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Incidence and forecasting of animal bites and trends in post-exposure prophylaxis (PEP) consumption in East Azerbaijan province

Bairam Mirzaei[1], Leila Doshmangir[1,2], Roghayeh Khabiri[1], Hossein Teimouri[3], Alireza Razzaghi[4]*, Vladimir Sergeevich Gordeev[5]

[1]Department of Health Policy and Management, Tabriz Health Services Management Research Center, School of Management and Medical Informatics, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Social Determinants of Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Medical Microbiology Research Center, Qazvin University of Medical Sciences, Qazvin, Iran
[4]Social Determinants of Health Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran
[5]Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

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Abstract

Rabies is one of the most common human and animal diseases threatening public health, and annually, many people in different parts of the world are treated for rabies. In Iran, challenges arise in obtaining rabies post-exposure prophylaxis (PEP), as these treatments are often imported, and there are problems with the procurement of vaccines and immunoglobulin. Thus, it is necessary to study the incidence of animal bites to inform PEP supply planning. This study analyzed data from 68,682 cases of animal bites registered at rabies prophylaxis centers in Tabriz, Iran. The cumulative incidence of animal bites and the rates of PEP consumption over the study years were calculated. The number of animal bites was forecasted using the Box-Jenkins time series model. From 2015 to 2022, the average annual incidence of animal bites in the covered population was 232 per 100,000 people. During this same period, the average yearly usage of rabies vaccines was 24,853 doses, totaling 1,136,238 units of antirabies immunoglobulin. The mean age of those bitten by an animal was 31.8 years (standard deviation = 17.24), with 85% being male. The majority of bites were from dogs (80%), and 58% of the victims resided in rural areas. The average forecasted annual incidence rates for 2023 and 2024 are projected to be 289 and 311 per 100,000 people, respectively. The increasing trend in animal bites necessitates the urgent need for public health interventions, including expanding vaccine supply and implementing targeted education programs to mitigate the risk and financial burden of rabies in East Azerbaijan Province. In addition, managing stray animals, especially dogs, and strengthening the healthcare system and immunization program are essential to reducing the incidence of rabies.

Introduction

Understanding and forecasting the needs for diagnoses, treatment, and consumption of vaccines over time are critical issues for disease control. Rabies is one of

*Corresponding author: alirezarazzaghi_21@yahoo.com
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the most common human and animal diseases that threaten the health of many people every year. Rabies is an infectious disease transmitted between humans and warm-blooded animals (1). The rabies virus, a neurotropic member of the Rhabdoviridae family belonging to the genus Lyssavirus, is the causative agent of rabies. Transmission of the disease (except in rare and exceptional cases) usually comes from an infected animal or through bites or by infection of wounds with the rabies virus present in the saliva of a biting animal. In rare cases, the disease can be transmitted by other means, such as inhalation, corneal transplantation, or scratches caused by saliva contaminated with the virus (1, 2).

There are approximately 59,000 human rabies deaths annually worldwide, mainly in Asia and Africa (3). Every year, more than 15 million people in different parts of the world are treated for rabies due to animal bites to prevent rabies, and more than 29 million people worldwide receive human rabies vaccine (4). Current zoonotic disease outbreaks, like the monkeypox outbreak, highlight the importance of vital public health initiatives that incorporate immunizations and other preventative measures (5). Rabies is one of the most critical zoonotic diseases in Iran due to its high fatality rate in both humans and animals. It is particularly prevalent in wildlife and frequently affects ruminants, dogs, and cats that come into close contact with humans (6). Both innate and adaptive immune responses play critical roles in managing zoonotic diseases like rabies, as seen in immune responses to other zoonotic viruses (7). In rabies, while the innate immune response provides early defense, the adaptive immune system, especially the production of neutralizing antibodies, is crucial for preventing the disease's progression and ensuring viral clearance (8).

