Travellers' Diarrhoea Vaccines – a good run for your money?

Dr. Nicholas Miller (Beremans Limited, Cambridge, UK) and Ingelise Saunders (ACE Biosciences AS, Odense, Denmark)

Overview

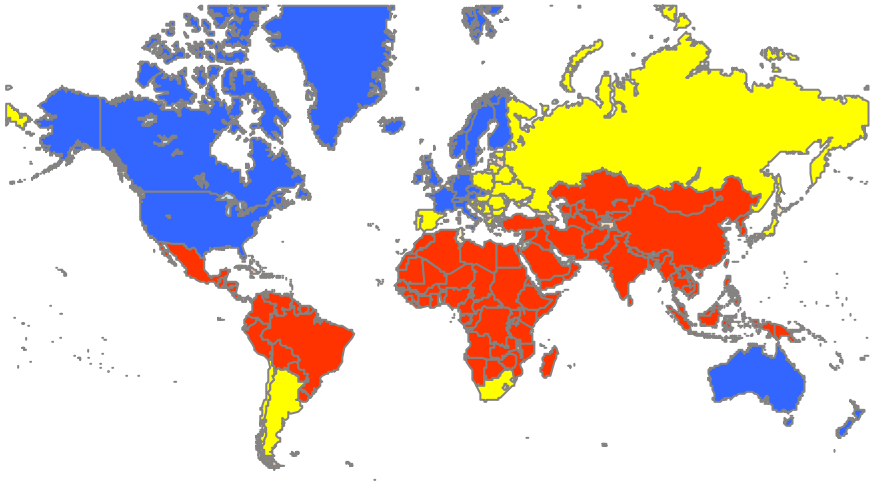
Travellers' Diarrhoea (TD) frequently occurs in individuals from industrialised countries when visiting destinations in developing countries. Consequences of TD include disruption of holiday and work capacity, and occasionally severe chronic disease. Existing methods of prevention are inadequate. We calculate that the number of travellers to TD risk regions was 88 million in 2003 and may reach 190 million per annum by 2020, suggesting that a significant potential market exists for a TD vaccine.

Travellers' Diarrhoea – running amuck

Travellers' Diarrhoea (TD) is usually defined as the passage of at least three unformed stools in 24 hours, together with one or more symptoms such as fever, vomiting, or abdominal pain [1; 2]. It may arise as a result of infection by any of more than 20 pathogens, and so should be thought of as a group of diseases. The most common causes of TD in adults are said to be enterotoxigenic *E. coli* (ETEC), *Shigella* and *Campylobacter*. However, there have been few studies to determine the relative significance of different TD pathogens in the developing world [3], at least partly due to the lack of diagnostic capabilities in these regions [4]. Current estimates on the relative importance of TD agents therefore must be treated with some caution.

Typically, TD occurs in individuals from industrialised countries when visiting destinations in non-industrialised countries. The incidence of TD among these travellers is often said to be 20-50% within two weeks of arrival [2; 5; 6; 7]; however, incidence rates may be far higher in some regions. Studies of TD incidence have been synthesised to provide a map which divides the world into three risk zones for travellers from industrialised countries [8; 9].

Figure 1: Relative risk of TD by country (redrawn from [9]).



High risk areas are shown in red; intermediate risk areas in yellow: and low risk areas in blue.

High risk TD destinations, with an incidence of 20-90% for a 2 week stay for travellers from the industrialised world, include most parts of Africa, Asia, the Middle East and Latin America, some islands in the Caribbean (notably the Dominican Republic and Haiti), and some remote destinations in Eastern Europe [10]. Intermediate risk destinations, ie with incidence rates of 8-20%, include South Africa, Israel, Japan, Argentina, Chile, some destinations in Southern Europe, and most destinations in the Caribbean [10]. Thus, TD is the most frequent health problem in travellers from industrialised countries visiting developing countries.

Consequences of TD – a protracted aftermath?

TD is usually thought of as a relatively mild, self-limited infection. However, among travellers to the developing world that contract TD, 30-45% may be obliged to modify their plans in some way. Some sources suggest that 1% of TD patients may be hospitalised, and that 20% are bedridden for at least one day [2; 11]. TD therefore may be associated with significant disruption of holidays and business trips.

However, TD may also have implications over and above inconvenience. In some cases, chronic complications may follow infection with TD pathogens. Thus, shigellosis and campylobacteriosis have been associated with the development of reactive arthritis, either alone or as part of a constellation of arthritis, conjunctivitis, and urethritis known as Reiter's syndrome [12]. It is said that a long term follow-up of a shigellosis outbreak on a US Navy cruiser found that of 10 sailors who developed Reiter's syndrome within 2 weeks of TD, 4/5 that were traced 14 years later were found to have chronic disease [13]. Myocarditis also has been associated with shigellosis and campylobacteriosis [14].

