**Forecasting Dog-Mediated Human Rabies Deaths in Bangladesh by 2030 through Time Series Model Analysis**

**Abstract**

To meet the global goal of eliminating human deaths from dog-mediated rabies by 2030 (Zero by 30), models of rabies virus transmission are imperative and have the potential to inform control efforts as countries continue to work toward elimination. Considering public health importance and disease dynamics, rabies forecasting may help in intervention strategies as Bangladesh is marching towards the shared goal of Zero by 30. Drawing from multiple datasets, including patient immunization record books of the Infectious Diseases Hospital, and the MDV database of the Directorate General of Health Services of Bangladesh, we used time-series forecasting models, the auto-regressive integrated moving average (ARIMA) and the ARIMA model with explanatory factors (ARIMAX) to predict human rabies cases from 2023 to 2030 where anti-rabies vaccine (ARV) and mass dog vaccination (MDV) were considered as explanatory variables. We identified a continuous declining trend between observed and predicted human rabies cases in Bangladesh from 2023 to 2030 using the models. The models predict that the current rate/face of MDV and ARV could be effective in declining human rabies cases but is not enough to achieve zero rabies cases by 2020, however, increasing MDV by a certain percentage could be led to achieving the global goal of Zero by 30. Providing evidence per the Zero by 30 plan will directly promote commitment to eliminating canine rabies while providing adequate resources for anti-rabies activities.

**Introduction**

Rabies is a zoonotic viral disease primarily transmitted to humans through the bite of infected dogs, kills tens of thousands of people each year, and has the highest case fatality rate of any infectious disease1,2. More than 15 million human exposures to rabies occur annually, primarily in Asia and Sub-Saharan Africa, causing 3.7 million Disability-Adjusted Life Years (DALYs) and an enormous economic loss of USD 8.6 billion1. Though the World Health Organization (WHO), the World Organization for Animal Health (OIE), and the Food and Agriculture Organization of the United Nations (FAO) have set a goal for the elimination of dog-mediated human rabies globally by 2030, there are few instances of extensive dog vaccination programs that have successfully achieved this goal outside of Africa and Asia3.

Bangladesh has a high public health importance for rabies and ranks third among rabies-endemic countries in the world in terms of human rabies deaths, about 96% of which are attributable to dogs4,5. The Government of Bangladesh (GoB) is taking all necessary actions through the National Rabies Control Programme launched in 2011 to direct the effective progress of rabies control to achieve goal Zero by 306. GoB was instrumental in driving the program forward by implementing strategies, including advocacy, communication, and social mobilization, modern treatment for dog bites, mass dog vaccination (MDV), and dog population management7. This program reduced the number of deaths from human rabies by approximately 50 percent in recent years in Bangladesh8.

The early administration of human post-exposure prophylaxis (PEP) can prevent rabies-related death but treating people (a dead-end host) after being bitten has little effect on the incidence of rabies in the canine reservoir population, leaving additional members of the community at risk of contracting the infection9. For over a century, it has been known that MDV may successfully eliminate rabies from the reservoir animal population, preventing virus transmission to humans and eliminating dog-mediated rabies in many regions9,10. The current rabies control program emphasizes the significance of attaining zoonotic disease prevention and control by considering human, animal, and environmental factors in a One Health approach11. MDV is an effective method to stop dog-to-dog or dog-to-human transmissions of rabies viruses. If annual pulse vaccination campaigns achieve over 70% coverage, rabies incidence in dogs is likely to be dramatically reduced and regional elimination is possible if this coverage is sustained over several years12,13. Because of the particular ecology of dogs in Bangladesh, where millions of dogs roam freely and are difficult to reach4, rabies is thought to be particularly challenging to eliminate, as evidenced by the complete paucity of examples of rabies elimination in any region of Bangladesh6.