After the onset of symptoms of the disease, humans and animals cannot be treated, and the patient is doomed to die. Hence, the increasing population of stray dogs and the increasing number of animal bites and rabies in some provinces are serious public health concerns and remind us of the need to pay more attention to disease control (9). The increase in human bites inevitably leads to a considerable financial burden on the country's health system through direct medical expenses, rabies control programs, and treatment for the disease (including the purchase of serum and rabies vaccine) (1, 10). Iran depends on imports of post-exposure prophylaxis (PEP) from India and France. Due to existing fiscal sanctions, there are problems purchasing vaccines and immunoglobulin in Iran (11). Hence, understanding and forecasting a pattern of rabies vaccine and immunoglobulin consumption is essential for Iranian disease control.

This study was conducted in the East Azerbaijan province, northwest of Iran. The study sought to address three goals: 1) calculate the annual incidence of animal bites in health centers of the cities covered by Tabriz University of Medical Sciences in 2015-2022, 2) Report the consumption of rabies vaccine and immunoglobulin doses in health centers of the cities covered by Tabriz University of Medical Sciences in 2015–2020, and 3) forecast the number of animal bites in the cities covered by Tabriz University of Medical Sciences in 2023-2024. The results of this study can be used by health policymakers for disease control planning and estimating future needs for rabies PEP supply, based on the current trends in PEP consumption and the forecasted incidence of animal bites. Results will also generate evidence to justify the need to launch domestic vaccine production.

Material and Methods

This longitudinal study is based on data regarding rabies from the Tabriz University of Medical Sciences health centers. We extracted data on animal bites and consumption of rabies PEP by sex, age, and place of residence (urban or rural) from 2015 to 2020 from the animal bite portal of Tabriz University of Medical Sciences, as well as the animal bite registration offices of the health centers of the cities covered by the University of

Medical Sciences. Reporting any person bitten by an animal to the city health center immediately is mandatory. Every city has at least one rabies treatment center from comprehensive health centers. All rabies prevention treatment centers are introduced in the portal system, and all have access to it. Animal bite cases are immediately registered in the portal system, and different steps are taken. Due to the unavailability of individual-level data for the years 2021 and 2022, data on animal bites and PEP usage were limited to the period from 2015 to 2020. In contrast, population data were updated through 2022 to ensure accurate calculations for incidence rates and future forecasts.

Statistical analysis

Using descriptive statistics in IBM SPSS Statistics version 20, we calculated the monthly and annual incidence of animal bites for the years 2015 to 2022, and the rates of PEP consumption during 2015 to 2020. We used the at-risk population as the denominator. The at-risk population includes all individuals of various ages who may potentially be bitten by an animal. Therefore, the population at risk consists of the total population of the Province. The incidence rate is equal to the number of new cases divided by the population at risk (12). The population of the province was obtained from census data provided by the Statistical Organization of Iran (13). The normality of data was assessed using the Kolmogorov-Smirnov test, and the findings indicated the establishment of normality in the data (p-value > 0.05). We then used the time series analyses (Box-Jenkins method) (14) to forecast the number of animal bites for the coming months, using a monthly time lag. The Box-Jenkins seeks to find the values of the parameters autocorrelation (Auto Regressive; AR) and Moving Average (MA) and operates using ARMA and ARIMA models. The model was constructed in four steps: model detection, parameter estimation, model fit evaluation, and prediction. Auto-correlation function (ACF) and partial auto-correlation function (PACF) functions and differentiating the data into monthly and seasonal logs were used to evaluate the data's stativity and supply. After estimating the model parameters, the detected models were assessed for accuracy. For this purpose, the data were divided into two parts: training data and test data, and then the model was evaluated based on the least squares of error. After model confirmation, the identified model was used for prediction. Analyses were performed using Minitab statistical software version 16.

Results

Eight years of data (2015-2022) contained frequency data for 68,682 cases of animal bites registered at rabies prophylaxis centers affiliated with the public health deputy of Tabriz University of Medical Sciences, Tabriz, Iran. The mean age of those bitten by an animal was 31.8 years (standard deviation = 17.24). Of them, 85.0% were male, and most were bitten by a dog (80.0%). 96.6% of bitten persons had Iranian nationality, and over half (58%) resided in rural areas. Most (62.6%) of the people bitten were freelancers, workers, and farmers (Table 1). The average incidence of animal bites in the covered population for 2015-2022 was 232 per 100,000 people (Figure 1). Over eight years, there was an overall upward trend in the incidence rate of animal bites, disrupted in 2022. In East Azerbaijan province, Kaleybar County had the highest average incidence rate at 756 cases per 100,000), while Tabriz County had the lowest 8-year average incidence rate at 98 cases per 100,000 for 2015 to 2022 (see Figure 2). Rabies vaccine consumption ranged from 25,532 doses in 2015 to 28,875 doses in 2019, with an average 6-year consumption of 24,853 doses. The consumption peak coincided with the highest incidence of animal bites in 2019. Rabies immunoglobulin consumption ranged from 1,295,800 units in 2015 to 808,540 units in 2019, with an average 6-year usage of 1,136,238 units. The peak in rabies immunoglobulin consumption was observed in 2018 (1,476,476

