FROM THE ARCHIVES OF THE ZAGREB ANTIRABIES CLINIC: HOSPITALIZED PERSONS DUE TO ANIMAL BITES FROM 1995 TO 2006

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Aim: In the Zagreb Antirabies Clinic, which operates within the Reference Center for Rabies at Andrija Štampar Teaching Institute of Public Health in Zagreb, in the period from 1995 to 2006, there were 12 380 patients examined for injuries inflicted by animals, of which 147 (1.18%) were hospitalized in various Zagreb departments and hospitals due wound severity. ***Methods:*** Data were retrospectively collected from the official patient registry of the Zagreb Antirabies Clinic. ***Results:*** Hospitalized patients were in an age range from 1 to 81 years, 63 (42.86%) were adults, and 84 (57.14%) children aged 1 to 16 years; among adults, there were 28 (44.44%) men and 35 (55.56%) women, while among children there were 45 (53.57%) boys and 39 (46.43%) girls. ***Discussion:*** Concerning animals involved in the incidents which led to hospitalization, dogs were by far the most frequent species, recorded in 74.82% of cases; other animals were, in the order of frequency, cats, rats, a pig and a donkey. The dogs of known owners were represented five times more often than stray dogs. ***Conclusion:*** There was no statistically significant difference in the frequency of hospitalization between children and adults, while dogs were significantly more likely to inflict injuries that ended in hospitalization than other animals, and patients were more often hospitalized after head and neck injuries or multiple injuries than due to injuries to limbs or hands and fingers.

Key words: rabies, animal injuries, children, adults, hospitalization

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INTRODUCTION

Rabies is a viral zoonotic disease responsible for estimated 59 000 human deaths and over 3.7 million disability-adjusted life years (DALYs) lost every year (1,2). Rabies is almost invariably fatal once the clinical signs appear, as a result of acute progressive encephalitis. Most cases occur in Africa and Asia, with approximately 40% of cases in children aged <15 years. All mammals are susceptible to infection by the rabies virus (RABV). Transmission of RABV by dogs is responsible for up to 99% of human rabies cases in rabies-endemic regions, the remaining small proportion being due to transmission *via* wildlife (mainly foxes, wolves, jackals, bats, raccoons, skunks or mongoose) (3).

Mass vaccination campaigns targeting dogs constitute the principal strategy for rabies control by interrupting RABV transmission between dogs and reducing transmission to humans and other mammals. This strategy has been effective in different settings in Africa, Asia, Europe, and the Americas. As dog-mediated rabies incidence declines as a result of effective control programs, rabies from other sources, although rare, becomes more prominent, as is currently noted in the Americas. Wild carnivore species and bats (*Carnivora* and *Chiroptera*) represent a higher risk of RABV transmission than other wildlife, as they themselves are the reservoirs of RABV (4,5). Human-to-human transmission of rabies has never been confirmed, with extremely rare exceptions resulting from infected tissue and organ transplantation (6,7).

Children make up the largest percentage of people bitten by dogs, with the highest incidence in mid-to-late childhood. The risk of injury to the head and neck is greater in children than in adults, adding to increased severity, necessity of medical treatment, and death rates. In some countries, males have a higher frequency of dog bites than females. Dog bites account for over 50% of animal-related injuries in people who are traveling (8).

The last human rabies case in Croatia was recorded in 1964 (9). Since then, we have only had two imported human rabies cases, one in 1989 and the other in 1996. Both came from the neighboring Bosnia and Herzegovina (10,11). Following three major waves of sylvatic rabies (in 1977, 1981 and 1983), practically the entire territory of Croatia was proclaimed affected by sylvatic rabies, with the exception of some coastal parts and islands (12,13). The situation began to change with the implementation of a program of oral vaccination of foxes. The first campaign began in 1991 and lasted until 1995, when it was discontinued due to war activities in a large part of the country's territory. The second campaign took place in 1998, but it only covered the City of Zagreb and Zagreb County area. The third and ultimately effective effort started in the autumn of 2010 with the autumn bait drop campaign, and since 2011 the bait drop campaigns have been carried out every spring and autumn (14). Signs of eradication of rabies in wildlife and domestic animals showed soon, and the last case of rabies in wildlife (involving a red fox, *Vulpes vulpes*), was recorded in 2014. From 2015 until the present day, we have not had cases of rabies either in wildlife or among domestic animals. This means that, according to the criteria of the World Organization for Animal Health, formerly the Office International des Epizooties (OIE), Croatia is a rabies-free country (15-17).

