Opinion

Threat of alveolar echinococcosis to public health – a challenge for Europe

Bruno Gottstein[1], Marija Stojkovic[2], Dominique A. Vuitton[3], Laurence Millon[3], Audrone Marcinkute[4], and Peter Deplazes[5]

1. Institute of Parasitology, University of Bern, Switzerland
2. University Hospital Heidelberg, Germany
3. WHO-Collaborating Centre on Prevention and Treatment of Human Echinococcosis and French National Reference Centre on Alveolar Echinococcosis, University of Franche-Comté and University Hospital, Besançon, France
4. University of Vilnius, Lithuania
5. Institute of Parasitology, University of Zürich, Switzerland

Corresponding author: Gottstein, B. (bruno.gottstein@vetsuisse.unibe.ch)

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Alveolar echinococcosis (AE) is a neglected 'malignant' parasitic disease. The European endemic area of *Echinococcus multilocularis* in foxes is larger than previously anticipated and there is new evidence that fox populations and *E. multilocularis* prevalences have increased in many areas, implicating an increased infection pressure with *E. multilocularis* eggs for intermediate and aberrant hosts, including humans. This may result in more human AE cases within the next decades. Current numbers of both immunocompetent and immunocompromised AE patients and anticipated future developments call for scaling up research to rapidly improve the development and respective implementation of prevention, early diagnosis and curative treatment of human AE.

Infection dynamics, disease burden and health economic considerations

Despite excellent public health systems, alveolar echinococcosis (AE), a zoonosis due to infection with the larval form of the fox tapeworm *E. multilocularis* [1] , is expanding in Europe (Figure 1) [2,3]. For many decades, *E. multilocularis* infection in definitive hosts (predominantly foxes) (Figure 1), and thus also AE, a silently progressing hepatic disorder in humans, was largely restricted to a defined region of Central Europe. Over the past two decades, intensive epidemiological research revealed significant expansion into Northern, Eastern and Western Europe (Figure 2). Emergence of *E. multilocularis* endemicity in fox populations has been confirmed in many European countries, including the Baltic States, Poland, Slovakia, Romania and Slovenia. Furthermore, countries previously documented to be free of *E. multilocularis* (e.g. the United Kingdom, Ireland, Malta, Norway, Finland) are taking great efforts to assess the risk of introducing *E. multilocularis* into their countries through imported dogs and wildlife animals [4]. Increased traffic of pet dogs and relocation of wildlife have already sporadically contributed to the spread of this zoonosis [5]. AE has even become a threat in primates of several European zoos [6,7] and breeding enclosures [8]. In Central Europe, expanding red fox populations and colonization of residential areas are a major factor for a significant increase of the infection risk [9-12]. With a time delay of 10-15 years, such changes in definitive host ecology can lead to an increase in the incidence of human AE cases as already documented in some areas [13-17]. Across the total population of endemic countries such as France, Germany, Austria and Switzerland, AE is considered as a rare disease with average incidences of 0.03 to 0.30/100,000 inhabitants/year. These numbers, however, do not reflect the situation of the actual population at risk; far higher incidences, from 4.7 to 8.1 cases per 100,000 inhabitants/years are observed in nested clusters of *E. multilocularis* infection in the same countries [15,15]. Several studies found a recent upward trend in incidence [13-16]: in Switzerland, for example, an average twofold increase of the annual incidence was reported between the periods 1993-2000 and 2001-2005 [13]. Observations in France and Austria revealed similar trends [14,16]. In some of the countries of Eastern-Central Europe, which were not considered to be endemic areas, a steady but limited increase in number of human cases has been observed [18,19], and in the Baltic countries, such as Lithuania, a tenfold increase of the AE-incidence was reported in 2009-