units), but it declined afterward, reaching its lowest level in 2020 (808,540 units). The total number of animal bites during the years studied was 62,443. The average forecast value for animal bites was 892 monthly cases in 2023 and 969 monthly cases in 2024 (Figures 3 and 4). Our predictions suggest that the expected number of animal bites in 2023 will be 10,706 cases per year, increasing to 11,623 cases annually in 2024. Regarding seasonality, the highest number of animal bites (1078 cases) is anticipated in June 2024, while the lowest (780 cases) is expected in February 2024 (Figure 4). The trends for rabies vaccine and immunoglobulin consumption are shown in Figure 5. In order to verify the accuracy of the model, forecasts for 2021 and 2022 were obtained and compared with actual data, which demonstrated the model's appropriateness. The forecasted and actual values of animal bites during the forecasted period are presented in Table 2.

Table 1. Distribution of animal bites by gender, nationality, area, job, and animal type (based on data from 2015 to 2020)

Characteristics	Sub-Categories	N	Percent
Gender	Male	41,408	84.5
	Female	7,452	15.2
	Unknown	145	0.3
Nationality	Iranian	48,933	99.8
	Other nationalities	72	0.2
Area	Rural	28525	58.1
	Urban	16032	32.6
	Nomads	269	0.5
	Suburbs	118	0.2
	Unknown	4334	8.6
Job	Freelancer (worker, farmer, livestock)	30654	62.6
	Housewife	4759	9.7
	Government employee, Retired	2710	5.4
	Teacher, student	7910	16..2
	Other	2241	4.6
	Unknown	731	1.5
Animal type	Dog	39222	80
	Cat	7660	15.6
	Donkey, Mule	422	0.9
	Cow, Cattle	209	0.5
	Horse	200	0.4
	Others	1292	2.6
Total	-	49005	100

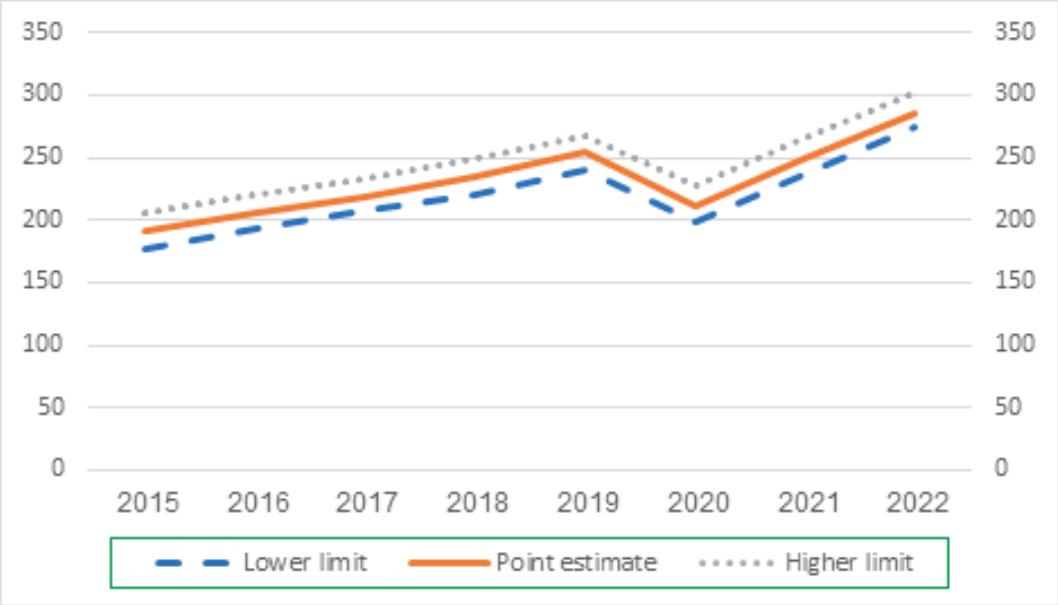

Fig1. Incidence rate with a 95% Confidence Interval of animal bites per 100000 population in the years 2015-2022.

