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Infectious diseases

A change in rabies post-exposure treatment guidelines after decision analysis in Israel

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Background: Rabies remains a significant public health problem in Israel. Some 16 000–20 000 persons come yearly to the district health offices after being bitten by animals and 16–18% receive rabies post-exposure treatment. A quality assessment of the rabies post-exposure prophylaxis decisions was never held in Israel before. The purpose of this study was to analyse the decision-making process and to update our rabies prevention guidelines accordingly. **Methods:** A retrospective evaluation study of physicians' compliance with rabies post-exposure treatment guidelines in Haifa District Health Office, Ministry of Health, during 1/11/1999 to 31/12/2002. Records of all persons seeking advice (5037) following exposure to animals during the 3 years of the study were examined. Of these 2477 were eligible for the quality audit. The remaining files were analysed for the relative contribution of the different variables considered in the decision-making process. **Results:** Observed agreement rate and Kappa coefficient were 0.984 and 0.803, respectively. The probability of recommending vaccination was greater when the exposure was from stray dogs as opposed to cats (OR = 48.9; 95% CI 17.9–133.3), if the wound was a bite rather than a scratch (OR = 29.0; 95% CI 19.5–43.2) or in a location defined as rabies enzootic as opposed to rabies free (OR = 7.6; 95% CI 5.8–10.1). **Conclusions:** The study demonstrated high compliance with the written guidelines. We weighted the relative importance of the variables determining the decisions. This information was used in formulating the updated guidelines.

Keywords: guidelines, post-exposure treatment, post-exposure vaccination, prevention, quality control, rabies

Rabies remains a significant public health problem in Israel despite the recent decline in its incidence among animals from 97 cases in 1998 to 43 cases in 2003. The incidence of rabies among quarantined and captured animals has declined from 50% in 1948 to 5% in 1997.[1] The continued presence of animal rabies, however, makes post-exposure prophylaxis retain its key importance in the overall policy to prevent rabies in humans.[2]

In Israel, the responsibility for deciding to vaccinate exposed persons is exclusively that of public health physicians in the district health offices. Some 16 000–20 000 persons come yearly to the district health offices after being bitten or scratched by animals and 16–18% receive rabies post-exposure treatment. The written guidelines issued by the Public Health Services in 1997 and updated in 2003 form the legal and professional basis upon which these decisions are based. When quarantine is implemented, the physician can base his decision on the results of the quarantine.

Objectives

(i) To assess the compliance of the physicians in the Haifa District Health Office with the written guidelines during the period between 1/11/1999 and 31/12/2002.
(ii) To analyse the decision to vaccinate according to the variables included in the guidelines: animal species, presence of provocation, presence of rabies in the geographic area, as well as demographic variables that were not included in the guidelines.
(iii) To build a database to assist in updating the Ministry of Health's guidelines for the prevention of rabies.

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Methods

Selection and description of participants

A Microsoft Access© computerized database of 5037 records of persons seeking advice following exposure to animals during the period between 1/11/1999 and 31/12/2002 was analysed. The database contains demographic information of the exposed persons, the address where the exposure occurred, the animal species, and the details of the physician's decision. The guidelines set out four different algorithms for the decision-making process for four different levels of risk based on the type of animal exposure. There are definitive instructions to vaccinate following exposure to wild or unidentified animals unless the animal can be quarantined or its brain sent for histological examination. The guidelines also clearly state that no vaccine is indicated following rodent bites. The guidelines similarly do not recommend vaccination following exposure to large domestic farm animals; however, in this case quarantine and veterinary supervision is required. The guidelines are not definitive in all cases and they leave room for physician judgement.

In accordance with the guidelines, the reviewed records were divided into four risk categories. The majority (4518) of cases of exposures were from dogs and cats. The remainders were from rodents (288), wild animals or unidentified animals (165) and large domestic animals (66). The cases of exposures from subsequently quarantined dogs and cats (1863) or from rodents (288), wild (165) and large domestic animals (66) as well as cases when no real exposure occurred (95) were included in audit analysis. We were able to do this quality audit on a total of 2477 (~50%) of the records. (figure 1)

