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Upsurge of tick-borne encephalitis in the Baltic States at the time of political transition, independent of changes in public health practices

D. Šumilo[1], A. Bormane[2], V. Vasilenko[3], I. Golovljova[3], L. Asokliene[4,5], M. Žygutiene[4] and S. Randolph[1]

1) *NHS Coventry, Coventry, UK,* 2) *State Agency 'Public Health Agency', Riga, Latvia,* 3) *National Institute for Health Development, Tallinn, Estonia,* 4) *Centre for Communicable Diseases Prevention and Control, and* 5) *Ministry of Health of the Republic of Lithuania, Vilnius, Lithuania*

Abstract

Despite evidence that socio-economic factors associated with political transition played a major causal role in the abrupt upsurge in tick-borne encephalitis (TBE) in the newly independent Baltic States, doubts are still repeatedly expressed about the importance of these factors relative to changes in public health practices that may have affected merely the registration of cases. In response to these doubts, evidence of relevant practices of surveillance, registration, diagnosis, awareness and immunization is presented as taken from archived data and interviews with experienced medical practitioners. There were changes that could have had neutral, negative or positive impacts on recorded TBE incidence, but the variable timing in these changes at both national and regional levels is not consistent with their having been responsible for the epidemiological patterns observed in the early 1990s.

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Corresponding author and reprint requests: D. Šumilo, NHS Coventry, Coventry, UK
E-mail: dana.sumilo@green.oxon.org

Introduction

One of the first questions provoked by a major discontinuity in disease incidence is whether it reflects a real epidemiological shift or is merely an artefact due to changes in surveillance, registration and diagnosis pratices, and awareness, or in other aspects of data quality [1]. This is especially applicable to the abrupt upsurge of tick-borne encephalitis (TBE) in many central and eastern European countries in 1993, because it coincided with newly independent rule at the end of the Soviet era. At this time, the three Baltic States—Estonia, Latvia and Lithuania—suffered 69%, 182% and 1065% increases in incidence, respectively, and suddenly became the region in Europe most affected in terms of both TBE incidence and the absolute number of registered patients [2,3]. Despite evidence that socio-economic factors associated with the political transition played a major causal role in the upsurge of TBE [4], doubts are still repeatedly expressed about the importance of these factors relative to changes in public health care practices.

TBE is a zoonosis caused by three subtypes of a flavivirus transmitted by the ticks *Ixodes ricinus* and *Ixodes persulcatus* in many parts of central and eastern Europe, Scandinavia, Russia, and some parts of northern Asia. With no aetiologically specific treatment available, it is one of the most severe vector-borne infections of humans in endemic regions, commonly involving a long recovery process, neurological sequelae, and a decrease in quality of life, and it is fatal in *c.* 1% to >10% of cases, depending on the virus subtype [5,6]. Protection against infection relies on vaccines (inactivated purified virus), which are up to 99% effective [7], on avoidance of tick bite (e.g. the use of tick repellents, protective clothing and self-examination), or, currently only in Russia and Latvia, passive immunization with specific immunoglobulins within 72 h of a tick bite [6,8]. A change in any of these practices could also affect incidence.

The first registration of a TBE patient in the Baltic States was in Latvia in 1946, and this was followed by the first diagnoses in Estonia in 1950 and in Lithuania in 1953. Latvia was also the first to include TBE in the list of compulsorily notifiable diseases in 1955, followed by Estonia, and finally Lithuania in 1968, after only sporadic cases had been registered there during the 1950s and 1960s [9]. The USSR Ministry of Health in Moscow adopted general methodological principles for clinical and laboratory diagnostics, and for the surveillance, prevention and treatment of TBE from the 1950s, and

added TBE to its list of occupational diseases in 1970. Each Soviet Republic followed the same general rules, taking into account its particular epidemiological circumstances and developing its own subordinate plans and orders for TBE control and prevention [10].

The major political changes following the end of Soviet rule in the Baltic States affected public health practices alongside a nexus of other abiotic environmental and socio-economic factors that appear to be causally linked to the increase in TBE incidence [4,11]. The changes in reporting and diagnosis, and the development of awareness of TBE, that occurred during this time are described; their likely effect on the recorded number of TBE cases in Latvia, Lithuania and Estonia is assessed here.