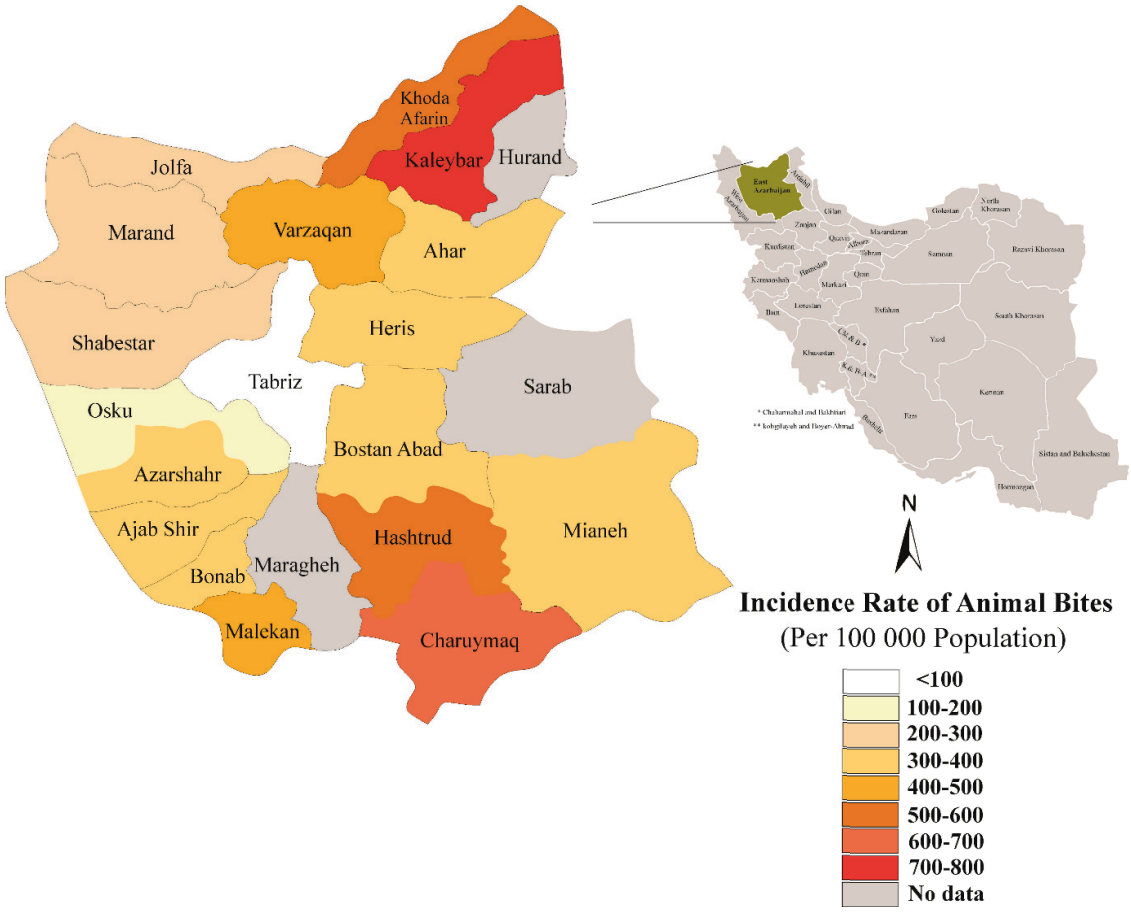

Fig 2. Animal bite incidence rates in East Azerbaijan counties (2015–2022).