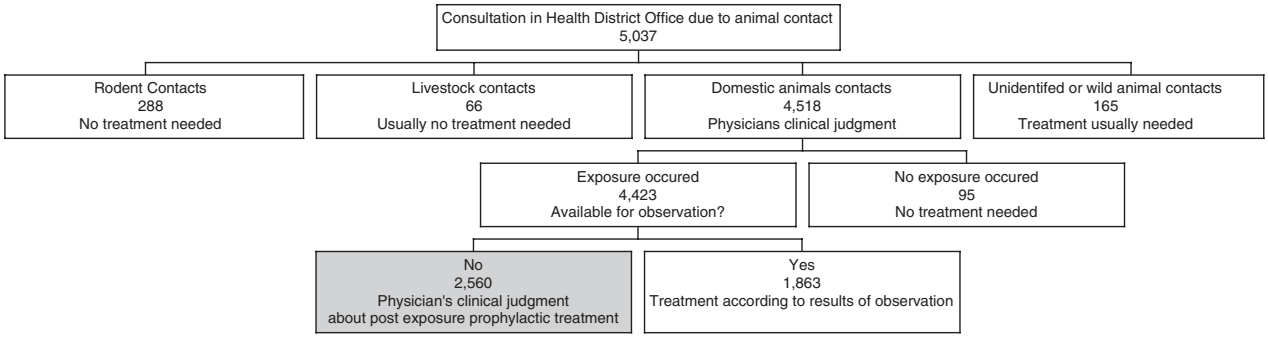

Figure 1 Distribution of study population to different risk groups. This figure demonstrates study population subgroups inclusion criteria in which the decision-making process analysis was done (different levels of risk based on the type of animal exposure). The grey frame depicts subgroup of cases in which analysis of the relative contribution of the different variables in the initial rabies vaccination was done.

Of the exposures to cats and dogs, 4423 were of the type that permit transmission of rabies; bites, scratches, or licks on mucosal surfaces or fresh wounds. There were 2560 exposures in which the animal was neither quarantined nor identified or found alive 10 days following the exposure. In the latter cases the physician needed to exercise his clinical judgement as to whether initiate rabies vaccination (grey frame in figure 1). In these cases in which the guidelines call for clinical judgement, we could not assess compliance but rather could analyse the relative contribution of the different variables considered in the decision-making process.

Definition of variables affecting the decision of whether to vaccinate

The queries used to assess compliance used those variables included in the decision trees that appear in the guidelines.

Provocation

This was defined as any action to which a healthy animal is likely to respond to by biting or scratching; this included playing with or feeding the animal, entering his living boundaries, touching his offspring, running or riding a bicycle in close proximity, extending assistance to a wounded animal, and attempting to distance the animal, etc.

Rabies affected area

The District Health Officer periodically defined geographic boundaries for areas considered rabies enzootic in accordance with the physical distance from the most recently reported cases of animal rabies, natural geographical barriers, and time since the last case of rabies was reported in proximity to the region. He used 3 years from the last reported case of animal rabies to operatively define a region as rabies free.

Deciding physician

Three senior physicians and nine resident physicians included in the analysis.

Statistical analysis

The data were analysed using SPSS®. Compliance with clinical guidelines comprised a 2 × 2 table computing observed agreement rate and Kappa coefficient (table 1). The probability of hypothesis testing of categorical variables was done using Chi-square or Fisher Exact Test, depending upon the distribution of the data. The null hypothesis was that the physician's decision to vaccinate was unaffected by demographic or animal exposure variables. We used multiple logistic regression to test the null hypothesis. A *P*-value <0.05 assuming a two-sided alternative hypothesis was considered statistically significant and sufficient to refute the null hypothesis.

Table 1 Physician's decisions compared with guidelines recommendations

Physician's decision	Guidelines		
	Vaccinate	Do not vaccinate	Total
Vaccinate	104	24	128
Do not vaccinate	16	2333	2349
Total	120	2357	2477

Results

Compliance with guidelines

The observed agreement rate (2437/2477) was 0.984 ($P < 0.001$) and Kappa coefficient was 0.803 (SE of Kappa 0.02 and $P < 0.001$).

The false negative rate (no vaccination recommended when the guidelines recommend vaccination) was 13.3% (16/120).

The false positive rate (a decision to vaccinate when the guidelines do not recommend vaccination) was 1.01% (24/2357).

