

I'm going on a journey, and I'm taking with me...

Oration delivered by Prof.dr. L.G. Visser, when accepting the position of Professor of Infectious Diseases, in particular travel medicine at Leiden University on Friday, 4 September 2015

"Inscribis chartae, quod dicitur ABRACADABRA"

That's how Quintus Serenus Sammonicus, personal physician to the Emperor Caracalla, begins in his "Liber Medicinalis", the magical recipe that wards off malaria, known to the Greeks as the "tertian fever". The word "abracadabra" was written on a piece of parchment, and repeated on the next line omitting the last letter each time, until there was only one letter left. This parchment with triangular text became a talisman, worn around the neck, that protected the wearer from malaria.

Mr. Rector Magnificus, highly esteemed listeners, what would you take with you on a tropical journey? You may turn to your GP, local health authority or travel clinic for travel advice. That advice would generally consist of educative information, vaccinations and medication prescribed to prevent health problems during the trip, all based on the assessment of the risks that you might run by visiting your tropical destination. But how effective is that advice? Is it better than ABRACADABRA?

Perhaps it sounds a little strange for a freshly appointed professor to say this about his field; but I'm afraid that travel medicine finds itself in a crisis. And something has to be done about it. Travel medicine has to change if it wants to keep up with the changed world of the 21st century.

I'd like to discuss the necessary changes with you. I will give you a short overview of the technological developments and the change in medical thinking that have led to the separate field 'travel medicine'. Then I will highlight three dilemmas that the field has been wrestling with for some time. Finally, I will put forward the solutions which, in my opinion, are necessary to make travel medicine future-proof.

Human Mobility

The human race has covered a lot of technological ground since its first steps out of Africa 700,000 years ago. Before the industrial revolution there was no motorised transport. We made use of draught animals and wind power. The average speed of a horse was about 8 to 15 kilometers per hour; the speed of a ship not much more. Technical improvements in shipbuilding and the discovery of the trade-winds marked the beginning of the European expansion and colonisation in which the Netherlands also played an important role. The industrial revolution brought radical change to this. The technological advancements

followed quickly, one after the other. With the constant improvement in the yield of the steam engine and the switch from the use of coal to oil as fuel, the journey time of a ship from Liverpool to New York decreased from 29 days in 1820 to 4 days in 1930.

On 26th October 1958 a Pan American Boeing 707 completed her first transatlantic flight from New York to Paris in 8 hours. That was a turning point for the human race's mobility. With the application of the jet engine to commercial air travel, vast numbers of people are travelling huge distances; a first in human history. A numerical example to give you an impression of the scale: in 2014 the human race travelled a total of 5,561, 171,753,059 kilometers by air. That equates to 18,000 return flights to the Sun, enough for half a lightyear! With the world's ever growing population, the improving standard of living and the expected developments in aviation costs and connections the number of passengers is expected to increase from the current 3.3 billion to a staggering 7.3 billion in 2034. The biggest increase is expected to happen in China, the US, India, Indonesia and Brazil.

Travel medicine, a separate field

In 1958 tourism, or travel for relaxation, was still a fairly new social phenomenon and holiday destinations were usually either the coast, the mountains or the Mediterranean. Due to commercial aviation and economic developments, tourist destinations soon changed to more remote and exotic parts of the world.

Travellers who came back sick from their tropical journeys in those days were usually treated by doctors trained in tropical medicine. These doctors had come back to Europe during the decolonisation in the '60s and '70s. That explains why many of the oldest travel polyclinics or travel clinics are linked to Tropical Institutes like those of Antwerp, Basel, London or Amsterdam. This was also the case in Leiden. The vaccination polyclinic for travellers and the polyclinic for imported diseases originated within the Institute for Tropical Medicine Leiden, situated at the Rapenburg 33. Piet Stuver was the first professor of imported diseases appointed to the University of Leiden and Rotterdam (1982).