Materials and Methods

Information was gathered from meetings during 2004 and 2005 with experts in Latvia, Lithuania and Estonia who had worked on different aspects of TBE (policy-making, surveillance, diagnosis, treatment and research) during both Soviet times and post-independence. Interviews were conducted with eight national public health policy-makers and chief specialists, and with 19 public health specialists, epidemiologists, general practitioners and specialists in infectious and neurological diseases at five regional Public Health Agencies (PHAs), and at other general practices and hospitals. Places in the regions were chosen to represent the full range of Baltic geography, TBE incidence levels, and changes in TBE patterns, as well as both primary vector species (*I. ricinus* and *I. persulcatus*) (Fig. 1). Only experts with extensive experience in the field of TBE were included in the study; 21 of the 27 experts interviewed had worked in the public health area for over 15 years, both during communist rule and post-independence. All the key experts in TBE surveillance at the national level were approached and agreed to participate.

A semistructured questionnaire was developed, focusing on each expert's specialty, to acquire information concerning the changes in the TBE surveillance system (including regulations concerning TBE surveillance and immunization policy), the changes in laboratory diagnostic methods and organization of TBE laboratory testing, and the changes in the dissemination of information about TBE in the local mass media. The interviewees were informed that the purpose of the questionnaire was to investigate the changes over time in public health practices relevant to TBE in the Baltic States as part of a larger project to examine the role of different biological and non-biological factors in the spatio-temporal changes of TBE incidence in Europe. The interviewees were asked to provide written documentation, when available, in the form of regulations, published and unpublished reports, archived materials, dissertations, and local publications, to support their claims. This documentation, however, is now extremely scarce, with only six public documents being found (four published articles cited below) and very little surviving historical documentation; hence the need for interviews. Information provided about the spatio-temporal differences in TBE incidence was checked against the national TBE databases.

FIG. 1. Places within Latvia, Estonia and Lithuania where meetings with experts took place. Capital cities are indicated by larger dots.

Results and Discussion

The factors considered, the changes over time and their likely contribution to the upsurge of TBE in 1993 are summarized in Table 1. Detailed information to support these summary statements is presented below.

TBE surveillance and reporting of cases

As the Soviet Union was particularly concerned about infectious diseases, many highly qualified epidemiologists and entomologists were employed in national and regional Sanitary Epidemiological Stations (SESs) (equivalent to the cur-

TABLE 1. Summary of changes in public health factors based on expert opinion, and their likely impact on the number of recorded tick-borne encephalitis (TBE) cases in the Baltic States as described in the text

Factor	Public health factor changes over time	Impact on upsurge in registered TBE cases
TBE surveillance	No	Most likely none
Reporting of TBE cases	No	Most likely none
Active surveillance	Undertaken in Latvia and Estonia during Soviet times	Most likely none
Diagnostic laboratory methods	From HAI to ELISA	Probably some positive
Organization of TBE laboratory testing	Decentralization, *c.* 2000 in Lithuania, 1999 in Estonia, 2000 in Latvia	Probably some mixed
Awareness of TBE among medical practitioners	Post-independence increase due to activities of professional medical organizations and vaccine distributors	Probably some positive
Awareness of TBE among the general public; active immunization and vaccination policies	Post-independence increase due to information in the mass media	Most likely some negative
Passive immunization	No statistics, but suspected post-independence increase in use of specific immunoglobulin after tick bite	Probably some negative

HAI, haemagglutination inhibition.

rent PHAs), which were responsible for the registers of infectious diseases, and provided a high standard of disease recording and investigation of each case (V. Nesaule, J. Turka, I. Vingre, personal communication). The principles of surveillance were consistent among regions, and have remained so through time (V. Vasilenko, unpublished data; J. Karaškēvica, B. Morkūnas, J. Turka, personal communication). The medical practitioner first sends an urgent notification of every suspected case of TBE to the local SES/PHA. The epidemiologist then investigates the case and registers the epidemiological protocol. Confirmation of the TBE diagnosis is based on serology (see below), together with epidemiological, clinical and sometimes also virological investigations. After laboratory confirmation, the final notification is sent to the SES/PHA (A. Bormane, V. Vasilenko, unpublished data; B. Morkūnas, personal communication).

With respect to active surveillance, in Latvia and Estonia blood donors and serum samples from healthy individuals were screened for TBE during Soviet times, but seropositive samples were not added to the number of registered TBE cases and thus did not affect the official statistics (V. Vasilenko, unpublished data; V. Nesaule, I. Vingre, personal communication). Thus, based on surveillance practices, the numbers of TBE cases should be comparable and reflect real differences among countries and time periods.

The consistent opinion of the Baltic experts was that, although there was a tendency to misreport the true morbidity of some infectious diseases in the Soviet Union, this was very unlikely to be true in the case of TBE (V. Vasilenko, unpublished data; J. Karaškēvica, B. Morkūnas, personal communication), as TBE was not considered a disease to be ashamed of, and the true incidence did not need to be hidden (L. Petruškina, J. Turka, N. Vološčuka, personal communication). This accords with a statement by the present Chief of the Laboratory of Vectors of Infections, Gameleya Institute for Epidemiology and Microbiology in Moscow (E. I. Korenberg, personal communication), who was himself one of the Russian inspectors of TBE epidemiology in the Baltic States.