We found very high compliance with the guidelines, and a low prevalence of 'unnecessary' vaccination. Unnecessary vaccination wastes economic resources on expensive vaccines and risks untoward responses. On the other hand, initially we found a high false negative rate (13.3%) in which the guidelines recommend vaccination and yet the physician decided otherwise. These 16 cases in which treatment was not recommended in contradiction to the guidelines constituted 0.3% of the total number of cases. Upon re-evaluation we found that most of these cases were actually due to misclassification. Eight of the 16 animals involved were initially misclassified as wild animals, whereas they were actually unidentified animals in apartments or on ships in Haifa harbour. These were most likely to be rodent exposures. Three other cases were from monkeys in zoos in unaffected areas and accordingly vaccination was not recommended. Another case initially classified as a wild animal exposure was found to be actually from a bird. In summary 12 of the cases were either misclassified or upon re-examination did not necessitate vaccination. In only four cases was there an actual indication to vaccinate according to the guidelines and this was not recommended. One case was from a horse bite exposure in a non-enzootic area. The other three cases were from unidentified animals in non-enzootic areas. Those four persons did not develop rabies.

The relative contribution of the different variables in the decision-making process 'to treat or not to treat'

Fifty-nine per cent (59.3%) of the 2560 persons exposed to animals that were not available for quarantine were civilians. The remainder were soldiers. The most common type of exposure was bites (58.4%). Most exposures were from stray cats (56.8%), followed by exposures from domestic dogs (20.4%). The majority of exposures were provoked (92.4%). Forty-two per cent (42.6%) of the exposures occurred in areas defined as enzootic for rabies. Most persons requested advice within 6 days following the exposure (90%). The deciding physician was a resident in ~60% of the cases. Vaccination was recommended for 804 cases (31.4%) of exposures (table 2).

A decision to vaccinate was more common for persons aged 15–44 and soldiers. A decision to vaccinate was 2.3 times more likely for bites as opposed to scratches. Of the decisions to vaccinate, 45.6% were after an exposure to stray dogs and 28.1% after exposures to pet dogs. Absence of provocation was 2.8 times more likely in those persons vaccinated than in those not vaccinated. If the event occurred in an area defined as rabies enzootic as opposed to rabies free, the likelihood of the physician recommending vaccination was 1.7.

Senior physicians recommended vaccine 1.2 times more than residents. The body part injured and the time since injury did not affect the decision to vaccinate.

Multivariate analysis

Table 3 demonstrates the results of the multiple logistic regression analysis. The decision to vaccinate was designated the dependent variable. Variables tested in the model included: age group, military service, type of injury, provocation, animal type, area, and physician experience. Those variables that demonstrated no significant effect in the univariate analysis were not included in the model. Those variables that affected the decision to vaccinate in descending order of importance were type of animal, type of exposure, and definition of geographic area as rabies enzootic. In addition, being a soldier, provocation, and being a senior physician were found to be statistically significant. No interactions were found between age group and being military personnel, between age and provocation and between type of animal and type of exposure.

Table 2 Distribution of exposed persons according to demographic characteristics and other parameters

Variable Type	Variable Subgroup	Distribution		Treatment advised		
		No.	%	No.	%	*P*-value
Age group	0–14	400	15.6	84	10.5	$P < 0.001$
	15–44	1702	66.6	605	75.3	
	64– 45	307	12.0	83	10.3	
	+65	148	5.8	31	3.9	
Gender	Male	1688	65.9	584	72.6	$P < 0.001$
	Female	872	34.1	220	27.4	
Military service	Civilians	1517	59.3	407	50.6	$P < 0.001$
	Soldiers	1043	40.7	397	49.4	
Injury type	Bite	1496	58.4	763	94.9	$P < 0.001$
	Scratch	1064	41.6	41	5.1	
Part of body injured	Head/Neck	114	4.5	27	3.4	NS
	Other body part	2446	95.5	777	96.6	
Animal type	Stray cat	1453	56.8	206	25.6	$P < 0.001$
	Domestic dog	521	20.4	226	28.1	
	Stray dog	464	18.1	367	45.6	
	Domestic cat	122	4.8	5	0.6	
Provocation	Yes	2365	92.4	695	86.4	$P < 0.001$
	No	195	7.6	109	13.6	
Area	Enzootic	1091	42.6	483	60.1	$P < 0.001$
	Not enzootic	1469	57.4	321	39.9	
Time interval*	Up to 6 days	2303	90.0	713	88.7	NS
	Longer than 6	257	10.0	91	11.3	
Physician experience	Resident	1529	59.7	440	54.7	$P < 0.001$
	Specialist	1031	40.3	364	45.3	

*Time interval (days) from the event until arrival to Health District Office

Table 3 Multiple logistic regression results for positive rabies post-exposure prophylaxis decisions