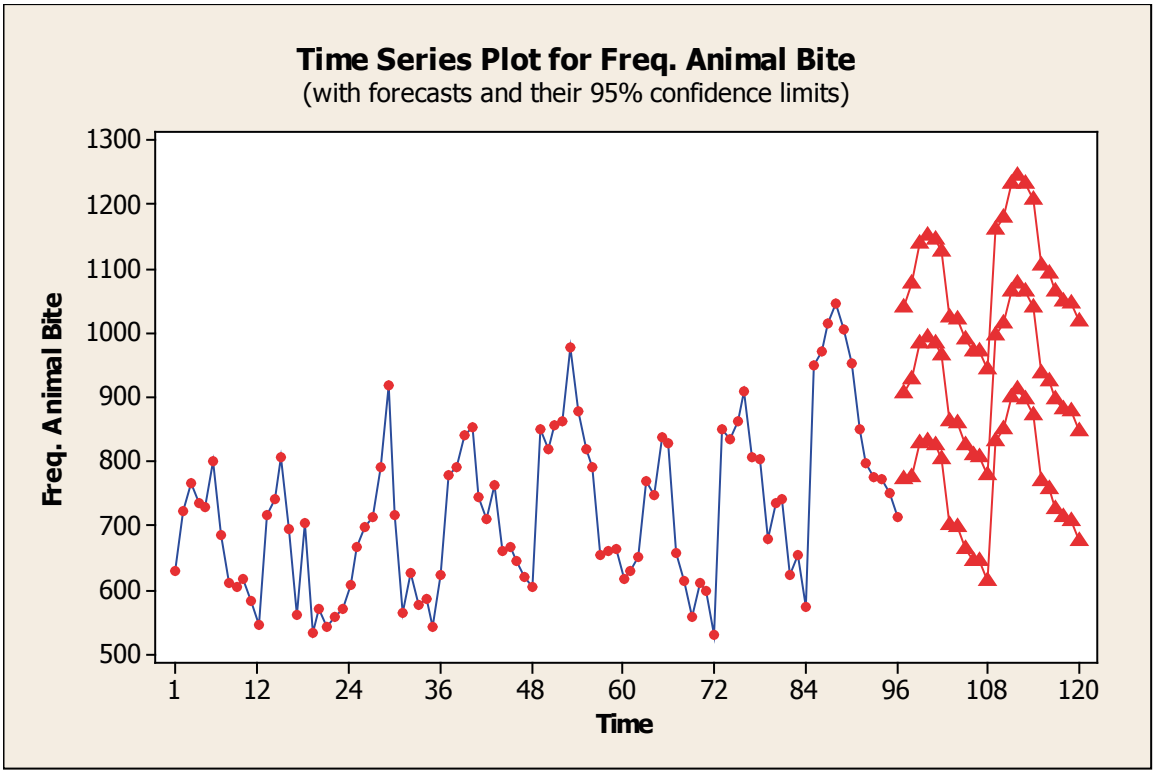

Fig 3. Prediction of monthly animal bite cases for 2023 and 2024 with a 95% confidence interval (The vertical axis of the graph represents the number of animal bites and the horizontal axis represents the month studied, which is displayed from the first month to the 120th month).