Throughout the period which we researched for our study, from 1995 to 2006, Croatia was affected by sylvatic rabies, with the red fox (*Vulpes vulpes*) being the most frequently diagnosed rabid animal. In 1995, that number was 390, increasing to 514 cases in 2006. The number of domestic animals which contracted rabies was 21 in 1995, increasing to 49 in 2006 (17).

AIM

In this paper, we give an overview of persons hospitalized due to animal bites in the hospitals and departments in the City of Zagreb from 1995 to 2006.

On approaching the archival data, we formulated three hypotheses:

1) children are more often hospitalized compared to adults;
2) patients are more often hospitalized due to dog bite than any other species of animal; and
3) injuries on limbs or fist and fingers are more frequent than those on the head and neck.

PARTICIPANTS AND METHODS

The data composed in the overview were collected from the official patient registry of the Zagreb Antirabies Clinic in the period from 1995 to 2006. We followed the system in which the registry is kept, i.e., age and gender of patients, animal species involved in the incident, veterinary analysis of the biting animal if any, wound localization, type of treatment received, whether patients were hospitalized and where. We reviewed a total of 12 380 patient files, extracting only hospitalized cases for further analysis. We expected, by doing so, to be able to compare our findings with those of other authors. The reason for limiting the overview to the above time span was that the practice of personal visits by physicians of the Antirabies Clinic to hospitalized patients was discontinued in 2006. Also, in that year, the computer program in which the patient registry was kept was changed and it was not possible to maintain consistency of data between the former and the latter period.

The sample was described by descriptive statistics and frequencies. Categorical variables were compared using χ^2-test and data were considered significant at $p<0.05$. All statistical analyses were performed using STATISTICA 13.1. (StatSoft, Tulsa, OK, USA).

RESULTS

In the Zagreb Antirabies Clinic at the Andrija Štampar Teaching Institute of Public Health, during the 1995-2006 period, we saw 12 380 patients presenting with animal bites, of whom 1941 (15.67%) were vaccinated and 147 (1.18%) were hospitalized (Table 1).

Hospitalized patients were in the age range from 1 to 81; 63 were adults (28 men and 35 women) and 84 children, aged 1-16 (45 boys and 39 girls). Children are at a greater risk of sustaining bite injuries, as well as hospitalization, primarily due to the lack of parental control and inattention.

As can be seen from Table 1, the rate of hospitalization was actually very low and did not differ significantly during the observed period.

It is apparent that the number of injuries inflicted on the head and neck was almost equal to the number of multiple injuries, while only one injury was inflicted on the trunk, which made it the rarest anatomic localization (Fig. 1).

Table 1.
Patients presenting with animal bites in the 1995-2006 period

Year	Examined	Vaccinated	Hospitalized incidence proportion (risk) (%)
1995	1380	186	17 1.2
1996	1297	185	11 0.8
1997	1214	197	15 1.2
1998	1058	177	16 1.5
1999	1129	188	11 0.9
2000	1010	159	20 1.9
2001	878	159	12 1.3
2002	956	147	11 1.1
2003	889	127	8 0,8
2004	902	111	6 0.6
2005	865	133	12 1.3
2006	802	172	8 0.9
Total	12380	1941	147
Percentage (%)		15.67	1.18

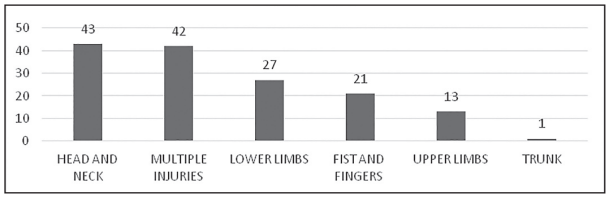

Fig. 1. *Wound localization in patients hospitalized during the 1995-2006 period.*

The χ^2-test showed statistical significance with regard to anatomic distribution of inflicted wounds ($\chi^2(4, n=146)=23.6$, $p<0.05$). The data proved that patients were hospitalized more often due to injuries on the head and neck or multiple injuries than due to injuries on the limbs or fist and fingers, contrary to our initial hypothesis.