Variable	Variable subgroup	Odds ratio	*P*-value	Confidence interval (95% CI)
Age group			0.012	
	0–14	1.0		
	15–44	1.8	0.003	1.21–2.58
	64–45	1.8	0.009	1.16–2.89
	+65	1.2	0.643	0.63–2.13
Military service	Civilians	1.0		
	Soldiers	1.9	$P < 0.001$	1.38–2.62
Type of injury	Scratch	1.0		
	Bite	29.0	$P < 0.001$	19.49–43.19
Provocation	No	1.0		
	Yes	1.9	0.002	1.38–2.62
Animal Type			$P < 0.001$	
	Domestic cat	1.0		
	Stray dog	48.9	$P < 0.001$	17.93–133.27
	Domestic dog	12.4	$P < 0.001$	4.64–33.32
	Stray cat	3.9	0.006	1.48–10.48
Area	Non enzootic	1.0		
	Enzootic	7.6	$P < 0.001$	5.76–10.11
Physician Experience	Resident	1.0		
	Specialist	1.6	$P < 0.001$	1.29–2.09

Relative influence of variables on the decision to vaccinate

The guidelines did not definitively delineate a specific decision in the 2560 cases where the animal was not quarantined and, thus, compliance to the guidelines could not be assessed. We, therefore, chose to analyse those parameters that affected the decision to vaccinate or not. We found some variables, which the 1997 guidelines did not delineate clearly to be significant in the decision-making process.

Type of injures: scratches or bites

The guidelines stated, 'bites are the most efficient means of transferring the virus but rarely infection can be caused by scratches that are contaminated with saliva'. We found that for the most part the deciding physicians inferred from this that in the case of scratches incurred as a result of provocation the relative risks of rabies infection was very low and chose not to vaccinate. The updated guidelines were changed accordingly to state that 'exposures from scratches are less dangerous than those from bites and licks on mucosal surfaces and therefore constitute another consideration in the decision not to vaccinate'.

Type of animal

The guidelines grouped all domestic animals in a single risk category whereby injuries from these animals sustained in the absence of provocation are to be considered from rabies-infected animals unless proven otherwise. This grouping did not take into consideration the particular epidemiology of rabies in Israel in which rabies has not penetrated the cat population and the identification of cat rabies remains a relatively rare occurrence. We demonstrated that the likelihood of a person exposed to a dog bite to be vaccinated was 48.9 times that of a person bitten by a domestic cat. The guidelines were accordingly updated to state explicitly the much lower risk from rabies in cats.

Geographic location: rabies enzootic or not

The guidelines included as one of the variables upon which the decision to vaccinate is predicated the geographic location and whether it was considered rabies enzootic or not. Our study showed that 52% of the decisions hinged upon the geographic location of the exposure occurred. This issue surfaced when updating the guidelines. The Veterinary Services maintained that Israel is a small country with no natural borders and so should be considered rabies enzootic en bloc. The public health physicians maintained that despite the arguments of the veterinary services, the areas of rabies activity have remained confined to certain geographical areas for long periods of time. No cases of rabies have been reported in the cities of Tel Aviv and Haifa for decades whereas continuous rabies activity has been reported in the Judean desert and in the areas bordering the Palestinian authority.

The multivariate analysis showed that the likelihood of recommending vaccination was 7.6 more if we defined the area as rabies enzootic as opposed to rabies free. If the position of the Veterinary Services were adopted, the variable of geographic location would be dropped and we would witness a 52% rise in the vaccination rate. According to our survey, of 853 annual exposures on average (2560/3) where the decision was dependent upon clinical judgement, in 268 cases (30%) the decision not to vaccinate was based upon the exposure occurring in an area, which was regarded as rabies free. Should we not take into account the area in which the exposure took place, and consider

all areas at equal risk for rabies, we would have vaccinated an additional 585 persons or 3.1 times as many persons. Extrapolating these estimates to the country at large would lead an additional 5850 person receiving vaccine per year at a cost of 2.6 million dollars. This information contributed to the decision to retain the use of rabies enzootic areas in the updated guidelines. The definition of areas contains elements of time and geography and is operationally defined as an area in which the Ministry of Agriculture has identified animal rabies in the past 2 years and in adjacent areas according to the judgement of the public health physician in the light of the circumstances.