It is crucial to evaluate the available data regularly at both the regional and global levels to adequately track the advancement toward the eventual goal of Zero by 30. The time series approach is commonly used to analyze a series of data points that are ordered in time and used for dealing with data that may include trends and seasonality14. Thus, time series analysis may be appropriate for developing a predictive model for rabies in humans14. ​Disease dynamics models are also a potent tool in the armory of attempts to prevent and control the disease that can be used to predict critical epidemiological characteristics, set control targets, and inform policy15.​

Modeling can also reveal counter-intuitive results that appear as interventions are put into practice, as well as endgame challenges when disproportionate resources are required to reach the final mile of elimination16. Given the global goal of eliminating human deaths from dog-mediated rabies by 2030, models of rabies virus transmission have the potential to inform control efforts as countries continue to work toward elimination. In Bangladesh, there is a lack of information on rabies trends and forecasting models as we march towards the shared goal of Zero by 30. The current study sought to investigate the trends of human rabies and to predict human rabies cases of anti-rabies vaccine (ARV) and MDV in Bangladesh. This model is expected to be useful for planning interventions and controlling rabies in humans in Bangladesh and other rabies-endemic countries with similar socioeconomic conditions.

**Results**

To predict dog-mediated human rabies deaths in Bangladesh from 2023 to 2032, we used several time-series forecasting models using reported cases in the near past, with MDV and ARV took into account as explanatory variables. Currently, few if any detailed studies into the forecasting of human rabies in Bangladesh have been published.

**MDV, PEP, and human rabies**

We subjected 12 years (2011–2022) of MDV data maintained at the DGHS of Bangladesh. During this period, MDV was scaled up for at least one round (conduct MDV at least once a year) in all 64 districts of the country, and three rounds of MDV were scaled up in whole two districts, namely, Gaibandha and Sirajganj and three other areas, namely, Cox’s Bazar district municipality, Satkhira Sadar sub-district, and Sreepur sub-district of Bangladesh. From 2011 onward, an upward trend of MDV was found, and the highest number of dogs was vaccinated in 2019 (n = 625,208) (Fig. 1, Supplementary Fig. 1). Under the MDV campaign, out of an estimated 3,096,086 dogs, an estimated 81% (95% CI: 81.36-81.44) have been vaccinated. The average dog population density in Bangladesh is 12 dog/km2 (95% CI 2.3, 22.2), and the human: dog ratio is 97 (95% CI 51, 179) (Fig. 2). From 2011 to 2022, a total of 257,3827 doses of ARV used to manage the animal bite cases at NRPCC, BITID and DRPCCs of Bangladesh with an average of 214,485 doses ARV used each year (Fig. 3). In total, 745 cases of human rabies were reported in Bangladesh between 2011 and 2022, with an average of five cases recorded monthly (0.004 cases per 100,000 population) and sixty-two cases recorded annually (0.04 cases per 100,000 population). The highest number of cases was seen in 2018 (20 cases, 5.5 cases per 10 million population). The districts in the middle of the country saw the highest number of cases (Fig. 4). We also found an increasing trend in ARV utilization and dog vaccination and a decreasing trend of human rabies cases in Bangladesh from 2011–2022 (Supplementary Fig. 1).

In Spearman rank correlation coefficients, we found an association between animal bites incidence and ARV utilization (Figure 1) where dog bites (r = 0.865, p<0.05), bites with other animals (r = 0.909, p<0.05), and total bites (r = 0.996, p<0.05) were strong and positively correlated with the ARV (Supplementary Fig. 1).

Two main clusters were revealed by the dendrogram (Fig. 5). The first strong cluster is displayed by the left main branch. This cluster exposed strong to moderate positive correlations between three variables (dog rabies vaccination, human rabies vaccination, and the year in which the vaccinations occurred). We have found strong positive correlations between years of vaccination and human vaccine. Moderate positive correlations have been found between the human rabies vaccine and the dog rabies vaccine. Dog rabies vaccination and year of vaccination show weak positive correlations. The next main cluster is the right main branch, in which there were moderate negative correlations for mortality. Mortality and human rabies vaccination have a moderate negative correlation. Year of vaccination and dog rabies vaccinations were found to have a weaker negative correlation.