In the City of Zagreb and the entire Republic of Croatia, we use ABCD categories of risk exposure, instead of I, II, III categories of risk of exposure of the World Health Organization (WHO) (18,19). We believe that our system is more precise and clinically better justified, depending on actual rabies situations in the city/country (Fig. 2).

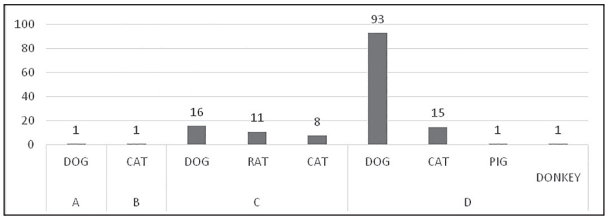

Fig. 2. *Animals involved in bite injuries that led to hospitalization according to ABCD risk scale during the 1995-2006 period.*

An overview of the animal species that injured hospitalized patients, by frequency and percentage from 1995 to 2006 showed the following: dogs 110 (76%), cats 24 (17%) and rats 11 (7%). Two extremely rare cases that can be considered an exception were excluded from analysis. Those two patients were bitten by a pig and a donkey.

The χ^2-test showed statistical significance with regard to animal species which attacked hospitalized patients ($\chi2(2, n=145)=119.86$, $p<0.01$). Patients hospitalized due to dog attack were by far more frequent (76%) than those hospitalized due to attack by cat (17%) or rat (7%).

The departments and hospitals in the City of Zagreb where the patients were hospitalized are presented in Table 2. The distribution among hospitals and departments reflects the reality that most of the hospitalized patients were children who were chiefly hospitalized in the Zagreb Children's Hospital. Most of the children received PEP with antirabies vaccine prepared on human diploid cells (HDC vaccine) or purified chick embryo cell vaccine (PCEC vaccine) with human rabies immunoglobulin, while in adults PEP was applied in only 4 cases. All patients were vaccinated either with the 'Zagreb" or '2-1-1' schedule or the 5-dose schedule (18,19).

Table 2.
Departments and hospitals in the City of Zagreb where patients were hospitalized

Name of department/hospital	Number of hospitalized patients
1. Zagreb Children's Hospital	60
2. Dr. Fran Mihaljević University Hospital for Infectious Diseases	37
3. Zagreb University Hospital Center, Pediatric Surgery	18
4. Dubrava University Hospital	14
5. Sestre milosrdnice University Hospital Center, Department of Traumatology	6
6. Sestre milosrdnice University Hospital Center	6
7. Merkur University Hospital	3
8. Sveti Duh University Hospital	2
9. Zagreb University Hospital Center, ENT Department	1
Total	**147**

Dr. Fran Mihaljević University Hospital for Infectious Diseases ranked second institution where adults were hospitalized due to complications after cat and rat bites (cat scratch disease, rat bite fever). It is important to note that physicians from the Zagreb Antirabies Clinic personally visited each of the 147 patients to ascertain their clinical status and, when applicable, administer rabies post-exposure prophylaxis.

DISCUSSION

According to Daniels *et al*., dog bites are a significant public health problem among children. Dog bite visits accounted for 1.5% of all pediatric injuries in their study (20). Other studies have shown that children under 15, predominantly boys, represent a high-risk demographic group for dog bites (21). In his paper about the public health impact of dog attacks in Adelaide, Australia, Thompson states that children aged 0-4 years were attacked and required hospital treatment twice as often as adults aged 21-59, and men aged over 76 were attacked twice as often as men aged 36-75 (22). Morales *et al*. describe dog bite accidents in a children's hospital in Lima, Peru, observing that most patients were male, 66.5% of bites were provoked, and 88.8% were inflicted by animals known to the victim (23). The National Canine Research Council in its analysis of injuries states that 96% of dog bite injuries presenting to emergency rooms are minor and that less than 1.5% require hospitalization (24). According to the report by the Centers for Disease Control and Prevention (CDC) from 2003, regarding nonfatal dog bite-related injuries treated in hospital emergency departments in the United States, 1.8% of a total of approximately 6000 persons were hospitalized, the injury rates being highest among children aged 5-9 (25). In our study, the total percentage of hospitalizations due to animal bites was 1.18%. This hospitalization rate is comparable to the CDC non-fatal injury reports 2001-2013 with the percentage rate of hospitalization below 1.5% (26). Within the 11-year span covered by our overview, there were 147 hospitalizations, 110 of which were due to bites from animals known to the victim.