In addition, *Campylobacter jejuni* infection may give rise to acute pancreatitis [15; 16] and to one of the most serious TD-associated sequelae, namely Guillain-Barre syndrome (GBS). GBS is a peripheral nerve disorder characterised by paralysis [17], and may leave patients severely impaired. A variant of GBS, known as Fisher syndrome, also involves neurological dysfunction, such as cerebellar ataxia and motor axonal neuropathy. GBS is thought to develop in about 1/1000 infections [16].

Furthermore, TD remains one of the most common problems encountered by deployed military personnel [18; 19; 20]. The Soviet military in Afghanistan sustained significant TD incidence [21], and during the Iraq war of the 1990s, 57% of US troops reported diarrhoea, 20% being unable to perform duties for some time [18]. An even higher TD incidence was reported [18] among the 140,000 US military personnel more recently deployed in the Middle East. Thus, 76% reported at least one episode of diarrhoea, and >50% reported multiple episodes [18]. In 45% this resulted in decreased performance for a median of 3 days, and 17% required confinement to bed for a median of 2 days. In conclusion, TD is a threat to military efficiency, and development of enteric vaccines is said to be a priority for the US Army.

Therefore, the high frequency of TD among travellers, the capacity of TD to significantly disrupt work / travel plans, and the potential for development of serious chronic conditions, suggests that there is a need for effective products to prevent or treat TD.

Going for the flow – TD treatment

Travellers often are advised to carry TD treatments in case of need. Products may be divided into those intended to control the infection (mainly antibiotics) and those which treat TD symptoms (anti-diarrhoeal agents).

Anti-diarrhoeal agents include loperamide and bismuth subsalicylate. Loperamide acts primarily by inhibiting intestinal peristalsis, although it may also have anti-secretory properties. However, anti-motility agents have been associated with prolonged fever in cases of shigellosis, and probably should be avoided in cases of inflammatory diarrhoea [22]. Also, it has been suggested that loperamide treatment should not continue for more than 48 hours since necrotising colitis may occur [23].

Bismuth probably works by direct antimicrobial action, but may also have anti-secretory and anti-inflammatory properties [2]. However, bismuth is associated with side-effects, including blackening of the tongue [22], constipation, and tinnitus [24]. In any case, bismuth subsalicylate (Procter & Gamble) currently is not licensed in Europe, Australia or New Zealand [23; 25], although it is available in the USA.

Appropriate antibiotic therapy may reduce the course of TD from about 3 days to 1 day [2]. However, TD is caused by a variety of different pathogens, which have differing sensitivities to the various available antibiotics. Indeed, the usefulness of the current range of antibiotics is increasingly limited by the spread of resistance among enteric pathogens. For example, strains of *S. flexneri* and *S. sonnei*, which are the most common causes of shigellosis, developed resistance to tetracycline, chloramphenicol, streptomycin, ampicillin, kanamycin, and TMP-SMX less than 10 years after each was licensed for use in humans [12; 26; 27]. It is also said that increasing numbers of ETEC strains from India are resistant to nalidixic acid [1]. Fluoroquinolone resistance may be a particular problem with *Campylobacter* [7], especially in Southern Asia [22].

This has obvious implications for therapy. For example, according to WHO guidelines, all shigellosis cases should be treated with an antibiotic chosen according to the resistance profile of locally predominant *Shigella* strains. Unfortunately, the inability to determine the causative agent when the patient is first seen, let alone the precise strain of a given agent, necessitates a degree of trial and error in the treatment, and often results in administration of inappropriate antibiotics [22].

Furthermore, use of inappropriate antibiotics may have implications beyond treatment failure. For example, it may disrupt the normal intestinal flora; not all antimicrobials are universally safe (for example, in the pregnant, in the elderly or in children); some antimicrobials have the potential to select for pathogen virulence properties and to prolong the carrier state; and widespread antibiotic use will hasten the development of resistance. In conclusion, although antimicrobial therapy is the best available treatment, it is not always beneficial.