**Phylogenetic tree**

Coordinated rabies control efforts in the area continue to be hampered by a lack of knowledge regarding the phylogenetic relationships between the rabies virus in Bangladesh and viruses in other countries. To explain its epidemiologic relationships, origin, and transmission dynamics, a phylogenetic analysis was performed to characterize the rabies virus circulating in Bangladesh and determine its relationship with viruses in neighboring countries. The phylogenetic tree revealed that the rabies viruses in Bangladesh are members of the Arctic/Arctic-like virus, also called Arctic-like-1. N gene sequences from rabies viruses in Bhutan and Bangladesh show a strong link, suggesting that they shared an ancestor and developed into distinct strains. The same lineage circulated in other countries in this region, including India, Nepal, Pakistan, and Afghanistan, as shown by the tree samples clustered separately from sequences generated in other studies (Fig. 6).

**Time-Series Analysis**

With R2, RMSE, and MAE values of 86.75%, 86.87%, 71.75%, 14.89, 14.87, and 15.08, and 12.50, 12.31, and 12.58, respectively, we found a continuous decreasing trend between observed and predicted rabies cases in three models (Table 1). In terms of accuracy, the ARIMA model performed better than the ARIMAX model (with better R2, RMSE, and MAE values). In comparison to the ARIMAX model with sensitivity, the ARIMAX model without sensitivity has a greater coefficient of determination and fewer errors. However, all these three models indicate a considerable decrease in rabies cases during the following ten years (Table 1) (Fig. 7).

Table 1: The summary of the Auto-Regressive Integrated Moving Average (ARIMA) and Auto-Regressive Integrated Moving Average with explanatory variable (ARIMAX) model.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **RMSE** | **MAE** | **R2** |
| **ARIMA (1,2,1)** | 14.89 | 12.50 | 86.75% |
| **ARIMAX (1,2,1)** | 14.87 | 12.31 | 86.87% |
| **ARIMAX (1,2,1) with a 50% increase in MDV** | 15.08 | 12.58 | 71.75% |

**Table 2: A forecasting of annual rabies cases in Bangladesh for the period of 2023-2030 using ARIMA and ARIMAX models.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **ARIMA (1,2,1)** | **ARIMAX (1,2,1)** | **ARIMAX with a 50% increase of MDV** |
| Year | **Point forecast (95% CI)** | **Point forecast (95% CI)** | **Point forecast (95% CI)** |
| 2023 | 36 (3 to 73) | 31 (-3 to 72) | 32 (-9 to 74) |
| 2024 | 31 (-9 to 80) | 32 (-15 to 90) | 32 (-25 to 91) |
| 2025 | 26 (-25 to 86) | 37 (-26 to 112) | 36 (-38 to 111) |
| 2026 | 21 (-40 to 91) | 33 (-46 to 125) | 31 (-59 to 123) |
| 2027 | 16 (-56 to 96) | 26 (-70 to 136) | 24 (-83 to 132) |
| 2028 | 11 (-72 to 101) | 26 (-87 to 155) | 24 (-100 to 149) |
| 2029 | 6 (-88 to 105) | 21 (-112 to 169) | 18 (-124 to 160) |
| **2030** | **2 (-104 to 110)** | **8 (-149 to 172)** | **2 (-158 to 162)** |
| 2031 | 0 (-120 to 114) | 3 (-177 to 186) | 0 (-183 to 174) |
| 2032 | 0 (-136 to 118) | 0 (-206 to 202) | 0 (-208 to 187) |

According to ARIMA and ARIMAX models, Bangladesh is expected to experience 2, and 8 cases of rabies in 2030, respectively, assuming the trend of decreasing rabies cases continues. But if we raised MDV by around 50%, we could eradicate rabies by the year 2031.