The children we observed were aged up to 16 years. They were often hospitalized after being bitten by a dog of a known owner, usually due to inattention and lack of parental control. The dogs that injured the children in our study were mostly German Shepherds, Dobermans, Rottweilers and Bull Terriers, or big dogs of mixed breeds. These dog species responsible for bite attacks correspond to those listed by Thompson (22). In the records of the Zagreb Antirabies Clinic, there were no dog-bite related fatalities in the observed period, although dog bites continue to be the main route of transmission of human rabies worldwide (9).

Chiam *et al*. in their study state that out of 277 children presenting with dog-bite injuries, 141 (51.0%) were referred to a hospital, the injury rates being highest in the 0-4 age group, thereafter declining with age. In their study, 89.5% of children were bitten by a familiar dog and 92.5% of bites occurred at home (27).

During the 11-year period analyzed in this study, wound localizations in bite victims in Croatia were the following: head and neck 43, multiple injuries 42, lower limbs 27, fist and fingers 21, upper limbs 13, and trunk 1. In their work on animal and human bite injuries in Victoria, Australia, MacBean *et al*. state that dog bite injuries were commonly sustained by the hands/wrists (31.3%), followed by face/head (25.4%) (28). Males were represented in greater numbers in cases of dog bite injuries, and females in cases of cat bites (29). Schalamon *et al*. in a study of dog bites in children observed that the annual incidence of dog bites was 0.5 *per* 1000 children in the 0-16 age range. Of 357 registered injuries, the face, head and neck region were the leading affected sites (50%) (30). Yurachai *et al*. in an epidemiological study of suspected rabies exposures in eastern Thailand conclude that most of the bites occurred on the street, involving stray dogs and the bites were unprovoked. Children and teenagers accounted for 55% of all victims. The most common wound localizations were lower extremities (54%) and upper extremities (20%), whereas 9% of the patients were bitten on the face or head (31). Interestingly, in their study, more people were hospitalized due to rat bites than cat bites. In our review of Croatian data, the face, head and neck region were represented in equal numbers (n=43) as multiple bite injuries (n=42). Of the total number of hospitalizations, 147 in the 11-year period, only one was associated with a proven rabid dog (category A of exposure risk). Another patient was hospitalized following a cat bite with suspicion of rabies (category B of exposure risk). However, the cat involved in this incident was caught and proven negative by the Croatian Veterinary Institute. In category C of exposure risk, we had 35 patients, of which 16 were in contact with stray dogs, 11 with rats and 8 with cats.

Some of the patients developed rat bite fever following rat bites and were admitted to Dr. Fran Mihaljević University Hospital for Infectious Diseases in Zagreb. Also, some of the patients developed cat scratch disease following cat bites and were also admitted to the hospital (32). A number of authors state that cat bite injuries can progress to serious infection (33-36). Vodopija *et al*. describe rodent bites in the City of Zagreb and Zagreb County in 2007. Although rare, such bites can have serious consequences (37). Of the pa-

tients bitten by an animal of known origin, 93 were bitten by dogs, 15 by cats, one by a pig, and one by a donkey. This distribution (except for pig and donkey) corresponds to findings of other authors (38-40). Out of 147 animals that injured our patients, 17 were killed and 130 stayed alive. In 5 cases, animal corpses were delivered for rabies analysis to the Croatian Veterinary Institute. Of these, 4 were proven negative and one positive. Veterinarian surveillance of animals was carried out in 97 cases (66% of bites), while the remaining 50 cases were without surveillance (34%). Veterinarian surveillance lasted for 10 days. When the animals did not develop rabies, human post-exposure prophylaxis was discontinued. According to Dunbar's Dog Bite Scale (10), all hospitalized patients from our study can be assigned to Levels 4 and 5.