A lot of the travel advice given in that time rested on expert opinion. As is often the case, the opinions of experts in this field were very diverse. And so the need to bring some sort of ranking to the chance of accidents occurring and diseases being caught during travels became more and more apparent. The first examinations, done by Robert Steffen and others, date back to the '70s. In the arrivals lounges of airports, returning travellers were interviewed about their health problems during their travels. Symptoms of sickness that became apparent after the journey were announced by postcard. From this research it became apparent that heart and vascular disease and accidents were the most common causes of death whilst travelling, and that travellers' diarrhea was the most common infectious disease.

In the '50s chloroquine was the remedy for malaria. In 1957 chloroquine resistance was first signalled on the Thai- Cambodian border. From there the resistance spread across Asia and finally reach the east coast of Africa in 1978. Twelve years after that, the resistance had spread across all of the African tropics. Because of the ever growing resistance of the malaria parasite to chloroquine, chloroquine became increasingly less

appropriate as a universal preventative remedy, or chemoprophylacticum, against malaria. The substances like sulfadoxine/pyrimetamine and mefloquine, which were substituting chloroquine, could have bad side effects. The result was an ever growing need for expertise on the geographical diffusion of resistance to malaria and what the best preventative measures were. This growing need for specialisation in travel advice was also strengthened by a huge advance in travel vaccinations. The first international congress about travel medicine took place in Atlanta in 1988 and should be seen as the starting point for a new field, travel medicine.

So we can recognise two different periods in the history of the origin of travel medicine. A first period until the '70s, in which travel medicine was part of tropical medicine. A specialisation that dealt with specific diseases in the tropics and with specific sanitary measures to fight diseases in the tropics. And a second period from the '70s to the '90s in which, because of the increased complexity of the malaria prophylaxis and an abundance of travel vaccines, travel medicine became a separate specialisation.

Travel medicine focuses on the protection of the individual traveller, usually from Western high-income countries, against health problems during and after travel, usually to non-Western middle- or low-income countries. Travel advice takes a central role. On the grounds of an estimate of the risks a traveller runs at their travel destination, sanitary advice is formulated and vaccinations and medicine are prescribed to avoid the worsening of existing diseases and the emergence of new health problems. In the Netherlands this advice has been formulated nationally by the national coordination centre for travel advice (or in Dutch: het landelijk coördinatiecentrum voor reizigersadviesing, LCR for short) since 1995.

Pirates on the coast

Here are the dilemmas that a travel medic wrestles with:

- 1) we can't estimate the risks accurately
- 2) the effectiveness of the travel advice is indefinite
- 3) the eurocentric approach is not in keeping with the current era of globalisation.

Let's look at these individually.

Firstly, the answer to the question "How big is the risk?" is, at the very least, uncertain for many illnesses one might catch abroad. In the simplest form the risk is presented as a ratio, the numerator 'the number of travellers that became ill during their journey' denominated by "all the travellers that made the journey". An exact measurement of the numerator is difficult; the determination of the correct denominator often impossible. Let me explain this further with an example. Let's say you'd like to travel to India and so you ask yourself how big the chance is you could catch typhoid fever there. In the Netherlands typhoid fever is a notifiable disease so we are required by law to declare it to government authorities. We can use these declaration numbers to determine the numerator in our ratio. Inaccuracies in the numerator 'the number of typhoid fever cases from India' can occur if for example the country of origin wasn't reported in the declaration. From 2011-2013, 25 travellers with typhoid fever from India were reported. Only 16% of these travellers was a Dutch national. A quarter of the declarations didn't report a nationality at all. So how can we best

determine the denominator 'all Dutch travellers from India'? We should probably use the Indian registration numbers of travellers coming from the Netherlands to India, because the travellers with indirect flights from the Netherlands are also counted. From 2011- 2013, 219,100 travellers from the Netherlands to India were registered. We don't, however, know how many of these were Dutch nationals. So the chance of catching typhoid fever is 11 for every 100,000 people travelling from the Netherlands to India. The chance of a Dutch national travelling to India from the Netherlands is even smaller and not defined.