**Discussion**

We investigated the trends and predicted the number of human rabies cases with respect to MDV in Bangladesh using time-series forecasting models, ARIMA and ARIMAX. To better comprehend the dynamics of the disease and assist with developing control strategies, infectious disease modeling is employed. Additionally, it might reveal how dynamics, consequently, intervention tactics may alter as management is put in place15,16. Our study shows a continuous declining trend between observed and predicted human rabies cases. In terms of accuracy, the ARIMA model performed better than the ARIMAX model whereas the ARIMAX model without sensitivity has a greater coefficient of determination and fewer errors than the ARIMAX model with sensitivity. Because of the low value of the model selection criterion, the ARIMA predictive model was found to be most appropriate for time series analysis and forecasting of rabies cases in some other studies17-19.

Based on the models, we found a considerable decrease in rabies cases during the following ten years (2023-2032).If the declining trend of rabies cases continues, Bangladesh would obtain 2, and 8 cases in the year 2030, according to ARIMA and ARIMAX models. However, if MDV could increase by about 50%, achieving zero rabies cases could be possible within the time frame. Model predictions and surveillance studies with similar socioeconomic settings showed that dog vaccination could save human lives (285) and prevent considerable human rabies exposure (6541) over a certain period20. If all public health veterinarians in endemic countries dedicated three months each year to dog rabies vaccination, the vaccination workforce could suffice to eradicate dog rabies21. Countries with vaccination coverage of 70% or higher were classified as Phase III, and it was suggested that countries vaccinate 70% of the canine population for 7 years to eliminate dog rabies1,21,22. Lack of knowledge that dogs needed rabies vaccinations and ignorance of where to find the vaccine were frequently cited as vaccination barriers23. One of the challenges to increasing the amount of MDV in Bangladesh could be budget allocation but there is a strong political commitment to eliminate dog-mediated human rabies8. It has been demonstrated that rabies prevention strategies, such as vaccination, are influenced by disease prevalence and that a simple model with intervention responses can accurately depict the host dynamics and periodicity of the disease24. Many other factors can influence the occurrence of rabies cases including literacy rate, GDP, awareness of rabies, access and availability of post-exposure vaccines, access to primary care, and primary contact related to sickness6,25,26. However, reliable data on these parameters or proxy variables are not available. Thus, we decided to keep MDV and ARV in the model as the key determinant of the occurrence of human rabies cases. After MDV was introduced in Bangladesh in 2011, the pattern of human rabies cases altered quite quickly. The annual incidence of rabies in Bangladesh has consistently decreased as a result of the combined effects of a mass awareness campaign, PEP, and MDV6.

The phylogenetic tree showed that the rabies viruses in Bangladesh are part of the Arctic/Arctic-like virus, and the N gene sequences from the rabies viruses in Bhutan and Bangladesh exhibit a significant link, indicating that they shared an ancestor before evolving into different strains. AAL2 spread into central Bangladesh 32.3 years ago (95% HPD 18.4-50.6 years) around 1978 (95% HPD range 1958-1991) where glycoprotein has three potential N-glycosylation sites influencing viral pathogenesis27. Separate lineages were also discovered in other countries in this region, including Iran, Nepal, Pakistan, and Afghanistan, according to some studies 9,27. The rabies virus's diversity may have public health consequences in Bangladesh. Given the ease with which people can travel between countries, AAL2 most likely entered Bangladesh from India rather than Bhutan.​

We observed that the average dog population density in Bangladesh is 12 dogs per km2, with a human-to-dog ratio of 97. A prior study in Bangladesh revealed 14 dogs per km2, with a human: dog ratio of 12028. The high ratio may be attributed to the abundance of edible waste on the streets, societal tolerance of stray dogs, and a lack of consistently implemented long-term birth control programs29. While Bangladesh has almost three times the benchmark number of dogs per km2 to become endemic for rabies, the threshold density for rabies persistence is only 4.5 dogs per km228,30. Bangladesh's dog population density is comparable to some other Asian30 and African countries31.