Variables not included in the guidelines

(i) We found that the physician's decision was associated with the increasing age of the exposed person (for age group 15–44 and 45–64 years ORs were similar (1.8) with 95% CI 1.21–2.58 and 1.16–2.89, respectively).
(ii) Soldiers were more likely to be vaccinated than civilians (OR = 1.9; 95% CI 1.38–2.62). The association between young age and the likelihood of contact with animals along with the locations in which the soldiers serve (non-urban and remote) as well as the absence of adequate veterinary services to enable quarantine all serve to increase the likelihood of exposures in soldiers requiring treatment. One may take into account the areas where many of the soldiers are based are rabies enzootic and the possibility of exposure to wild animals high.

Discussion

Our analysis has shown a very high level of compliance with the guidelines among public health physicians who are responsible for rabies prevention (observed agreement as 0.984 and Kappa coefficient as 0.803). We believe that this result supports the prevention policy in Israel of a sole decision taker who has experience and expertise in rabies prevention as opposed to other countries where all physicians are entitled to decide about rabies prevention.

Few audits that examine the quality of decisions regarding rabies prevention have been published. Conti[3] examined 160 decisions of post-exposure prophylaxis that were made in Florida between 1997 and 1998. Most of the exposures were from household pets. The researchers concluded that in one-fourth of the cases there was no justification for treatment. Their recommendations to prevent unnecessary treatment with the potential for iatrogenic complications and unnecessary costs were to establish a system for professional feedback for community physicians. Haryana's (2000) survey of physicians' knowledge[4] found significant variance in the level of knowledge of human rabies and preventive treatment.[4] A 1994 survey conducted in Kentucky demonstrated that the majority of persons receiving post-exposure prophylaxis following household pet exposure received unnecessary treatment.[5] In the light of the absence of rabies in the area during the period when the decisions were made, the animal could have been either quarantined or examined. The researchers concluded that had the guidelines been rigorously applied the majority of persons would not have been vaccinated. In the same year as that of the survey a mass exposure to a kitten in a pet store in Concord, New Hampshire, was reported.[6] Hundreds of exposed persons were interviewed by telephone and 665 persons received post-exposure prophylaxis. These researchers found no justification for vaccination in most of those cases because the exposure was not one at risk for rabies transmission. The total cost of the mass treatment was 1.1 million dollars.[6]

We found a single report, which conducted a serious audit of decisions similar to ours.[7] Moran[7] examined compliance of emergency room physicians to the Advisory Committee on Immunization practices (ACIP) guidelines. Their audit differs from ours in two important ways: the organization of services and the sample size. In Israel public health physicians in the health offices bear sole responsibility for decisions regarding the necessity of post-exposure prophylaxis. Relegating this responsibility to just a handful of physicians permits a degree of expertise, which would otherwise be impossible. Our audit included 5037 entries over the course of 3 years. Moran examined less than half this number of decisions that were made over the course of 2 years. Our level of compliance with the guidelines was 98.4% as opposed to the 91.5% level reported by Moran (our Kappa coefficient was 0.830).

Our rate of unnecessary treatment was lower than that reported in the US study (1% as opposed to 40%) whereas our rate of missed treatment was ostensibly higher (13.3% versus 6.3%). As we noted above, this high rate of missed treatment was found upon further examination to be due to misclassification and was recalculated to be only 3.7%.

Using a computerized database for post-exposure prophylaxis decisions permits quality audit as well as analysis of the composite clinical judgement used to make the decisions in order to adjust the guidelines upon which these decisions are based. The Israeli experience of limiting the number of physicians who decide upon the need for post-exposure prophylaxis probably makes economic sense.

Acknowledgements

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Conflicts of interest

The authors of this article hereby declare that they have no conflict of interests related to this paper and that since the analysis of clinical data is population based rather then an individual one, it is unlikely that this paper will bear in any way a risk of breach of privacy. We also wish to clarify that there was no involvement of the indirect funding source (Ministry of Health) in the research.

Key points

- Relegating the responsibility for rabies prevention to just a handful of physicians permits a degree of expertise, which would otherwise be impossible.
- The Israeli level of compliance with the guidelines was 98.4% as opposed to lower levels of compliance as reported by similar works in the literature.
- Limiting the number of physicians who decide upon the need for post-exposure prophylaxis probably makes economic sense.
- Measuring relative influence of different variables on the decision to vaccinate have shown that : type of injures, type of animal and geographic location (rabies enzootic or not) are determinant variables in final decision making.
- Determinant variables should be, therefore, carefully included and defined in any rabies prevention guidelines.

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