Dogs and cats represent two species that are generally responsible for almost 85% of all animal bites (1). According to the WHO data (9), some studies reveal that dogs account for 76%-94% of animal bite injuries. Children make up the largest percentage of people bitten by dogs, with the highest incidence in mid-to-late childhood. The risk of injury to the head and neck is greater in children than in adults, adding to the increased severity, necessity for medical treatment, and death rates. Cat bites account for 2%-50% of injuries related to animal bites. They are commonly second to dog bites in terms of incidence, with the highest rate among female adults (41,42). In his study, Matter states that dogs accounted for more than 60% and cats for about 25% of all cases reported. Animal bites and scratches were frequent in patients under 20 years of age, and in most cases the incidence was higher among women than among men, but not in children under the age of ten years. Bites to the head and neck were most frequent in infants and young children, and accounted for approximately one-third of the reported cases (40).

CONCLUSION

Croatia is today a rabies-free country. The last case of sylvatic rabies (red fox, *Vulpes vulpes*) was recorded in February 2014. Since then, there has not been a single confirmed case of rabies either in wildlife or domestic animals. This proves the efficacy of oral bait campaigns which have been carried out in Croatia consistently twice a year since 2011. Hospitalization data which we present are historical, but they paint a picture of the period when sylvatic rabies was still present in the country, and, with a rate of under 1.5%, they are comparable to countries in which sylvatic rabies is still endemic. These data also attest to the efficacy of PEP administered according to the bilateral 2-1-1 application schedule originally invented in Zagreb in the 1980s and endorsed by the WHO in 2010. The Zagreb Antirabies Clinic (formerly Pasteur Institute in Zagreb) has been in operation continuously since 1918. It has been on the forefront of worldwide efforts to eradicate both urban and sylvatic rabies, as well as of the early implementation of the 2nd generation of purified cell culture derived vaccines (CCDV) and embryonated egg-based rabies vaccines and innovative administration schedules.

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SAŽETAK

IZ ARHIVE ANTIRABIČNE AMBULANTE GRADA ZAGREBA: HOSPITALIZIRANE OSOBE ZBOG UGRIZA ŽIVOTINJA U RAZDOBLJU OD 1995. DO 2006. GODINE

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Cilj: U antirabičnoj ambulanti Referentnog centra za bjesnoću pri Nastavnom zavodu za javno zdravstvo „Dr. Andrija Štampar " u Zagrebu u razdoblju od 1995. do 2006. godine ukupno je zbog ugriza životinja pregledano 12.380 bolesnika, od kojih je 147 (1,18%) hospitalizirano u bolnicama i klinikama grada Zagreba. ***Metode:*** Rezultati su prikupljeni retrospektivno iz službenog registra antirabične ambulante u Zagrebu. ***Rezultati:*** Hospitalizirani bolesnici bili su u dobnom rasponu od 1 do 81 godine, 63 (4,86%) odrasle osobe i 84 (57,14%) djece u dobi od 1 do 16 godina; od odraslih bilo je 28 (44,44%) muškaraca i 35 (55,56%) žena, a od djece 45 (53,57%) dječaka i 39 (46,43%) djevojčica. ***Rasprava:*** Od životinja koje su sudjelovale u incidentima koji su doveli do hospitalizacije psi su bili daleko najviše zastupljena vrsta (74,82% slučajeva), dok su ostale životinje po redu učestalosti bile mačke, štakori, svinja i magarac. Psi poznatih vlasnika bili su zastupljeni pet puta češće od pasa lutalica. ***Zaključak:*** Nema statistički značajne razlike u učestalosti hospitalizacije između djece i odraslih, dok su psi statistički značajno češće nanosili ozljede koje su završile hospitalizacijom u odnosu na druge životinje, a bolesnici su bili češće hospitalizirani nakon ozljeda glave i vrata ili višestrukih ozljeda nego zbog ozljeda udova ili šake i prstiju.

Ključne riječi: bjesnoća, ugrizi životinja, djeca, odrasli, bolničko liječenje