TBE diagnosis

Serological testing for TBE started in the Baltic States during the 1970s, and was performed centrally in each state [12–14]. Until then, blood samples were usually tested at the USSR Institute of Poliomyelitis and Viral Encephalitis in Moscow. In addition to the standard haemagglutination inhibition test (HAI), the complement-binding reaction and the neutralization reaction were also recommended in diagnostically unclear cases [9]. A special committee was established in Latvia at the end of the 1970s to improve TBE diagnosis and to investigate all unclear cases of serous meningitis (V. Nesaule, I. Vingre, personal communication). The reported TBE incidence in Latvia was lower throughout the 1980s (1980–1989: mean, 6.17; SD, 1.66) than previously (1975–1979: mean, 11.85; SD, 2.15), although this was not necessarily due to more specific diagnosis and may be attributable to other factors. In Estonia, from 1976 to 1999, all unclear cases of meningitis serosa and all patients with unexplained fever who were hospitalized in Tallinn during the TBE season were investigated serologically for TBE. All positive results were registered as TBE cases (V. Vasilenko, I. Golovljova, unpublished data).

The HAI test is a TBE strain-specific reaction, but the need to treat serum samples with caoline as part of the procedure may have given false-negative results when immunoglobulin levels were low. Therefore, in Estonia, two methods (HAI and complement fixation tests) were always used. During the 1990s, HAI was gradually replaced by ELISA, as the latter method is more sensitive, specific and economical. Furthermore, the use of commercial ELISA kits allows better

standardization and yields more comparable results. This change might be expected to increase the number of TBE cases diagnosed (V. Vasilenko, unpublished data; A. Duks, V. Kilčiauskienė, B. Morkūnas, personal communication), not because of any inadequacy in the HAI method itself (which, although complex, was carried out by well-trained staff in the centralized laboratories), but because of the longer time and greater number of blood samples required for the HAI test than for the ELISA test (V. Vasilenko, unpublished observation; A. Laiškonis, personal communication). The former test required more attention from a doctor, and the stipulated four-fold increase in the titre of TBE antibodies caused some borderline cases, which the doctor had to resolve (A. Laiškonis, personal communication).

The changes in diagnostic methods and TBE epidemiology, however, were not synchronous at either the national or the county level. In Lithuania, the HAI test was still the only diagnostic method in use in 1993, when the number of blood samples sent for laboratory analysis, and the number of registered TBE cases, increased by an order of magnitude relative to the previous decade [15]. A further change was the decentralization of laboratory services from 2000 in Lithuania, 1999 in Estonia and 2000 in Latvia (V. Vasilenko, unpublished data; A. Duks, V. Kilčiauskienė, personal communication). This might have had either a positive impact on TBE diagnosis, with each laboratory being closer to the affected population, or a negative impact if some new workers initially lacked experience. Yet, among the 85 Baltic counties, across all three countries, 13 experienced the start of the abrupt upsurge in TBE incidence between 1990 and 1992, 43 in 1993 or 1994, and 19 between 1995 and 1998, whereas ten counties experienced no consistent change [11]. Furthermore, in each county, the ratio of the mean TBE incidence for five years post-increase to the mean for ten years pre-increase ranged from 2.5 to 74 in Estonia, from three to 34 in Latvia, and from eight to 706 in Lithuania, independently of the incidence prior to 1980 [11]. Neither new diagnostic methods nor decentralized laboratory services can account for this heterogeneous pattern of epidemiological changes.

TBE awareness and immunization

Latvia, and to some extent Estonia, were already considered to be endemic regions for TBE during Soviet times [14] (V. Nesaule, personal communication). Collaboration between Russian and Baltic scientists started earlier in Latvia and Estonia than in Lithuania, which was the last of the Baltic States to start surveillance and research on TBE and ticks, which it did particularly intensively during the 1980s (G. Regalienė, personal communication). Despite education to raise awareness of TBE among doctors in all three Baltic States during Soviet times (V. Vasilenko, unpublished observation; G. Regalienė, I. Vingre, personal communication), any lower level of awareness among medical practitioners in Lithuania might have led to some degree of underdiagnosis there [16]. Nevertheless, it seems improbable that the 25-fold increase in TBE case numbers registered in Lithuania during the period 1993–2002, as compared with the previous decade, was due entirely to underdiagnosis during Soviet times. Furthermore, neither the TBE incidence, nor the degree of upsurge, was consistently higher in the counties where doctors were believed to be particularly knowledgeable about TBE, e.g. in Tauragė and Kupiškis in Lithuania (G. Regalienė, personal communication) and Gulbene, Rezekne and Daugavpils in Latvia (V. Nesaule, personal communication).