2012, and the incidence ranged from 0.03 in 1997-2002 to 0.5-0.77 in 2009-2012 per 100,000 inhabitants [20]. Such trends all over Europe may not only be due to the increase in infection potential but also other causes, e.g. to the growing number of patients under immunosuppressive therapy with a significantly higher risk of developing AE [21,22]. In the new endemic areas such as the Baltic region, awareness of the disease and improved diagnostics may have contributed to the increase of AE cases registered. Conversely, in historically endemic areas of Western-Central Europe, where ultrasound and CT-scans have been widely available since the end 1970s, no alterations in the severity of liver infections, or in the rate of radical surgery cases have been observed in the last decades in immunocompetent AE patients [13,23]. In France, asymptomatic cases were shown in the 1980s, as a result of the systematic use of ultrasound (19% of patients not diagnosed by mass screening were asymptomatic at the time of diagnosis in the 1983-1993 period compared with 9% in the 1972-1982 period) [24], and the ratio of symptomatic/asymptomatic cases, as shown from the systematic recording of cases in a dedicated registry, was stable [25,26]. These facts indicate that the increase of incidence in Western-Central Europe is not primarily based on an earlier diagnosis. One known parameter that accounts for an annual increase in AE cases includes those patients with immune suppression who were subsequently found with AE: earlier diagnosis in these patients could be partially due to better recognition of AE as these patients were already receiving medical attention because of their primary underlying disease (cancer, chronic inflammatory disorders), or because these patients also present faster progression of AE [22].

High environmental contamination pressure for intermediate hosts is also illustrated by the occurrence of AE in accidental/aberrant intermediate hosts that usually do not take part in the parasite cycle, such as dogs, pigs and primates [2,6,7,27].

Globally, AE causes an annual loss of approximately 660,000 disability-adjusted life years as determined in 2008 [28]. In terms of new cases, it may be estimated that Central, North and Southeastern Europe together might in the near future face close to 1,000 new cases per year, as extrapolated from data of the Central European highly endemic area[1]; these regions may not yet have reached a plateau, because of the geographical extension of fox infection, and in new endemic areas transmission rates will likely continue to increase for several years, as anticipated for the Netherlands [29]. As determined in 2008, the costs per AE patient in Europe yields a mean of € 110,000 [28]. This is due to the fact that too many patients continue to present at advanced disease stages, necessitating life-long chemotherapy, complex interventions (endoscopic, liver surgery), or, as a last resort, liver transplantation [24,26,28,30]. Prolonged survival of the population in general and of AE patients in particular may increase this cost in the

[1] The accumulated population size of all AE-affected countries (Figure 1) were derived from <http://en.wikipedia.org/wiki/List_of_European_countries_by_population> and yielded 290 million inhabitants. Extrapolation was based on Swiss data and is as follows: 28 new annual cases divided by 8 (Switzerland) and multiplied by 290 (Europe) = 1015.

future. If early detection and treatment options do not make progress beyond current practices, based on current Swiss and French estimations of cost per patient that will be reached by most of European countries in a near future, Europe could well face costs in the range of one (or more) billion(s) € [2] to care for the numbers of AE patients to be expected in 10-20 years.

Control problems

The very nature of the life cycle of AE, with predominantly wildlife as intermediate (rodents) and definitive (fox) hosts, precludes eradication. So far, long-term baiting of foxes with appropriate medication is the most effective tool to locally decrease the environmental contamination and prevalence in wild hosts (and consequently in dogs as well) in a significant, although temporary, way [31]. However, the implementation of this approach strongly depends on public attitude, available financial resources and priority setting of political decision-makers. The European Food and Safety Authority (EFSA) realized the urgency of the problem and launched a project (GP/EFSA/AHAW/2012/01) to meta-analyze present surveillance data on *E. multilocularis* infection in animals. From currently available published literature and EU reports, the situation is clearly different in the various European countries, depending on the kind of national regulations and funding [2,9,10,29,32-38]. Information on epidemiological changes in animal populations may help to predict the emergence of AE in humans, and to take appropriate measures. In addition, *E. multilocularis* reproduces very well in domestic dogs as definitive hosts, and based on the high dog population in Europe, even a low average prevalence estimate (i.e. 0.3% in Switzerland) [32] can significantly contribute to environmental contamination by eggs, and to infection risk for humans [31,39]. Furthermore, dogs with particular infection risk (free roaming and with access to rodents) can reach remarkably high prevalence of infection with *E. multilocularis* [40]. A monthly deworming scheme for domestic dogs with access to rodents [32] represents an effective measure to reduce the risk of infection in humans, provided that an appropriate drug such as praziquantel is used. The European Scientific Counsel on Companion Animal Parasites (ESCCAP) has started informational campaigns in Europe [41]. An appropriate surveillance scheme at the EU level is, however, absolutely necessary to set up similar standards in the various member states and associated countries: it may be noted that the 2010 EU surveillance report [37] does not always properly discriminate between *E. multilocularis* and *E. granulosus*, which precludes any precise knowledge of the respective epidemics in animals and of the incidence of the related –and notably different- diseases in humans. Several at-risk-countries that do not belong to the European Union have no legal obligation to declare their cases to the European Centre for Disease Control (ECDC) and EFSA [37,38]; for instance, the 2010 report [37] does not include data from Switzerland.