The second question is "What is effective travel advice"? The aim of travel advice is to educate, motivate and provide travellers with the knowledge and measures to react to health problems that may occur during their travels. In the Netherlands a usual travel consultation takes about 10 minutes and is focused on the determination of a traveller's risks and the counselling of a traveller with regards to preventative measures, vaccinations and malaria medicine they should take. Research on the effectiveness of this advice is limited. But in a Swedish study 12% of the examined people couldn't even remember having had a consultation. Especially younger travellers took more risks and were often the victims of traffic accidents and violence. Counsel that leads to changes in travellers' behaviour requires different communication skills which take into account the risk perception and attitudes of the traveller. So although the contents of the travel advice is clearly described, it currently lacks coordination with what the actual measurable end goals of a consultation are.

The third dilemma is more fundamental in character and regards the question whether and what role travel medicine should play in a time of rising globalisation. Currently travel medicine's main focus is the protection of individuals from mostly Western high-income countries. The question is how sustainable this eurocentric approach is.

Due to developments in communication and information technology, the increase in the freedom of trade and the availability of cheap labour, and especially due to the scale up of people and goods transportation, the process of globalisation has gone through an irreversible gear change. And so in 2034 the top six in the aviation market will be China, the USA, the UK, Japan, Brazil and Indonesia. The world has changed so that what happens in faraway parts is also of vital importance to the rest of the world population.

You probably know lots of examples. The most heartbreaking perhaps, is the recent stream of refugees from war zones in Syria to Europe. The lack of a common European vision and decisive dealing is a shameful example of denial and everyone- for-themselves mentality.

Reciprocal connection has big consequences for the spreading of infectious diseases, the field that houses this professorship. This is why I'd like to discuss two examples in more detail; the worldwide commotion around the recent Ebola epidemic in West Africa and the threat of untreatable infections through the spreading of multi-resistant microorganisms.

Firstly, the outbreak of Ebola in Guinea, Liberia and Sierra Leone. This outbreak is unique because of its scale and length, but it also illustrates the fragility of our global society. Like many suddenly surfacing infectious diseases, this outbreak also originated in human intervention, because of which pathogens that were dormant in the animal kingdom were suddenly able to cause infections in people. Research has found that the Zaire ebolavirus

had been circulating amongst fruit-eating bats in the jungles of Guinea since 2004. Because of population growth, large scale deforestation, the planting of fruit trees, and the hunting of bats for food, the chance of human infection increased. The consequent spreading of the disease in hospitals and villages went hand in hand with the deficient healthcare and extremely risky local burial rituals. Gueckedou, the city where the epidemic began, is a crossroads in an area of porous to non-existent national borders. In the space of a few months, displaced people fleeing civil war at home spread the disease to other big cities. Nigeria, which has 173 million inhabitants, managed to avoid a disaster in the nick of time when the outbreak came to a halt at only 20 cases. The epidemic has to this day claimed 27,988 victims and 11,299 lives and isn't over yet.

Analysis of the flight patterns and passenger numbers teaches us that 11% of the travellers leaving those three countries travel to destinations in low-income countries where healthcare may not be adequate for the committal of a new import case of ebola.

The increase in infections amongst the nursing staff in Spain and Texas also caused unrest and sometimes draconian measures in the West. Retrospectively it was found that the staff involved were inexperienced and made grave mistakes in their personal protection measures.

Extremely contagious infections can keep suddenly surfacing in the future. Hopefully the lessons learned with regards to the prevention of infection during this ebola epidemic won't be forgotten and every healthcare professional in the Netherlands will know to use the right personal protection measures with the next patient who has contracted an unknown infectious disease. The care of patients with suspected ebola demands extreme accuracy in the implementation of infection prevention measures. It is recommended that we centralise these patients in the Netherlands in two specific centres that have dedicated and well-practised personnel.

As a second example I'd like to mention the global spread of antibiotic resistance. Bacteria's increasing insusceptibility to antibiotics is one of the biggest threats to medicine. Especially the resistance of Gram-negative intestinal bacteria has been increasing recently. Bacteria exchange mobile genetic elements amongst each other, called plasmids, which contain the code for resistance against multiple antibiotics. In the arms race between man and bacteria, man is pulling the short straw. Resistance develops sometime after the introduction of every new class of antibiotics. Thus extended-spectrum beta- lactamases, or ESBL for short, break down third generation cephalosporins, and so only the carbapenems are left to combat an ESBL-producing bacterial infection.