Among the general population, patterns of TBE awareness and active immunization appear to be an effect, rather than a cause, of increased incidence. In the second half of the 1990s, information about TBE in the mass media increased in all three Baltic Republics, distributed both by public health specialists, because of increasing numbers of TBE cases, and by vaccine distributors (E. Brūvere, O. Ivanauskienė, A. Laiškonis, V. Nesaule, L. Sparāne, personal communication). Increased awareness of TBE among the general population, as well as among medical practitioners (L. Sparāne, personal communication), thus followed the upsurge in cases.

Official statistics show a marked increase in the initiation of vaccination from the mid-1990s, with the number of completed vaccination courses being most strongly correlated with TBE incidence 2 years earlier [17]. This is as expected, considering that people seek vaccination (including the 12-month vaccination regimen) at the start of each tick season (spring–autumn) in response to press releases about TBE cases during the previous season [7]. In Latvia, this was evidently reinforced by a campaign, started in 1998, to vaccinate children free of charge in some rural areas of high risk [18]. Further evidence of vaccination in response to the publicly perceived risk of TBE is the positive relationship between initiation of vaccination in each county during the period 2002–2005 and TBE incidence during the period 1993–1998 [17]. In many counties in Latvia, and to a lesser extent in Lithuania, however, TBE incidence decreased from 1999 onwards to a higher degree than can be accounted for by vaccination, but in proportion to prior incidence, suggesting a change in behaviour, i.e. avoidance of exposure to infected ticks [17]. Thus, empirically, it seems that increased awareness of TBE *per se* during the past decade is likely to have resulted in a decrease in incidence and would not explain the upsurge in 1993.

There is no indication that larger numbers of mild infections were correctly diagnosed as a result of increased awareness of TBE; from 1970 to 2004, *c.* 20–35% caused fevers, *c.* 60–70% caused meningitis, *c.* 5–12% caused encephalitis, and <2% were fatal, with no change in these figures over time [19].

Indeed, in a large (n = 1488) serological survey in 2000, 16.6% of the 36 Lithuanians with memory of viral meningoencephalitis, but no diagnosis of TBE, were seropositive for TBE virus [20]. This measure of absence of diagnosis of symptomatic infections, however, is much lower than the 70–95% of infections thought to remain asymptomatic in endemic areas in Russia (cited in [21], and the 97% estimated for the Baltic States (S. Randolph, unpublished data).

Awareness of the risk of TBE might, however, lead to a greater demand for passive immunization, which can be 98% efficacious if specific immunoglobulin is administered within 3 days post-bite [6]. This generally applies only to Latvia, where specific immunoglobulin is recommended after tick bite, and is available free of charge for children up to the age of 18 years. During Soviet times, passive immunization was administered only to occupational high-risk groups. No data have been routinely collected to estimate how many post-exposure injections with immunoglobulin have been administered in Latvia each year (A. Bormane, unpublished data), but higher numbers of post-exposure injections would have decreased rather than increased the number of clinical TBE cases reported in Latvia.

In conclusion, it is clear from the information reported here that, among the public health factors thought to have changed with the political transition of the early 1990s, only two, improved diagnostic methods and awareness among medical practitioners, are likely to have had a positive impact on the reporting of cases of TBE (Table 1). The timing of the change from HAI to ELISA (1993 in Latvia and Estonia, but 1994 in Lithuania), however, did not coincide consistently with the abrupt upsurges in case numbers, which occurred variably between 1990 and 1998 in each county of the Baltic Republics [11]. It is possible that in some counties where TBE was especially rare, medical personnel may have been newly alerted, but there were no delays in the reported upsurges consistent with low prior incidence [11]. Others who were highly experienced in the clinical diagnosis of TBE, including those in Bialystok, north-east- Poland, have reported being overwhelmed in 1993 by patients with identical symptoms and diagnoses (M. Kondrusik, personal communication). Other changes in public health practice (e.g. the cessation of active surveillance in Latvia) evidently had no effect or even decreased TBE incidence (e.g. by increasing awareness among the general public, and by making passive immunization for children freely available in Latvia).

Furthermore, the variable degrees of upsurge in TBE in eight central and eastern European countries are closely correlated with specific measures of post-independence socio-economic conditions [4]. This would be unlikely if the upsurges were merely artefacts of changing public health practices, unless the net impact of the latter were itself correlated with these socio-economic conditions. Although improvements in public health practices were among the reforms associated with political independence and may therefore have contributed decisively to the degree of increase in TBE incidence, all the evidence points to a real upsurge in all three Baltic Republics during the early 1990s.

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Transparency Declaration

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