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Assessment of the human medical significance of the rabies zoonosis in Germany – analysis of available data and desiderata

Abschätzung der humanmedizinischen Bedeutung der Zoonose Tollwut in Deutschland – Analyse der verfügbaren Daten und Desiderate

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Summary

In order to assess the human medical significance of the rabies zoonosis in Germany, the data of the relevant surveillance and of the registration systems as well as prescriptions submitted to the statutory health insurance (SHI) were assessed. In all, 2441 of the 81 280 total examinations for rabies conducted on animals were performed subsequent to contact with humans. In this context 54% of exposures were attributed to wild animals and 46%, to domestic animals. In 2006 and 2007 there were still 0.42 and 0.34 veterinary medical analyses per 100 000 inhabitants, respectively, subsequent to human contact. After the proclamation that Germany was free of terrestrial rabies, these indices dropped to 0.2 in 2009 and 2010. During the survey period, 21 700 doses of rabies vaccine were issued annually for SHI prescriptions on average; they would have been adequate for approximately 7230 complete courses of rabies pre-exposure prophylaxis or 4340 complete post-exposure treatments. For which of these two principal indications the vaccines were actually used cannot be determined from the SHI prescriptions. Taken together, the officially available data from rabies surveillance or registration systems even in combination with a nearly complete record of SHI prescription numbers did not allow an even nearly adequate reconstruction of the human medical significance of the rabies zoonosis in Germany. If one desired to achieve this, one would have to use, for example, an approach that is known from other European countries such as France, Finland, or the Netherlands.

Keywords: surveillance, rabies diagnosis, exposures to rabies, rabies prophylaxis, statutory health insurance

Zusammenfassung

Um die humanmedizinische Bedeutung der Zoonose Tollwut in Deutschland abzuschätzen, wurden für die Jahre 2006–2010 Daten der einschlägigen „Surveillance" und des Meldewesens sowie die in der gesetzlichen Krankenversicherung eingelösten Rezepte ausgewertet. 2441 der insgesamt 81 280 an Tieren durchgeführten Untersuchungen auf eine Rabiesinfektion gingen Personenkontakte voraus, wobei 54 % der Expositionen auf Wild- und 46 % auf Haustiere zurückzuführen waren. Entfielen in den Jahren 2006 und 2007 noch 0,42 und 0,34 veterinärmedizinische Analysen nach Personenkontakt auf 100 000 Einwohner, so reduzierten sich diese Kennzahlen nach der Proklamation Deutschlands als frei von terrestrischer Tollwut auf jeweils 0,2 in 2009 bzw. 2010. Im Erhebungszeitraum wurden jährlich durchschnittlich 21 700 Dosen Tollwutimpfstoff auf „Kassenrezept" bezogen, die ausgereicht hätten, um etwa 7230 vollständige Tollwut-Prä- oder 4340 komplette Post-Expositions-Prophylaxen vorzunehmen. Für welche dieser beiden prinzipiellen Indikationen die Vakzinen faktisch verwandt wurden, war den eingelösten GKV-Verordnungen ebenso wenig zu entnehmen, wie beispiels-

weise der Ort einer erlittenen Exposition (Inland bzw. Tollwutendemiegebiet) oder Angaben darüber, ob die Impfserie abgeschlossen werden konnte oder aber unvollständig blieb. Insgesamt erlaubten so die aus der Tollwut-„Surveillance" sowie dem -Meldewesen offiziell verfügbaren Daten selbst in Kombination mit einer fast vollständigen Erfassung von „GKV-Verordnungszahlen" keine auch nur annähernd adäquate Rekonstruktion der humanmedizinischen Bedeutung der Zoonose Tollwut in Deutschland. Wollte man diese erreichen, so müsste man sich beispielsweise eines Vorgehens bedienen, das aus anderen europäischen Ländern wie Frankreich, Finnland oder den Niederlanden bekannt ist.