In 2008 a patient in Sweden was found to have a new bacterial gene that coded carbapenem resistance. The patient had been transferred from a hospital in New Delhi and had been colonised with multiple intestinal bacteria that contained plasmids with the new resistance-gene New Delhi metallo-beta-lactamase-1, or NDM-1. The gene was found in *Escherichia coli* and *Klebsiella pneumoniae*, intestinal bacteria that can easily cause infection in humans. Not only were these intestinal bacteria insensitive to carbapenems, but also to almost every other type of antibiotic. Moreover, it appeared that the plasmids

with NDM-1 could be transferred effortlessly to unrelated bacteria, making the spreading of resistance extraordinarily easy.

From further research it appeared that the NDM-1 resistance gene had already widely spread amongst the Indian population in 2009. The overpopulation in the large cities, the poverty, the lack of safe drinking water and sanitary toilet facilities, the uncontrolled use of often multiple antibiotics simultaneously in healthcare and the bio-industry, the lack of microbiological diagnostics and infection prevention in hospitals and the lack of knowledge about antibiotics amongst doctors have created a serious health issue. The state of healthcare in India but also in other places far from there is in fact an enormous challenge. Until December 2012, literature mentions 895 patients in whom NDM-1 producing bacteria were isolated. Most of the patients were from India, Pakistan and China. Most of the imported cases were from the Indian subcontinent or the Balkans. By comparing the air traffic details from India with the published infections with NDM-1 producing bacteria, we can suppose that there are unreported infections in the Middle East, a destination that many travelling from India fly to. Most of the imported cases with NDM-1 are travellers who have been in contact with the Indian healthcare system, some being medical tourists who had undergone cosmetic surgery there.

But travellers who don't come into contact with the Indian healthcare system are also colonised with the multi-resistant intestinal bacteria during their travels. Research by Marguerite Bruijning, Sunita Paltansingh and Jessica Vlot at the vaccination polyclinic of the LUMC shows that 8% of healthy Dutch travellers were colonised with ESBL-producing bacteria before their departure, 30% of the travellers came back from their travels with newly acquired ESBL-producing bacteria.

With India as a travel destination the percentage was as high as 72.

Every doctor should carefully conduct a travel history with a patient with an infectious disease. Not only because the infection could have originated in another part of the world, but also because the patient could be colonised with multi-resistant microorganisms. Especially when patients have been in Asia in the last 6 months, the doctor should move quickly to deploy a culture in order to redirect the antibiotic treatment in time.

The future of travel medicine

I have outlined which insecurities plague the daily practise of travel medicine. We can't estimate the risks properly. The effectiveness of the travel advice is unknown. Above all, the worldview that travel medicine operates in doesn't correspond to current times. With this professorship I hope to find solutions that can make travel medicine more future-proof.

How can the first question, "How big is the risk?" be solved? A well-tried method is to select travellers from specific target groups. Then the nominator and denominator are already specified. With the information obtained future travellers from the same target group can be given better advice made to measure. Let me give you an example. Since 2006 in Leiden all medical students who chose to do an internship in the tropics are given an online questionnaire to fill in before and after their trip. From an initial analysis by Darius

Soonawala it became apparent that the counsel given did not correspond to the risks the students actually ran during their trip. It turned out that a third of the younger students who were doing their so-called "hands-behind-your-back" internship were in fact carrying out operations with a chance of needle stick injuries. From these findings the travel advice was adapted, the coordination between the different instances were adjusted to work together better and a checklist was created with health items that each student had to be checked for upon return.

Currently there's a second questionnaire in circulation with questions regarding culture shock, sexual health, the relationship between weight loss and the preventative malaria medicine's side effects, and the development of chronic stomach aches after the internship. Medical students from VU Amsterdam, Groningen, Leuven and Gent are also taking part in this study.

Furthermore, information and communication technology needs to be adapted to gain insight into risk behaviour and the materialisation of travellers' complaints. More and more people are in possession of and make use of a so-called smartphone. In 2015 82% of Dutch people owned such a device. By using the global positioning system (GPS) one can pinpoint a telephone's location to a ten-meter radius. It's possible to use this information to investigate the mobility of a population. This kind of research was done, for example, to investigate where adolescents loiter during the week. Location information of living and meeting places were linked to the location details of off-licenses to see which routes crossed the most. You can guess the result.

