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as a reminder that although the term sepsis is a valuable clinical descriptor of a condition that almost every doctor will encounter, the catch-all nature of the term often conceals more than it reveals.

Determining the true incidence of sepsis and its underlying causes is important, not just to quantify the burden of disease and to ensure that adequate resources are provided to deal with it, but also because it informs priorities for clinical research. However, the use of registry data can have unexpected pitfalls.<sup>3</sup> Factors such as ascertainment artefact, subtle changes in definitions, better and earlier diagnosis, and even reimbursement considerations can falsely seem to increase incidence in a population.<sup>4</sup> Kaukonen and colleagues have published an analysis of trends in the incidence and mortality associated with sepsis in adults in Australia and New Zealand that carefully avoided these dangers.<sup>5</sup> They showed that, as for the data for children, incidence was rising but mortality was falling. But they also reported significant differences in outcome depending on age and presence of comorbidities. The overall crude hospital mortality in patients with comorbidities was 33% compared with just 5% in patients younger than 44 years of age without other underlying complications.

These data have important implications. Imagine planning a phase 3 trial of a new intervention for sepsis in which the primary endpoint was hospital mortality. The calculation of the number of patients to enrol would be based on the anticipated effect size of the intervention and the mortality rate in the placebo group. If the study population contained a subgroup with a much lower than expected mortality, the calculations would be wrong (mortality in the placebo group would be lower) and a true effect of the intervention might be missed (a type 2 error). This possibility has concerned many people studying sepsis. Furthermore, by using broad enrolment criteria, investigators might have included a very mixed

population, only some of whom might be responsive to the intervention, thereby lowering the signal-to-noise ratio to a point where potentially valuable treatments have not been identified.

This possibility is the reason why accurate information about the incidence and severity of sepsis, be it in children or adults, is so important. It is also why researchers should be careful in describing exactly which patients they are talking about and in interpreting data. Although sepsis is instantly recognisable (although sadly, not always as instantly as it should be), many investigators are increasingly uneasy about using it as the basis of clinical trials.<sup>6,7</sup> Schlapbach and colleagues have provided valuable data showing that sepsis in children remains a significant challenge, and discarding the term sepsis would not be wise. But paradoxically, meeting that challenge might mean that researchers no longer use sepsis as the starting point for clinical research in this difficult and frustrating field.

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## Reflections on travel-associated infections in Europe

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In *The Lancet Infectious Diseases*, Patricia Schlegelhauf and colleagues<sup>1</sup> analyse travel-associated morbidity in 32136 travellers presenting to European sites of the GeoSentinel Network with a post-travel illness over the period 2008–12. Knowledge about illness in travellers contributes to the understanding of disease

epidemiology in our interconnected world. In addition to their own ill health, travellers serve as sentinels of infectious diseases; moreover, they can also transmit and disseminate infections.<sup>2–4</sup> Travellers have shown these important roles in emerging infections such as SARS (severe acute respiratory syndrome), dengue

virus infection, chikungunya infection, and currently Ebola virus disease, and also in antibiotic resistance.<sup>3-6</sup> The GeoSentinel Surveillance Network, a collaboration between the International Society of Travel Medicine and the US Centers for Disease Control and Prevention, has described significant disease epidemiology in travellers, and has also identified emerging infections through travellers such as sarcocystis on Tioman Island and the ongoing dengue outbreak in Luanda, Angola, in 2013.<sup>7-10</sup>

The strength of the GeoSentinel data, including the EuroTravNet data analysed by Schlagenhauf and colleagues, is the large number of reported cases from different parts of the world. The weakness, however, is that they are mainly descriptive and variations in disease patterns over the years might be attributed to evolving travel patterns including changes in destinations and itineraries. Thus, shifts in disease trends should be interpreted with caution because they might simply be related to changing exposure. Moreover, some diseases (eg, dengue fever) also occur in countries not reporting to GeoSentinel, simply because they are not tourist destinations.

Even with these inherent shortcomings in the dataset, the findings that tuberculosis transmission within Europe remains a problem and that dengue transmission has occurred in Europe provide new and very valuable insights into the transmission dynamics of these infections. The analysis of subgroups is an additional strength of the study showing reduced rates of malaria, HIV, and hepatitis type A in travellers who received pre-travel advice.

The authors identified travel to sub-Saharan Africa and Asia to be significantly associated with acquisition of travel-related illnesses; data for immigration travel also showed increased acquisition in travellers from Africa.<sup>1</sup> Interestingly, the trends over time showed an increased proportionate morbidity of vector-borne diseases, particularly malaria and dengue, from 2008 to 2012. Further, the authors show the association between dengue virus and certain destinations and countries of origin, highlighting the popular destinations for various nationalities. Previous analysis of dengue from the GeoSentinel Network detected an increasing trend in travellers before national outbreak trends came to public recognition.<sup>11</sup> The detailed information provided by the authors might help national health authorities to formulate optimum advice for their travellers.