Schlüsselwörter: Surveillance, Rabies-Diagnostik, Rabies-Expositionen, Rabies-Prophylaxe, gesetzliche Krankenversicherung

Introduction

The rabies virus and rabies-like viruses are typically transmitted to humans by bites of infected animals. They cause an encephalitic or paralytic disease that nearly always has a lethal course (World Health Organisation, 2005; Bleck and Rupprecht, 2009). In many European countries it has been possible to successively eliminate rabies in the past 25 years by orally immunising foxes, and thus the Federal Republic of Germany – following many of the neighbouring countries – was able to declare that it is free from classical (terrestrial) rabies in accordance with the criteria of the World Organisation for Animal Health in September 2008 (Cliquet and Aubert, 2004; Anonymous, 2008; World Organisation of Animal Health, 2008; Müller et al., 2012).

The official status of freedom from rabies initially misleads one to describe the current human medical significance of the rabies zoonosis in Germany as practically no longer existent. However, a more detailed consideration of the situation shows that such a conclusion is inappropriate because: (1) even in officially rabies-free Germany bat lyssa viruses are still endemic (van der Poel et al., 2006; Müller et al., 2007; Deleré et al., 2011); (2) despite strict statutory regulations illegal import of domestic animals infected with rabies from endemic regions still occurs sporadically (Johnson et al., 2011); (3) German citizens are furthermore potentially exposed to rabies since, in accordance with conservative estimates, at least one out of eight of them travelled to rabies endemic areas in 2010 (Statistisches Bundesamt, 2011).

The following presentation attempts to assess the human medical significance of the rabies zoonosis in Germany based on available, representative data and to demonstrate existing desiderata in this context. The interval from 2006–2010 was selected as the survey period in order to be able to compare the last two years of national rabies endemism with the first two after proclamation of freedom from rabies. The focus of attention was particularly on the determination of exposure-relevant human contacts and the number of rabies vaccinations performed – both of which are considered to be important indirect markers for the (national) human medical significance of the rabies zoonosis (Rimhanen-Finne et al, 2009).

Material and Methods

The investigations performed in the years 2006–2010 on domestic and wild animals in total and after previous human contacts in accordance with the Ordinance for Protection against Rabies (Verordnung zum Schutz gegen die Tollwut; Anonymous, 2010) were centrally recorded by the Friedrich-Loeffler-Institut.

In rabies surveillance, the direct immunofluorescence test (dIFT) was used as the analytical method of choice. Subsequent to previous human contact, the clarification of initial dIFT negative or questionable results was possible by means of the Rabies Tissue Culture Infection Test with three serial passages (Dean et al., 1996; Webster and Casey, 1996; World Health Organisation, 2005; World Organisation for Animal Health, 2008; Roß et al., 2009).

The nationwide registered rabies cases and exposures in the field of human medicine were recorded by the Robert-Koch-Institut. According to Sections 6 and 7 of the Infection Protection Act (Infektionsschutzgesetz, IfSG; Anonymous, 2011a), the following are all equally subject to compulsory notification: (1) the traumatic injury of a human being by an animal that is infected with rabies, suspected of having rabies, or suspected of being contaminated; (2) contact with such an animal or animal cadaver; (3) the suspicion of disease for a person and his or her death due to the zoonosis.

The investigation of the nationwide rabies vaccine doses sold in the years 2006–2010 was conducted by the information service provider INSIGHT Health (Waldems-Esch and Berlin). In this context, the prescriptions invoiced by the pharmacy computer centres in the scope of statutory health insurance (SHI) served as the data source. The data recorded by INSIGHT Health attained 99.8% coverage (http://www.insight-health.de. Last accessed: 15 February 2012).

Results

The number of domestic and wild animals examined in the framework of rabies surveillance in the years 2006–2010 is summarised in Table 1.

During this five year period, a total of 81 280 animals underwent veterinary medical examinations for the presence of rabies infection by means of dIFT. The rabies surveillance, which performed 96% of the analyses on the indigenous wild animal population, particularly focused on the target species fox.

In 2441 (3%) of all the tested animals there was prior human contact. In this context, wild animals were involved in 54% of exposures and domestic animals, in 46% of them. Foxes dominated the spectrum of necessary veterinary medical examination subsequent to wild

animal contact with 59%, whereas cats and dogs made up 47% and 20%, respectively, of the analyses performed after domestic animal exposure.