In the same way, we can gather the GPS-information of travellers to specify our numerator as 'all passengers that took the same travel route'. Besides, using small programmes known as applications or apps, it's possible to answer short questionnaires on smartphones and to communicate using messages. And so the denominator 'traveller with risky behaviour or complaints' can be measured in 'real time'. Recently the results of a preliminary study in which an app was used to measure the rate of respiratory infections in pilgrims going to Mecca were published.

Forty-one pilgrims from 12 different countries had downloaded the app. Twenty-five of them, or 61%, filled in all the daily questionnaires. The first respiratory complaints emerged on the 4th day of their stay in Mecca. One in 5 had complaints of a respiratory infection after the trip, of which one person was Australian and had had contact with dromedaries. This preliminary study shows that we can effectively use an app to gather important epidemiological information. Dromedaries can carry the Middle-East-Respiratory-Syndrome coronavirus (MERS-CoV), which can cause serious respiratory infections in humans. The developments in the realm of information and communication technology in medicine are very fast. This consumer e-health will undoubtedly also start to play an important role in travel medicine, not just in the form of targeted research but also for advice and perhaps even self-diagnosis and treatment. These new implementations also raise new questions like guaranteed property rights, the safety of data, the right to privacy and medical liability.

In that context, the Raad voor de Volksgezondheid en Zorg (or Council for Public Health and Care) presented the Public Health minister with an advisory report on consumers e-health in April 2015. In this report the Council makes a number of recommendations for the development of consumer e-health to be safe and usable for people and society. For example, by guaranteed access to the information with reliable authentication methods and the protection of the information through "privacy by design", with which the privacy standards are embedded into the design of the information system.

The second question is about the improvement of the effectiveness of travel advice. The foundations of an effective health care advice are known. The art is to apply this knowledge to the field of travel advice. We implicitly assume that attendees of a travel consultation intend to follow all the measures to avoid possible risks. It's important to realise, however, that people think differently about risks and that this influences their willingness to take actions to avoid these risks. And so travellers adapt the advice to their own understanding of health. On these grounds it's probably most effective if the informed traveller, after assessment of the pros and cons, can decide alongside their advisor on the basis of a shared decision making to adhere to the advice given or not. This requires a completely different way of working, because currently there is an unwritten rule that all the health risks have to be avoided.

Perhaps an example from the malaria prophylaxis can show us how things can be done differently. For 3 or more nights spent in destination X the LCR advises to take anti-malaria medicine to prevent malaria. Let's say that one gets stung by an infected mosquito once a week on average in that destination. The duration of the trip is 2 weeks. A traveller who prefers avoiding all risks opts to follow LCR's advice. Another traveller can choose to limit the chance of damage as much as possible should they catch malaria, in which case the choice of what's known as an emergency treatment is much more obvious. In the case of infection, if no doctor can be consulted, start with a treatment as if it's malaria. This nuanced way of advising is very different to the way we work now, and its effectiveness needs to be scientifically tested.

This is where, in my opinion, there is an important task for the LCR and the association for travel medicine professionals. I hope they will accept the challenge of determining the end goals of an effective travel advice and of investigating scientifically how the advice consultation can be tangibly renewed and improved.

The third question regards how travel medicine can contribute to everyone's health. So that there is not just attention to the traveller, but also to the health of the local population of the country the traveller is travelling to. Or, to quote David Shlim, past president of the International Society of Travel Medicine, "The ideal form of travel medicine is that kind that would make it unnecessary". How do we handle this?

I'd like to briefly discuss four different strategies.

In the first instance through education. I'd like to advocate the absorption of the principles of Global Health into travel advisors' curriculum. Global Health is an interdisciplinary health science that brings together individual and public healthcare and that focuses on the promotion of health for everyone. With this implemented knowledge the travel advisor is

better equipped to form an image of the development and health conditions of the population in a certain travel destination.