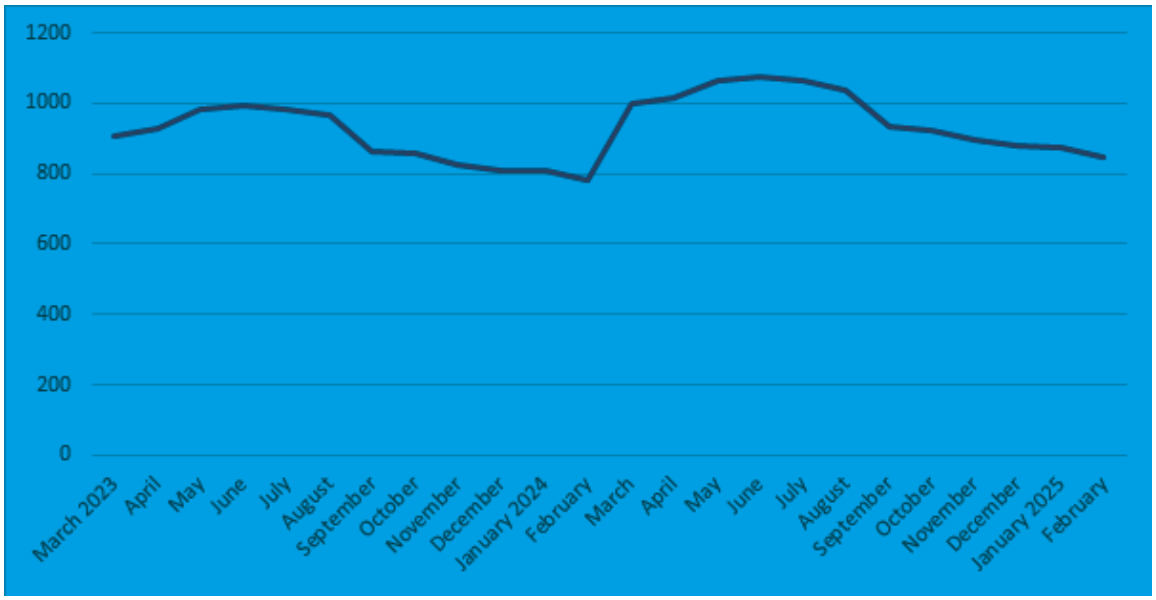

Fig 4. Predicting the monthly animal bites with the highest and lowest bites for the years 2023 and 2024.

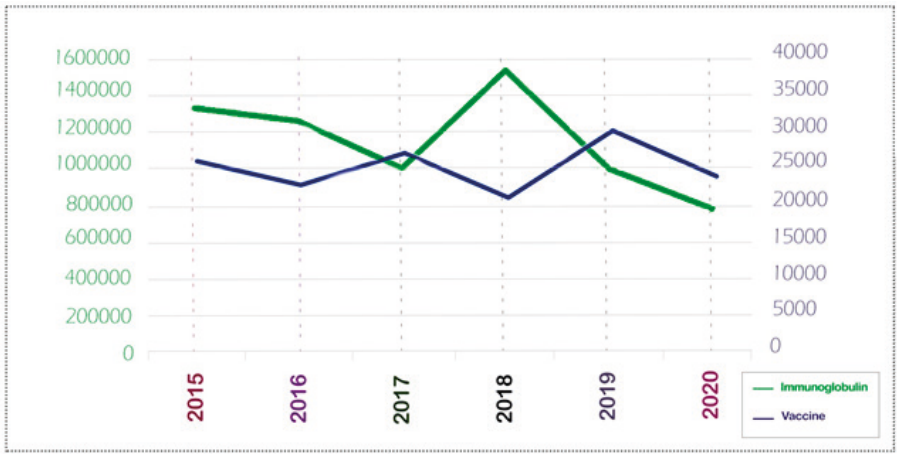

Fig 5. The trend of rabies vaccine and immunoglobulin consumption in all health centers of the Tabriz University of Medical Sciences.

Table 2. The forecasted and actual values of animal bites during the forecasted period.

		Forecasts for the years 2021 and 2022			
		95% Limits			
Year	**Month**	**Forecast**	**95% Limits**	**Actual**	**Error (%)**
2021	1	864	830-899	849	1.77
	2	903	865-932	836	8.01
	3	905	882-932	864	4.75
	4	896	858-927	909	-1.43
	5	867	839-899	805	7.7
	6	780	751-812	802	-2.74
	7	769	732-801	680	13.09
	8	731	795- 762	736	-0.68
	9	720	698-752	740	-2.7
	10	711	668-744	624	13.94
	11	702	632-725	654	7.34
	12	669	632-725	573	16.75
2022	1	877	830-923	949	-7.59
	2	934	909-979	972	-3.91
	3	933	909-945	1016	-8.17
	4	944	902-979	1047	-9.84
	5	919	880-955	1007	-8.74
	6	818	755-856	954	-14.26
	7	801	781-839	851	-5.88
	8	761	726-800	798	-4.64
	9	762	722-803	775	-1.68
	10	753	726-800	773	-2.59
	11	734	702-780	751	-2.26
	12	780	729-831	712	9.55