Giving pathogens the run-around – TD prevention

Obviously it would be preferable to prevent TD rather than to be obliged to treat it. Travellers often are advised that dietary precautions may reduce the risk of TD. Unfortunately, some evidence suggests that TD does not appear to be easily preventable by such behavioural modification. For example, travellers usually cannot know the extent to which good hygiene practises are followed at a given restaurant, and in many developing world environments contamination of food may be difficult to prevent. Since most travellers must depend on restaurants and similar sources for their food, there is considerable potential for infection, and indeed TD is frequently contracted even when standard advice of avoiding high risk items (for example, ice, water, and salads) is strictly followed [11; 29].

Other potential prophylactic approaches include probiotics, bismuth, prophylactic antibiotics and vaccines. However, at present, there is very little evidence to suggest that any probiotics can provide clinically significant levels of protection against TD worldwide [7; 11; 24], and the proposed mechanisms of action of probiotics are all substantially speculative at present. Bismuth subsalicylate may be an effective prophylactic for TD [25], and is sometimes prescribed in North America. Nevertheless, in view of the side-effect profile noted above, some sources suggest that bismuth should not be given prophylactically [2]. Similarly, the consensus view is that antibiotic prophylaxis should almost always be avoided, partly because of the potential for side-effects. Hence, the US CDC does not recommend antibiotic prophylaxis, even for high risk travellers [11].

A safe and effective vaccine against TD therefore would be a desirable option for many travellers. Unfortunately, despite significant effort in this field, there is as yet no marketed vaccine conferring broad protection against TD pathogens. The current feeling therefore seems to be that travellers should be informed that exposure to enteric pathogens probably is unavoidable in some destinations, and that disease may occur despite their best preventive measures [29].

Demand for a TD vaccine – a product that will run and run?

Given the difficulty in modifying the risk factors for travellers, and the lack of effective prophylactic measures, it is not surprising that there appears to have been no significant decrease in the global incidence of TD for many years [6]. For example, some sources suggest that there has been no change in the rates of TD in travellers to developing countries in 50 years [28], and that TD incidence in destinations in Kenya and India has not changed over a period of 20 years [30]. This is despite attempts by the tourist industry in many parts of the world to improve the local infrastructure [6], eg in terms of

water, sanitation and hygiene. This would suggest that there would be a market for an effective prophylactic measure, such as a vaccine.

Demand for a TD vaccine is likely to be driven mainly by the extent of travel from significant economies to destinations at risk of TD. Below, we attempt to quantify the travel from significant economies to destinations at high or intermediate risk of TD. In brief, the main aspects of our methodology are as follows.

1. 'Significant economies' were defined as France, Germany, Italy, Netherlands, Scandinavia (comprising Denmark, Finland, Sweden, Norway) Spain, UK, USA, Canada, Australia, Japan, China and South Korea.
2. Data were collected on international tourist arrivals from each significant economy, using mainly World Travel Organisation sources. Data were used from the five year period 1999-2003.
3. The above data were rearranged to calculate arrivals from each significant economy to countries at, respectively, high or intermediate risk of TD (as defined by the map presented in Figure 1). These data (1999-2003) were averaged to provide a baseline annual figure for market projections.
4. The figures for total reported arrivals (cf 3 above) were then revised downwards by the application of three factors.
    a. Factor A is based on an estimate of the number of countries visited per tourist per year. We could not find this information for every significant economy; where such information was not available, we used the average of the available figures from culturally similar countries. Factor A therefore attempts to correct for the double-counting of travellers (eg when one traveller visits more than one country) in the World Travel Organisation data.
    b. Factor B is based on an estimate of the immigrant effect. The assumption is that immigrant communities with an ethnic origin in the developing world, but living in developed countries, are less likely to perceive a need for, or indeed to actually require, a TD vaccine when visiting the country of their ethnic origin. For example, acquired immunity could be present in first generation immigrants or in those that have been visiting their country of origin on a regular basis. Therefore, a factor was applied to reduce the reported international arrivals from the main significant economies to regions of origin of the immigrant populations associated with the economy in question.
    c. Factor C is an estimate of the total effect of other inaccuracies in the data, eg the potential for inclusion of long-term expatriate residents (who are likely to have acquired TD immunity and therefore will not need a vaccine) in the World Travel Organisation data.

The effect of applying these factors is to provide an estimate of the actual numbers of travellers from significant economies who are (i) visiting areas at risk of TD, and (ii) likely to perceive the need for a vaccine. (This is not the same as estimating the numbers of travellers who will choose to receive a given TD vaccine, which will be affected by factors such as marketing effort, price of product and competition).

The above process provided figures which suggest that between 1999 and 2003, an average of about 40 million visitors per year travelled from the significant economies to regions of high risk of TD. Similarly, between 1999 and 2003, about 48 million visitors per year travelled from the significant economies to regions of intermediate risk of TD.