From 2011 onward, we identified an increasing trend of human ARV utilization and MDV followed by decreasing trends of human rabies cases in Bangladesh. After MDV was introduced in Bangladesh in 2011, the pattern of human rabies cases altered quite quickly6,8. In recent years, the number of human rabies fatalities has decreased by approximately 50%, and annual cases have decreased at a rate of approximately 12 per year, while the number of vaccinated dogs has grown at a rate of 3200 dogs per year6,8. The annual incidence of rabies in Bangladesh has consistently decreased as a result of the combined effects of a mass awareness campaign, PEP, and MDV. All 64 of Bangladesh's districts now have at least one facility that offers PEP and wound care to people who have been bitten by animals6. More than 250,000 people have received this care from skilled nurses and doctors without having to pay anything out of pocket. The rise of MDV has confirmed the potential for successful rabies elimination strategies to result from a multi-sectoral, One Health strategy combining innovation, capacity-building, and broad implementation6,8.

Our findings demonstrated that well-established interventions like MDV could be used to address important public health issues. This is a wonderful example of how a genuine One Health approach should be used to control zoonotic diseases. A few additional factors, such as increased awareness and availability of PEP by victims of animal bites, along with MDV, may contribute to changes in the detection of human rabies cases in Bangladesh6.

Our investigations had some limitations. Based on the cases that have been identified at public hospital facilities (NRPCC/DRPCCs), we determined the mortality rates for human rabies which limited our scope. We are conscious of the possibility that we may have overlooked some cases, particularly those who sought care at private hospitals or from traditional healers and never went to a public hospital. Therefore, the percentage we are giving may only represent a small portion of all cases found in Bangladesh. However, we think that only a small number of rabies deaths have been missed by the government's primary data-collection facilities thanks to advancements in education and awareness. Due to the patients' reliance on their relatives for historical recollections, there may have been recalled bias. However, we made an effort to lessen this bias by speaking with some of the patients' relatives on the phone. Even though there are issues like these, we think that our research has provided insightful information on rabies in Bangladesh and can be applied to rabies control in countries with similar socioeconomic settings.

The current rate/face of MDV and ARV could be effective in declining human rabies cases but is not enough to achieve zero rabies cases by 2020, however, increasing MDV by a certain percentage could be led to achieving the global goal of Zero by 30. Providing evidence per the Zero by 30 plan will directly promote commitment to eliminating canine rabies while providing adequate resources for anti-rabies activities. The results of our research can be used to support national rabies control planning in Bangladesh and other nations with comparable socioeconomic environments, accelerating similar examples of success in achieving the 2030 target of eliminating dog-mediated human rabies worldwide.

**Methods:**

**Data Source**

We obtained data from the patient's immunization record books maintained at the National Rabies Prevention and Control Center (NRPCC) of the Infectious Disease Hospital (IDH) in Dhaka, Bangladesh, from January 2011 through December 2022. NRPCC is the main referral center for animal bites and rabies patients in Bangladesh, and the majority of the animal bite cases from throughout the country come here for free vaccination and treatment. There is another center similar to the IDH located in the southern city of Chittagong, namely the Bangladesh Institute of Tropical and Infectious Diseases (BITID) which is the secondary referral center for rabies after NRPCC. In addition to the NRPCC and BITID, there are 66 public District Rabies Prevention and Control Centers (DRPCCs) with at least one center in each of the 64 districts that offer a free anti-rabies vaccine (ARV) and treatment to dog bite victims. For data regarding MDV, we used the MDV database of the CDC, Bangladesh's Directorate General of Health Services (DGHS) from November 2011 through December 2022. The database includes data on all estimated and vaccinated dogs, human-to-dog ratio, and vaccination coverage in all 64 districts of Bangladesh.

**Human Rabies Surveillance**

The Directorate General of Health Services has a central core committee to oversee the surveillance activities. This committee is led by the Director of Disease Control and Line Director, Communicable Disease Control (CDC), as well as additional personnel like the Deputy Director, Deputy Program Manager, and Surveillance Medical Officer. The Upazila (sub-district) Rapid Response Team (URRT), comprised of medical professionals, health assistants, and other health personnel, has been investigating reports of patients who have had contact with animals (typically bites or scratches) immediately while the start of the human rabies surveillance program. The CDC and NRPCC's central rabies teams and the intermediate-level (Civil Surgeon) rabies teams have received information and aggregate statistics regularly from the local level.