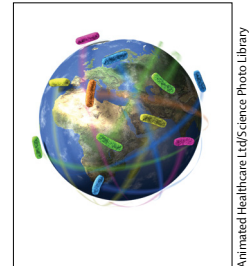
The patterns of disease shown by the European sites relate to global disease outbreaks—eg, the predominance of influenza H1N1 pandemic among respiratory infections in 2009.<sup>1,12</sup> Another relevant and timely example is chikungunya, which emerged in 2004 in the island countries in the Indian Ocean including Comoros and Reunion, and subsequently affected India, Sri Lanka, Maldives, southeast Asia, and more recently the Americas and Pacific islands.<sup>10</sup> The EuroTravNet data parallel such developments in the localities affected, again showing the utility of travellers as sentinels of emerging infections. Because chikungunya was first documented in the Caribbean in December, 2013, travellers with exposure in the Americas would not have been included in this report by Schlagenhauf and colleagues.

Importantly, the association of pre-travel consultation with significantly reduced proportionate morbidity for *Plasmodium falciparum*, HIV, and AIDS validates the goals of travel medicine practice. The finding that smaller proportions of travellers visiting friends or relatives obtained pre-travel advice compared with tourist travellers supports policies aimed at improving the provision of pre-travel interventions for travellers visiting friends or relatives.

Despite all its merits, a final challenge remains. That is, the analysis cannot derive actual risk of acquiring each travel-related infection in view of its method of sampling through a consortium of travel and tropical medicine centres, which lacks a denominator—that is, the population at risk. Nevertheless, this report on European travellers provides valuable information: an association of illness when travelling to sub-Saharan Africa and Asia; the potential of acquiring endemic infections even when travelling to other parts of Europe; an increased reporting of some vector-borne infections over time; the role of travellers as sentinels and disseminators of infections; and finally, the benefits of pre-travel health preparation. These findings contribute to the creation of targeted pre-travel advice for particular diseases, populations, and destinations.

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## HPV transmission in adolescent men who have sex with men



Corbis

Men who have sex with men (MSM) have a substantial burden of disease associated with human papillomavirus (HPV) infection, including anogenital warts, anal cancer, penile cancers, and oropharyngeal cancers.<sup>1</sup> However, the dynamics of HPV transmission in young MSM are poorly understood. Understanding of the natural history of HPV infection in men has become increasingly important for policy as more countries consider and adopt sex-neutral HPV vaccination programmes.

In *The Lancet Infectious Diseases*, Huachun Zou and colleagues<sup>2</sup> report high incidence of HPV infection in 200 Australian adolescent and young MSM aged 16–20 years (median age 19 years). Over the 1 year follow-up period, they detected 48 incident definite HPV infections in the anus and ten incident definite HPV infections on the penis. Definite incidence rate per 100 person-years for any anal HPV infection was 57 (95% CI 46–68), and 12 (6–21) for any penile HPV infection.

The authors estimated per partner transmission through comparison with data from a study by Goldstone and colleagues,<sup>3</sup> reporting higher probability from the penis to the anus than from the anus to the penis. The transmission estimates are the best we have for adolescent MSM and the best data for this population that we will have any time soon. The data reported are best seen as rough estimates, albeit very good ones, in view of the many differences between the two samples. It will be important as others cite and use these data to

keep some of their limitations in mind. First, estimates of partner incidence from Goldstone and colleagues<sup>3</sup> are of a somewhat older sample of MSM than those used by Zhou and colleagues.<sup>2</sup> Only half of the Zou and colleagues' sample reported older sexual partners. Furthermore, although the entire sample used by Zou and colleagues was from Australia,<sup>2</sup> only 15% of the Goldstone sample was from Australia,<sup>3</sup> and they had markedly lower prevalence of HPV infection compared with the rest of the study sample. Second, the transmission estimates do not account for penile to penile transfer of HPV, such as through frottage. Third, 4–6 years separate the collection of data in the two studies. These differences could bias estimates to be somewhat higher or lower than true rates. Despite these and other potential limitations that Zou and colleagues note, their data are novel and valuable.

HPV transmission estimates are useful for many reasons, including to increase the precision of HPV vaccine cost-effectiveness models.<sup>4,5</sup> Zou and colleagues' findings can inform policy decisions for the several countries that are debating routine provision of HPV vaccine to boys and men. HPV vaccination programmes that target young MSM are appealing because they have higher risk for HPV-related disease than do other young men and are thus especially likely to receive benefit from vaccination.<sup>6</sup> However, evidence suggests that risk-based vaccination strategies are not successful. For example, the USA abandoned risk-based vaccination when national efforts to give hepatitis B vaccine to MSM

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