Discussion

The results of the current study indicate an increase in the incidence of animal bites from 193 cases per 100,000 people in 2015 to 256 cases in 2019 in East Azerbaijan Province. Although there has been a decrease in this rate from 2019 to 2020, this decline can be justified considering the constraints present at the onset of the COVID-19 pandemic. After that, the results show an increasing trend in the years 2021 and 2022. A study conducted in India also showed an increasing trend in animal bites from 2010 to 2019. Still, with the implementation of restrictions related to the COVID-19 pandemic in 2020, this trend faced a decline. However, after lifting restrictions, the upward trend resumed (15). The rising trend of animal bites in this study aligns with the findings of other studies conducted in Iran during our study period in cities such as Najafabad (16), Shirvan (17), Nahavand (18), Neyshabur (19), Rostam (20), and provinces of Yazd (21), Golestan (22), and Fars (23).

According to the findings of the present research, the average incidence of animal bites in East Azerbaijan Province has been 232 cases per 100,000 people, which is lower than the national average (253 per 100,000 population), based on reports published on the portal of the Center for Disease Management in 2020. These rates are also lower than those reported by Bay et al., where the incidence of animal bites in Golestan province was 652 cases per 100,000 people in 2019–2020 (24). The lower incidence of animal bites in East Azerbaijan compared to the national average may be attributed to various factors, including geographical, socio-cultural, economic, and health interventions. The region's mountainous terrain and colder climate may reduce the number of stray and wild animals (25). Limited access to food sources, and shelter, and the harsh winter conditions in these areas significantly reduce their populations. Additionally, rugged mountainous terrain creates natural barriers that limit the movement of animals like stray dogs, reducing their range and interaction with humans (25). As a result, the frequency of human-animal encounters is decreased, leading to a lower incidence of bites. Nevertheless, our results are higher than the findings reported by Dehghani et al., who documented an incidence rate of animal bites in Yazd Province from 2013 to 2017 as 168.4 per 100,000 (21). The average incidence of animal bites in East Azerbaijan province is lower than 20 studies in Iran and higher than 13 studies based on the meta-analysis conducted by Shakerian et al. (26).

The average age of those bitten by animals was 31.8 years, consistent with studies by Qasemi et al., Amiri et al., and Karami et al., who reported average ages of 31.5, 31.28, and 31.3 years, respectively (16, 20, 27). The average age in the meta-analysis study conducted on recent data in Iran was also reported as 29.97 (26). In the Esmaeilzadeh study, the highest incidence of animal bites was observed in the age group of 21–30 years (28). Since the average age of individuals bitten by animals is close to the average age of pet owners, this may be one of the reasons for the youthfulness of animal bite victims (29). Additionally, young individuals are more involved in feeding animals and exhibit more aggressive behavior toward them.

We found that about 85% of those bitten were males, and approximately 58% were rural residents. This is also in line with the Amiri et al. study, which reported 88% of bite victims were male (16). Men's higher incidence of animal bites can be attributed to their increased presence in outdoor environments, more excellent daring in facing animals, and occupational conditions. The higher incidence of animal bites in rural areas is consistent with the results of studies conducted in the cities of Nahavand, Rostam, Shirvan, and Babol, which reported percentages of 67.4%, 78.2%, 73.4%, and 65.9%, respectively (17, 18, 20, 30). This contrasts the results of studies conducted in Lar, Yazd, and Najafabad, which indicate a higher percentage of animal bites in urban areas, conflicting with our study findings (16, 21, 23). Additionally, the results of a meta-analysis study conducted in Iran also reported equality in the incidence of animal bites between urban and rural areas (26). The differences

in the accuracy of recording animal bite results in rural and urban areas, urban development, rural population, the prevalence of pet ownership in urban, and other factors in different regions contribute to variations in the incidence of animal bites between urban and rural areas in various areas.

Overall, our findings showed that residents of rural areas and people with freelance farming jobs reported higher rates of animal bites. Moreover, most bites were dog bites (80.0%), which is in line with studies by Bahonar et al. (31) and Bokaei et al. (32), which also reported the highest number of bites being attributed to dogs, arguing they are among the most aggressive animals (31-33). Considering that 80% of animal bites are caused by dogs, managing and controlling the reproductive of stray dogs, providing education and information regarding domestic dog vaccination programs, and offering training in appropriate behavioral skills when dealing with dogs can be effective in reducing the incidence of animal bites and associated risks.