A comparison of the numbers of veterinary medical examinations based on human contact in the years 2006 and 2007 with those registered after Germany's proclamation of freedom of terrestrial rabies in the years 2009 and 2010, revealed a decline of 53 (wild animals) and 37 (domestic animal) percentage points, respectively. This tribute to freedom of terrestrial rabies also naturally manifested itself in the extrapolation to the population as a whole. In 2006 and 2007 there were still 0.42 and 0.34 veterinary medical examinations per 100 000 inhabitants subsequent to prior human contact, but in the years 2009 and 2010 these indices dropped to 0.2, respectively.

According to Sections 6 and 7 IfSG, only one rabies notification was reported in the years 2006–2010. It concerned a man, who was 55 years old at that time and was bitten by a stray dog in Morocco in 2007. He indeed attempted to obtain medical assistance there, but did not receive any rabies post-exposure treatment. After his return to Germany, initially unspecific symptoms developed into hydrophobia, which could ultimately be ascribed to a rabies infection by means of medical laboratory tests. Despite an experimental treatment by a modified version of the Milwaukee Protocol (Willoughby et al., 2005; Anonymous, 2009), the patient died 31 days after onset of symptoms (Schmiedel et al., 2007).

In the years 2006–2010, 108 536 doses of rabies vaccine were prescribed to patients in the German SHI system (Tab. 2). This corresponded to an annual average of approximately 21 700 doses. 56% of all prescriptions were made by general practitioners. 17% were issued by internal specialists, whereas 9% each were accounted for by physicians working in hospitals and institutes or paediatricians. The remaining 9537 prescriptions were made by surgeons (6%) and physicians with other or unknown specialities, (3%), respectively.

TABLE 1: *Examinations performed on domestic and wild animals in accordance with the Ordinance for Protection against Rabies (Verordnung zum Schutz gegen die Tollwut; Anonymous, 2010) in the years 2006–2010 total examinations and examinations conducted subsequent to prior human contact*

Year	Type of animal	Total examinations (N)	Examinations subsequent to human contact (N)	Examinations subsequent to human contact/100 000 inhabitants[1]
2006	Domestic animals			0.36
	Dogs	124	56	
	Cats	429	164	
	Other	279	78	
	Wild animals			0.41
	Foxes	14 453	201	
	Raccoon dogs	402	24	
	Bats	77	21	
	Other	1086	90	
2007	Domestic animals			0.32
	Dogs	85	33	
	Cats	330	158	
	Other	288	72	
	Wild animals			0.43
	Foxes	14 848	212	
	Raccoon dogs	248	40	
	Bats	100	26	
	Other	1446	79	
2008	Domestic animals			0.27
	Dogs	83	46	
	Cats	211	111	
	Other	288	62	
	Wild animals			0.36
	Foxes	12 561	162	
	Raccoon dogs	203	38	
	Bats	76	24	
	Other	1246	68	
2009	Domestic animals			0.21
	Dogs	78	43	
	Cats	188	-	
	Other	200	127	
	Wild animals			0.21
	Foxes	15 641	103	
	Raccoon dogs	148	17	
	Bats	66	12	
	Other	1413	38	
2010	Domestic animals			0.22[2]
	Dogs	118	47	
	Cats	187	104	
	Other	248	30	
	Wild animals			0.19[2]
	Foxes	13 012	97	
	Raccoon dogs	149	20	
	Bats	86	20	
	Other	883	18	
Σ	-	81 280	2441	-

[1] The respective population level was determined using information from the Federal Statistical Office (http://www.destatis.de/jetspeed/portal/cms/Sites/destatis/Internet/DE/Navigation/Statistiken/Bevoelkerung/Bevoelkerungsstand/Bevoelkerungsstand.psml. Last accessed: 15 February 2012).

[2] Since no official figure for the total population for 2010 was available, the value from the previous year was used for the calculation.

Discussion

In the above, an attempt was made to assess the human medical significance of the rabies zoonosis in Germany for the years 2006–2010 based on available representative data. In the process the focus was placed on the determination of exposure-relevant human contacts and the number of performed rabies vaccinations.