For that matter, Global Health should be covered in every modern medicine curriculum. For students who plan to do an internship in Second or Third World countries the obtaining of an education in Global Health is absolutely necessary.

In the second place, by actively contributing as a doctor to the surveillance of suddenly occurring or abnormal infectious diseases and where possible offering care to migrants and asylum seekers.

Doctors working in travel medicine and tropical medicine have united in organisations such as TropNet, GeoSentinel or Eurotravnet. Via the internet information is shared about abnormal syndromes or infectious diseases. This was how when visitors to the Tioman island increasingly complained of muscle ache and eosinophilia, an outbreak of muscular sarcocystosis, a parasitic muscle illness, was discovered.

Here too the information technology offers new unknown possibilities. In English literature there is talk of digital disease detection. With the help of search engines, it's possible to screen data files and social media looking for reports of infections in humans and animals. An example of such an initiative is Healthmap. Healthmap is an automated system that constantly collects information and filters out online news, witness reports, discussion fora and official reports to give an extensive view of signalled infections in people and animals on a world scale. With the app "Outbreaks near me" one can find all recent reports of infectious disease in your area. Another example is Bluedot. Bluedot analyses information about air traffic, passenger streams and the spreading of infectious diseases. With these analyses predictions can be made about where infections, like the flu, could spread through air travel. With this knowledge public healthcare measures can be implemented more efficiently.

In third place, by stimulated research that is also useful to the local population of the country people are travelling to. An example of this is an investigation of yellow fever or rabies vaccine. On travel medicine discussion fora, the most questions posed about these two vaccines. Yellow fever and rabies are so-called neglected tropical diseases, or forgotten disease that mainly affect the poorest in the world. At the vaccination policlinic research is being carried out to find out how, by using other vaccination schemes or an alternative means of administration, more people can be protected with less amount of vaccine. An example of an alternative means of administration is into the skin, also known as intradermal administration. Anna Roukens showed in her PhD research that the intradermal administration of a fifth of standard dose of the yellow fever vaccine gives the same amount of protection as the full dose using the usual means of administration, injecting into the fatty tissue just under the skin. So it is possible to treat five times as many people with the same amount of vaccine during times of shortage, such as during an epidemic, if the intradermal route is used. Emile Jonker is researching what the minimal basic vaccination scheme is to create a robust immunologic memory against rabies. It would appear that a reduced vaccination schedule with only one or two visits and one or two

injections, is sufficient. If these initial observations are confirmed, preventative rabies vaccination could be implemented on a much larger scale.

Finally, by putting pressure as an international organisation like the International Society of Travel Medicine on local councils to ban forms of exploitation in tourism and to support initiatives that improve the health of local populations.

The first steps are being carefully taken in this area. Thus in the most recent world congress the exploitation within volunteer tourism was denounced. But the ISTM could go further with this. For example, not by just recommending rabies vaccinations to people travelling to Bali, but also by supporting projects that eradicate rabies from all of Bali via mass vaccination of dogs.

Conclusion

My inaugural oration is coming to an end. I started my oration by supposing that travel medicine is in a crisis. A crisis is good. It forces change. That's why I'd like to end with my future vision of travel medicine in the 21st century.

In the future we will fly to the Sun more than 18,000 times a year. Whether that is ecologically responsible and how it could be done differently is perhaps a question for another professorship.

The traveller of the future will personally contribute to providing real-time information about risk behaviour and the development of complaints, through digital tracks left on the web. There is an urgent need for a scientific and ethical framework to ensure that this goes smoothly.

Travel advice will carry on existing. But I think that its current form has had its moment. Modern travel advice will take risk perception and the attitudes of the traveller into consideration and will come about through shared decision making. But also during travels, the traveller will stay in contact with their travel advisor through an app. There will be opportunities for self-diagnosis and self-treatment to be offered. It is important that a suitable system standard is developed for this.

Perhaps we will determine a recombinant travel vaccine for malaria. The first research results are encouraging, but there is still a long way to go.

Every modern educated doctor has knowledge of Global Health and infectious diseases with travellers. Scientific awareness also covers the so-called forgotten diseases or neglected tropical diseases.

And what do you think travellers will take with them for sure? Their mobile phone, the talisman of this century.