Clinical problems

[2] 1000 new AE cases per year (see footnote 1) = 10'000 new cases per 10 years multiplied by 110'000 € = 1'100'000'000 €.

Due to the malignant nature with infiltrative growth and metastatic spread characteristics of the metacestode tissue that clinically behaves like a tumour, AE can principally cause premature death in advanced stages, especially if remaining untreated or improperly treated. In Europe (and some other endemic regions), thanks to life-long administration of benzimidazoles in those patients who cannot benefit from radical surgical resection of the lesions, i.e. two third of patients, it has become a chronic disease, with far less threat to their life than 30 years ago but significant impairment of quality of life' [26,28,30,42,43]. Numerous types of complications do occur in these patients, including e.g. biliary obstruction with jaundice, septicemia due to repeated cholangitis and bacterial infection of necrotic cavities in the lesion, portal hypertension, chronic Budd-Chiari disease, among many others [24,26,42,44] Compared to cancers with similar incidence (http://www.rarecancerseurope.org), AE receives, from the clinical point of view, appallingly little attention. Currently, treatment options for AE are few. Surgery is reserved for early stage treatment when lesions can be completely resected with a safe margin of unaffected tissue and no distant metastases [44]. Advanced cases may be only saved by surgical ventures, such as major palliative surgery or liver transplantation, requiring appropriate infrastructures and surgical experiences [45] Drug treatment for all other cases has its own limitations. Only two closely related drugs (albendazole and mebendazole), which are not always available, can be used to treat AE and significantly contributed, in the last decades, to a relevantly longer survival of AE patients as compared to the situation prior to drug treatment [23,24,28,44]. Nevertheless, they rarely kill *E. multilocularis* and thus life-long treatment is required to inhibit or at least suppress parasite growth in AE patients who could not benefit from radical surgery [44]. Some patients do not tolerate these compounds because of hepato- and/or hemato-toxicity [44,46]. Studies to precisely assess the proportion of patients who cannot be treated by the drug because of adverse effects are in need. This proportion seems to be higher in patients suffering immune suppression due to a pre-existing condition and associated treatments [22]. In addition, these drugs cannot be used during pregnancy, with a risk of even faster progression of AE in pregnant patients [47]. The increased incidence of AE in young adults in recent years has made the management of the disease in women of childbearing age problematic.

Present challenges and future perspectives

The anticipated increase in number of human AE cases in Europe within the next decades call for scaling up research in key areas such as prevention, early diagnosis and curative treatment of human AE, among others.

Management of clinical AE cases

The cancer-like growth behavior of *E. multilocularis* larvae has been stressed, which requires staging and stage-based multidisciplinary clinical management of AE, as it is now for cancer [48]. In cancer care management, tremendous progress has been made through centre-based

care, in particular in rarer forms of malignancies. Shared experiences between oncologists and AE-specialists can effectively be translated into clinical decision-making. In particular, various imaging modalities to improve AE diagnosis and staging, radical surgery to achieve cure also in advanced disease, as recently proposed but not evaluated [45,49], psychosocial programs and long-term care bear potential for cross fertilization from cancer to AE.