Several risk factors contribute to the incidence of animal bites, as highlighted in our study and other literature (16, 20). Individual factors such as being male and younger age were significant, as men often engage in outdoor activities and occupations with higher exposure to animals. Rural residency is another critical factor due to proximity to stray or wild animals and occupations like farming (34). Among socio-environmental factors, the presence of stray dogs is a major risk, emphasizing the need for better control measures. Migration of wild animals to human-populated areas due to habitat destruction can also increase human-animal encounters (35). Additionally, cultural and economic disparities impact awareness, vaccination rates, and access to preventive measures (36). Addressing these risk factors through education, vaccination programs, and stray dog management can effectively reduce animal bites and rabies transmission.

Our forecasting suggested that the average expected incidence of animal bites would be 300 per 100,000 people between 2023 and 2024. The forecasting data showed an increasing trend in animal bites in the coming years, with average of 289 and 311 bites per 100,000 people in 2023 and 2024, respectively. In order to verify the accuracy of the model, forecasts for 2021 and 2022 were obtained and compared with actual data, demonstrating the model's reliability. Similarly, Punyapornwithaya et al. conducted a study in Thailand forecasting the incidence of animal bites from 2023 to 2025 (37). Their findings also indicated an increasing trend, which aligns with the projections from our model.

As expected, the trends in the use of rabies PEP for the years 2015-2020 corresponded to the incidence of animal bites, and the fluctuation observed in the process of rabies PEP was most likely due to cross-sectional deficiency of vaccine and serum. Also, announcing the approvals of the National Committee for the Prevention and Control of Rabies on April 20, 2019, and changing the method of injecting the vaccine from intramuscular to intradermal could affect the consumption trends in the rabies vaccine.

Considering the population of East Azerbaijan Province (approximately 4 million people) and the average PEP cost of 148.04 USD per person reported in prior studies in Iran (38), we estimate that the financial burden of PEP for the predicted incidence of animal bites in the province would be approximately 1.78 million USD per year. This calculation is based on the forecasted animal bite incidence rate of 300 per 100,000 population. Such financial implications highlight the need for effective prevention strategies to reduce the number of animal bites and optimize the allocation of PEP resources. Considering the "Zero by 30" global strategic program (39) aiming to prevent human deaths from rabies transmitted by dogs by 2030, conducting provincial studies to monitor trends in animal bites can significantly contribute to achieving this goal.

Limitations

One of the limitations of this study is that one

should be cautious in generalizing the findings related to this province to other provinces. It is suggested that a similar study be conducted for each of the provinces so that while creating an epidemiological picture of animal bites, the findings can be compared with each other. Another limitation of the present study was the lack of access to individual data for the years 2021 and 2022. Therefore, analyses related to vaccines and immunoglobulins were conducted for the period from 2015 to 2020.

Conclusion

Based on the findings of this study, the incidence of animal bites in the population of East Azerbaijan Province is rising, despite a downward trend observed during COVID-19 pandemic. Overall, during the last decade, the incidence of animal bites in the East Azerbaijan Province was lower than in the rest of the country, potentially indicating that the existing system is functioning properly. However, projected trends for the coming years suggest an increase in animal bites, which would likely lead to a rise in the use of vaccines and immunoglobulins, particularly during warmer seasons. Given the existing and projected prevalence of animal bites, the considerable financial burden associated with rabies, and dependence on imported PEP, we urge policymakers to invest more in rabies control programs and consider initiating the production of vaccines locally. We also suggest that a more systematic approach and funding are needed for preventative measures, such as training at-risk groups for animal bites, especially residents of rural areas, freelance working in farming, better management and organization of stray animals such as dogs, and strengthening the care system and immunization program.

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Conflict of interest

The authors declare that they have no competing interests.

Ethical approval

This study was approved by the Research Ethics Committee of Tabriz University of Medical Sciences under the No IR.TBZMED.REC.1400.975. All data was anonymized entirely before access. This research was conducted regarding the ethical principles, national norms, and standards for conducting medical research in Iran.

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