The data recorded in the scope of the veterinary medical surveillance in accordance with the Rabies Ordinance (Anonymous, 2010) verified that approximately 3% of all the examined animals had been previously responsible for the exposure of a person. However, it is conceivable that some of these animals had been shot and were examined without a real exposure-relevant incident simply because a hunter had touched the cadaver. Beyond this, the above-mentioned numbers concerned only those cases in which it had been possible to obtain the causative animal and subsequently examine it. Therefore, one must assume that the officially available data was indeed an underrepresentation of the actual autochthonous incidence of exposure. The population-oriented

indices determined in our survey (0.77 [2006] to 0.41 [2010]) therefore could not be easily compared with corresponding information on exposure-relevant incidents in other countries – for example, with existing data from Finland (0.23/100 000, Rimhanen-Finne et al., 2009), France (16/100 000, Gautret et al., 2008), or the United States of America (27/100 000, Blanton et al., 2005). Despite this principal restriction, foxes (59% of wild animal contacts) as well as cats and dogs (47% and 20%, respectively, of the domestic animal contacts) had been shown to be particularly responsible for the potentially significant incidents of exposure to rabies in human medicine. The fact that the number of examinations performed on wild and domestic animals subsequent to human contacts decreased by 53 and 37 percentage points in the years 2009/2010 compared to 2006/2007 might primarily be due the meanwhile altered rabies epidemiology in Germany. This fact was evidently recognised in veterinary medicine much earlier than in its human medical counterpart and consequently also resulted in earlier corresponding changes in the "ordering behaviour" there.

According to conservative estimates, every eighth German citizen travelled in rabies endemic areas in 2010 (Statistisches Bundesamt, 2011). How many of these individuals actually underwent pre-exposure vaccinations against rabies infection is unknown. The little data available in this respect, however, suggests that serious flaws might exist. Travel health advisors in one of Germany's largest public health offices, for instance, in 2002–2004 only provided pre-exposure vaccination to 7.0–11.2% of those persons desiring to visit a country where rabies is endemic (Heudorf et al, 2006). Reliable information on the exposure of German citizens to rabies outside of Germany is also lacking. An approximate perception of their extent can solely be conveyed by general statistical considerations. Since the exposure frequency elicited only by dogs in Africa and Asia can be estimated to be a minimum of 100/100 000 (Meslin, 2005), at least 10 000 German citizens must have suffered from rabies exposure that required a post-exposure prophylaxis during their holidays.

Germany does not have a general vaccination registry in human medicine and mandatory vaccination registration exists only in Saxony Anhalt. The means for vaccination surveillance stipulated in the IfSG are therefore unavoidably restricted to school entry examinations (section 34, para. 11). Furthermore, in section 20, para. 4, the Federal Ministry of Health is entitled to regulate the funding of vaccinations via the SHI companies by legal decree as well as to promote the transmission of anonymised data with regard to such vaccination campaigns (Anonymous, 2000; Oppermann et al., 2009; Anonymous, 2011a).

Our survey therefore had to search for sources able to give a reliable estimate on the administered rabies vaccine doses nationwide in the years 2006–2010 beyond the information available from the government. INSIGHT Heath provided us with the missing data. This is based on the number of prescriptions redeemed by the German federal SHI. Approximately 90% of all Germans are insured by this type of medical service provision. Therefore, the data collected by INSIGHT Health represents a nearly complete registration of the SHI prescriptions invoiced in the pharmacy computer centres (http://www.insight-health.de. Last accessed: 15 February 2012; http://www.gkv-spitzenverband.de/GKV_was_ist_das.gkvnet. Last accessed: 15 February 2012).

