, Miura T, Maruyama H. Efficacy and safety of atovaquone-proguanil in treating imported malaria in Japan: The second report from the research group. Parasitology International 2012;61:466–9.
[16] WHO. Amoebiasis. Weekly Epidemiological Record 1997;72:97–9.
[17] Kojima S, Uchikawa K, Kaji R, Takeuchi S. Diphyllobothriasis with special reference to treatment with paromomycin sulfate and bithionol [Article in Japanese]. Shinshu Igaku Zasshi 1982;30:461–6.
[18] Yazaki S, Takeuchi S, Maejima J, Fukumoto S, Kamo H, Sakaguchi Y. Efficacy of paromomycin sulfate in the elimination of *Diphyllobothrium* species and *Taenia saginata* in clinical cases [Article in Japanese]. The Japanese Journal of Antibiotics 1983;36:638–43.
[19] Hayashi S, Kamo H. Studies on the effect and the mode of action of paromomycin sulfate against tapeworm [Article in Japanese]. The Japanese Journal of Antibiotics 1983;36:552–65.
[20] Wagner ED. Paromomycin in the treatment of amebiasis in Ethiopia. Antibiotic Medicine & Clinical Therapy 1960;7:613–7.
[21] Simon M, Shookhoff HB, Terner H, Weingarten B, Parker JG. Paromomycin in the treatment of intestinal amebiasis; a short course of therapy. American Journal of Gastroenterology 1967;48:504–11.
[22] Sullam PM, Slutkin G, Gottlieb AB, Mills J. Paromomycin therapy of endemic amebiasis in homosexual men. Sexually Transmitted Diseases 1986;13:151–5.
[23] Pamba HO, Estambale BB, Chunge CN, Donno L. Comparative study of aminosidine, etophamide and nimorazole, alone or in combination, in the treatment of intestinal amoebiasis in Kenya. European Journal of Clinical Pharmacology 1990;39:353–7.
[24] Blessmann J, Tannich E. Treatment of asymptomatic intestinal *Entamoeba histolytica* infection. The New England Journal of Medicine 2002;347:1384.
[25] Watanabe K, Gatanaga H, Escueta-de Cadiz A, Tanuma J, Nozaki T, Oka S. Amebiasis in HIV-1-infected Japanese men: clinical features and response to therapy. PLoS Neglected Tropical Diseases 2011;5:e1318.
[26] Gardner TB, Hill DR. Treatment of giardiasis. Clinical Microbiology Reviews 2001;14:114–28.
[27] Danziger LH, Kanyok TP, Novak RM. Treatment of cryptosporidial diarrhea in an AIDS patient with paromomycin. The Annals of Pharmacotherapy 1993;27:1460–2.

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REVIEW

Prioritising immunisations for travel: International and Japanese perspectives

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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

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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

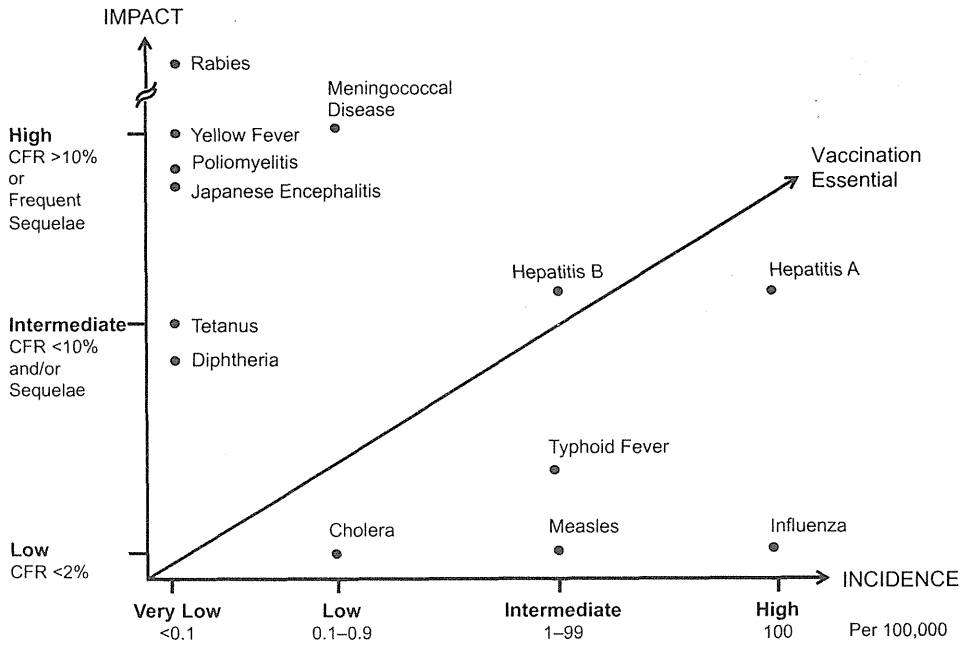

Fig. 1 Incidence and impact of vaccine-preventable diseases in travellers to developing countries. CFR = case fatality rate (reproduced with kind permission from Steffen et al. [3]). This figure differs from the original in that the incidence and impact of rabies acquisition in travellers rather than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