Based on the long-term clinical experience of Swiss, French and German clinical AE centers, standardized AE diagnosis and treatment protocols can be developed, validated and disseminated. Networking with reference centers in AE-endemic countries including Baltic and Central-Eastern European countries is essential to meet the threat of increasing numbers of AE patients and to achieve commonly agreed standards. Specific immunological tests (such as e.g. Em18 and Em2-ELISAs, and Immunoblotting; reviewed in [44]) in combination with high-performance imaging techniques promise substantial improvements in early diagnosis, essential for curative treatment, as well as in staging and follow-up of patients. Furthermore, standardized registration and follow-up protocols are essential to properly assess the epidemiology of the disease and its trends in all European countries, and to prepare the ground for multi-centric clinical trials to formally test new treatment options. So far, a population-based publicly-funded registry, designed on the model of the Cancer Registries, only exists in France with a satisfactory level of exhaustivity [15,26,50]. Mandatory notification, at least as it is organized in Germany, has proved to be inefficient [51]; academic reports have stressed that many published AE cases were not recorded by the national notification system [9]. An extended patient registry at the full European level would not only significantly contribute to improve the clinical management of AE, but also to better delineating areas and populations at risk to test new prevention strategies, and in promoting disease awareness in these populations [10,39] [15,52] .

Chemotherapy of AE cases: a huge place for improvement

Chemotherapy currently relies on albendazole and mebendazole, but there is clearly a need for improvement. The availability of the *E. multilocularis* genome sequence and comprehensive gene expression data [53], as well as significant progress in molecular biology, have now opened the door for a more targeted drug discovery approach, which allows exploitation of defined pathways and enzymes that are essential for the parasite [53,54]. Better management of the currently available drugs, with the definition of markers that would allow physicians to stop treating when the metacestode has actually aborted, might also possibly reduce the duration and thus individual burden and collective cost of treatment by several years in selected patients [30,55,56].

Immunological tools to prevent or treat AE in humans

There is strong evidence for the potential to induce protective immunity against primary infection with E. multilocularis [57]. As a rough estimate, only 1-10% of exposed/infected persons will develop disease, while others eliminate the infection due to innate and/or acquired

immunity [40,57,58]. This holds promise for an immunization-based prevention or immunotherapy of AE.

On the prevention side, vaccine development has a good potential, since it can be assumed that most resistant persons eliminate infection at the early oncospheral stage, and some at the early metacestode stage [40]. Large-scale animal experiments in sheep have already demonstrated the excellent efficacy of vaccination of sheep against E. granulosus infection using the recombinant antigen EG95 [59]. The same antigen from *E. multilocularis* is effective in mice [60], and experimental vaccination studies with defined recombinant proteins such as 14-3-3 protect against primary (egg) *E. multilocularis* infection at an even higher degree [61]. This 14-3-3-vaccine has already been applied in a preliminary explorative study in macaques [27]. Therefore, an anti-AE-vaccine to be applied in humans at risk of infection may become realistic not only from the scientific point of view, but also in terms of economic considerations. Examples of other vaccines developed against rather rare but severe and geographically restricted diseases, such as tick-borne encephalitis in endemic regions in Europe, support this approach [62].

On the treatment side, immunotherapy, i.e. modulating the AE-patient's immune response, could be an attractive treatment option. For this, tracing the efficient immune pathways of infection-resistant persons, and those in immunosuppressed and susceptible patients is required. Specifically selected candidate-immunomodulating agents such as those tackled by Bardonnet et al. [30] should be evaluated for their clinical application.

Concluding remarks

The currently observed trends of *E. multilocularis* infection in the European fox and dog populations and the expected increase of annual case numbers of human AE in many areas of Europe strongly advocate for scaling up research that can improve the fields necessary to yield better management of this infectious health problem in Europe (Box 1):

- prevention has to be tackled at two specific levels: (a) decreasing or abrogating infection intensity and extensity in definitive hosts (foxes and dogs) and (b) preventing humans from contacting *E. multilocularis* eggs (via contaminated food/water or physical contact with contaminated surfaces such as e.g. fox and dog fur). Emphasis should be given to (a), as efficient control at this level automatically renders (b) redundant.