The 108 536 doses of rabies vaccine obtained with an SHI prescription in Germany in the years 2006–2010 were issued by physicians of different specialisations. The observed distribution of disciplines may have corresponded to the spectrum of the respective first specialist contacts of the patients to a large extent. The decrease in number of sales in the year 2009 could very probably not be explained by Germany's proclamation of freedom from terrestrial rabies, but much more likely by the bottlenecks in the supply of rabies vaccine, which were observed at that time. They occurred for production-technical reasons and at the international level even resulted in a curtailment of the post-exposure prophylaxis according to the classical "Essen Scheme", which had been adhered to for decades (Rupprecht et al., 2009). The 21 700 vaccine doses sold annually across Germany would have sufficed to have performed 7230 complete courses of rabies pre-exposure prophylaxis or 4340 complete post-exposure treatments. Based on the actual SHI sales figures, it was not possible to determine for which of these two principal indications the vaccine had actually been used. Nor did they provide any information on whether, for example, an underlying exposure occurred in inland or on trips in rabies endemic areas or whether the respective vaccination cycle could be com-

TABLE 2: *Number of nationwide prescriptions of rabies vaccine in the years 2006–2010, as determined from the sum of the redeemed prescriptions in the SHI under consideration of the medical speciality of the prescribing physician*

Year	Medical speciality	Prescriptions (N)
2006	General practitioners	11 544
	Internists	3137
	Physicians working in hospitals or institutes	2298
	Paediatricians	2364
	Surgeons	1682
	Other	228
	Unknown	338
2007	General practitioners	14 625
	Internists	4557
	Physicians working in hospitals or institutes	2521
	Paediatricians	2709
	Surgeons	1630
	Other	337
	Unknown	251
2008	General practitioners	12 938
	Internists	4384
	Physicians working in hospitals or institutes	1889
	Paediatricians	2181
	Surgeons	1184
	Other	455
	Unknown	176
2009	General practitioners	9478
	Internists	2736
	Physicians working in hospitals or institutes	1379
	Paediatricians	1204
	Surgeons	801
	Other	288
	Unknown	301
2010	General practitioners	12 066
	Internists	3904
	Physicians working in hospitals or institutes	1626
	Paediatricians	1459
	Surgeons	1037
	Other	524
	Unknown	305

pleted. A certain improvement in this regard would have been expected from the generally welcomed extended and standardised documentation key in accordance with the Annex 2 of the so-called "Vaccination Guideline" („Schutzimpfungs-Richtlinie"; Anonymous, 2011b). Unfortunately, however, this regulation is not applicable to rabies because it, on the one hand, does not include the post-exposure administration of sera or chemotherapeutics and, on the other hand, travel vaccinations and an occupational hazard due to the zoonosis normally do not justify an entitlement for benefits from the SHI (Oppermann et al., 2009).

The representative data available from veterinary medical surveillance, from the official compulsory notification in human medicine, and from the analysis of redeemed SHI prescriptions do not currently allow an even semi-adequate reconstruction of the human medical significance of the rabies zoonosis in the Federal Republic of Germany. In order to obtain as complete a picture as possible, one would have to follow the example of some of our European neighbours. France, for instance, has a blanket coverage network of specialised rabies treatment centres. They transmit all the collected information including the details of a possible initiated treatment to the National Reference Centre for Rabies. This, in turn, publishes an annually updated bulletin with all relevant information on the national epidemiology and prophylaxis of rabies in humans (Institut Pasteur, 2011). In Finland there is not only the veterinary medical surveillance data, which is also available in Germany. Additional information exists on the actual number of incurred human exposures since at least those contacts which require a rabies post-exposure prophylaxis must be compulsorily recorded in a registry especially set up for human medicine (Rimhanen-Finne et al., 2009). Finally, in the Netherlands, rabies vaccines and hyperimmunoglobulin preparations are only available from the National Vaccine Institute. Furthermore, their application is subject to a quality control to the extent that a team of experts of the Preparedness and Response Unit at the Centre of Infectious Disease Control critically checks the respective decentrally prepared prescriptions and corrects them if necessary (Beaujean et al., 2008).

On the one hand, if Germany was also to proceed according to the example of one of the three above-mentioned countries, essential data on the current human medical significance of the rabies zoonosis would be generated. On the other hand – and at least as important – in this manner it would be possible to achieve a far-reaching standardisation in the determination of the indications for rabies post-exposure prophylaxis. Thus, substantial uncertainties, which exist even for experienced physicians in the field, might be eliminated (Schönfeld et al., 2003; Hossain et al., 2004; Ross et al., 2006; Gautret et al., 2008, 2009; Pavli et al., 2011; Wijaya et al., 2011).

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