We then extrapolated the above figures to provide figures for 2004, using the World Travel Organisation estimates of 2004 growth in international arrivals. We then used this 2004 estimate as a baseline figure from which to forecast growth in numbers of 'at-risk' travellers (ie travellers from significant economies visiting regions at high or intermediate risk of TD) from 2005 to the year 2020, using World Travel Organisation predictions for growth in international arrivals by region. Our results are summarised in Figure 2, below.

Figure 2: Projected growth in numbers of travellers from significant industrialised economies to regions at high or intermediate risk of TD

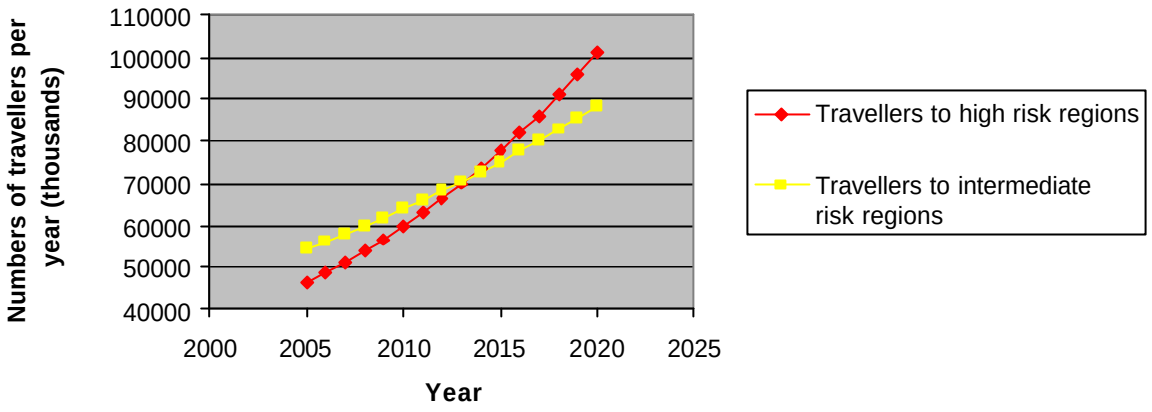


Figure 2 suggests that the number of travellers from significant economies visiting regions at high risk of TD would have been in the region of 45 million in 2005, and will reach 100 million travellers per year by 2020. Figure 2 also suggests that the number of travellers from the significant economies visiting regions at intermediate risk of TD would have been in the region of 55 million in 2005, and will approach 90 million travellers per year by 2020.

Travellers' Diarrhoea – the bottom line

Current travel patterns suggest that in 2020 there will be about 100 million susceptible individuals travelling from significant economies to regions at high risk of TD. Under current conditions, between 20 and 90% of these individuals would be expected to develop TD within 2 weeks of arrival. Similar numbers of individuals are likely to visit regions at intermediate risk of TD, and about 8-20% of these individuals would be expected to develop TD. The potential for TD to significantly disrupt business and holiday activities, and at worst to result in severe chronic disease, suggests that a broadly effective TD vaccine would be useful for at least a proportion of these travellers. Even low levels of product take-up would result in the purchase of millions of TD vaccine units per year. Therefore, the TD vaccine market may represent a significant commercial opportunity.

However, the precise extent to which a TD vaccine will penetrate the market is likely to be dependent on a number of factors. For example, since travel vaccines in general are not mandatory, vaccine uptake is likely to be the result of a complex interplay between a physician's willingness to recommend the vaccine and a traveller's willingness to purchase the vaccine. These in turn depend on criteria that may include the types of TD pathogens covered by the vaccine, the relative proportion of TD cases caused by these pathogens at a given destination, the price of the TD vaccine, the duration of protection provided by the TD vaccine, the effectiveness of the TD vaccine, the number and price of other desirable or mandatory travel vaccines, cultural attributes of travellers, perceptions of vaccines among travellers, and the administration route / regime of the TD vaccine. We have recently carried out original research in this field, including a survey of current attitudes among US and UK physicians [31]. This work has allowed us to estimate the likely market penetration of proposed TD vaccines, and shall be the subject of future articles.

Questions and comments should be directed to Dr. Nicholas Miller at nm01@beremans.com

Disclosure of interests

Nicholas Miller works for Beremans Limited (www.beremans.com), an analysis firm which provides due diligence, market research and independent analysis services in various Life Sciences fields, including the vaccines field.

Ingelise Saunders works for ACE Biosciences AS (www.acebiosciences.com), which is developing vaccine products, including TD vaccines.

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