- as long as prevention, as outlined above, cannot be optimally implemented, society has to face the fact that new clinical cases of AE will occur. Prognosis of AE can be considerably improved when an early diagnosis and a respectively appropriate treatment option can be offered.

- alternatively, if people e.g. at high exposition risk could be vaccinated against AE, such an approach might represent an attractive option especially for areas with high infection risk.

From the medical point of view, the focus on developing improved therapeutic tools and strategies appears as a key requirement, as this is often the only option for handling AE cases. Nevertheless, other steps should be developed and implemented to rather prevent the disease from occurring. Thus, a sustainable way to handle the problem of AE clearly requires an integrated (One-Health) solution. This includes prevention through information campaigns and education on how to deal with potentially egg-contaminated food (e.g. outdoor-grown vegetables or berries) as well as with potentially infected pets, and finally personal hygiene for categories at risk (immune-compromised patients, professionals or people spending a lot of time outdoor). Surveillance on wild definitive hosts is another element of prevention: monitoring the existence of hyper-endemicity areas would allow small scale cost-effective campaigns to reduce the local risk. Finally, it would be interesting to be able to type the haplotype and genotypes of human infections, and to compare them with the genotype distribution in the sylvatic cycles. This would help tracking the route of infections and better focusing prevention campaigns.

Box 1 Suggested areas of research to be further developed

(i) Design of a systematic, specific, and standardized surveillance of AE in humans and *E. multilocularis* infection in animals, to base all further actions on sound epidemiological data.

(ii) Improve the management of *E. multilocularis* infection in definitive hosts (wildlife and domestic domain).

(iii) Promote earlier diagnosis through improved imaging, immunological and molecular tools.

(iv) Promote accurate treatment assessment and prognostically improved follow-up of AE patients through improved laboratory and imaging tools, center-based multidisciplinary care management of AE patients, exploiting experience and approaches developed for cancer, including psychosocial care, standardized data collection and multicenter clinical trials.

(v) Development of new therapeutic tools for AE patients through identification and development of parasitocidal drugs, immunomodulatory interventions and radical curative surgery.

(vi) Acquire an novel prevention option for AE in humans through the development of a infection- or disease-protecting vaccine and be developing a risk group- or area-targeted vaccination strategy.

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Figure 1. Life cycle of *Echinococcus multilocularis*. Main definitive host in wildlife is the fox, and, more recently, in certain areas, the raccoon dog; domestic dogs are also highly susceptible. Small intestinal parasite load can reach several ten thousands of adult stage worms. Definitive hosts fecally shed *E. multilocularis* eggs after a prepatency of at least 28 days. Peroral ingestion of parasite eggs leads to infection in intermediate hosts (mainly small mammals/rodents), where the larval stage (metacestode) develops in the liver by formation of a tumour-like tissue, which consists of a conglomerate of small parasite vesicles. Within fluid-filles vesicles, protoscolices are formed, which will develop into adult stage worms in the intestine of definitive hosts, following ingestion of infectious rodents by these.
A: Adult stage fox tapeworm with skolex (head) and proglottids; on the right hand, top view on a fox intestinal mucosa with plenty of worms.
B: *E. multilocularis* egg, infectious for intermediate hosts, such as to yield for the development of a metacestode tissue in the host liver (indicated by an arrow in the CT picture of a human AE patient)
C: Protoscoleces, developing in a mature metacestode tissue, represented by the liver lesions in intermediate hosts.

Figure 2. Approximate distribution of *E. multilocularis* in red foxes in Europe. A: Known distribution in central Europe, status end of 1997 [63]; B: 2015 update: basically according to Eckert et al. [1] and actualised with information for France by Combes et al. [9]; for Scandinavia by Wahlström et al. [34], and for the Eastern Baltic region by Marcinkutė et al. [20]