**MDV**

The MDV program was coordinated by the Communicable Disease Control Division (CDC) of DGHS as part of the National Rabies Elimination Programme. They also supplied dog rabies vaccines for MDV. Along with the DGHS, the MDV program in Bangladesh also received contributions in various forms from the Department of Livestock Services, the Local Government Division, the Education sectors, and non-governmental organizations (NGOs) or development organizations. The goal was to vaccinate at least 70% of the dog population annually using a Capture Vaccinate Release (CVR) method1. Each dog received a free dose (1 ml) of the rabies vaccination (CaniShot RV-K -(CAVAC); CANVAC® R - Dyntec; Rabisin® - Merial) that was given either subcutaneously or intramuscularly, depending on the animal's posture and mode of restraint. To facilitate the identification of vaccination status on post-vaccination surveys, each dog was marked with non-toxic paint on the top of the head, which lasted for many days before vaccinating dogs that could be attributed to an owner, and consent was acquired from the owner. Vaccination teams were formed and trained through animal control staff training conducted by MDV experts before the MDV campaign. Vaccination team direction and program monitoring were preplanned in a program before conducting each vaccination campaign, called 'microplanning'. Each site will consist of 2-3 days of planning, training, and community mobilization, 3-4 days of vaccination, and 1 day of follow-up and evaluation. Typically, a vaccination coverage evaluation is conducted on vaccination day 2 or 3, vaccination continued if necessary for another 1-2 days, and then a final coverage evaluation is completed.

At the time of vaccination, the following information was recorded for each dog: vaccination team ID, time, date, GPS, sex, age, ownership, neuter status, confinement, previous vaccination history, and health status/body condition status. An electronic data capture device (i.e., GPS data logger or mobile phone application) was also used to assist with data collection and final evaluation. In November 2011, MDV was first piloted in Bangladesh, covering a small municipality. Following the pilot's success, more comprehensive MDV campaigns were implemented nationwide6.

Since 2011, CVR is currently practiced as the primary mass vaccination strategy in Bangladesh. CVR teams are typically comprised of five-six members who travel by vehicle: one vaccinator, three dog catchers who use nets, one driver, and one rapporteur. Dogs that could be held in the owner's or team's hands were manually restrained for vaccination. Nets were used to catch dogs that could not be restrained manually. (Supplemental Figure 1).

It is expected that two vaccination teams can cover an area containing roughly 200 dogs in 3 days. Previous studies estimated a dog density of 52 dogs/km2 in Dhaka32, so each urban zone would be about 3.8 km2 (1.5 mi2).Previous studies also estimate a human: dog ratio of 120:1 and a density of 14 dogs/km2 in rural areas28, so rural zones will be defined based on a population of 24,000 people per zone, or about 14 km2 (5.4 mi2).

Post-vaccination dog survey was conducted to estimate the coverage of free-roaming dogs in the community and the dog population was estimated using the 'Capture-mark-recapture' method32.

Lincoln—Petersen’s formula with Chapman’s correction was used to estimate the dog population estimation: ] – 1 ……………… (1)

where, **n** is the estimate of the total population size, **n1** is the total number of animals sighted on day 1, **n2** is the total number of animals sighted on day 2, and **m** is the number of marked animals on day 1 that were sighted on day 2.

Seber's formula was used to estimate an approximately unbiased variance of N33.

……………… (2)

and the 95% confidence interval for N is estimated as:

……………… (3)

Dog vaccination coverage for free-roaming dogs was estimated from the proportion of dogs counted after the vaccination campaign that was marked by vaccinators.

*Time-Series Analysis*

Any variable that is measured across time is potentially influenced by earlier observations, which is a key aspect of time-series analysis (autocorrelation). Time-series models use previous observations as the foundation for forecasting future behavior to take advantage of these linkages. This is the significant difference between time-series analysis and conventional statistical tests for assessing change, such as regression analysis, which relies on variation in independent variables to explain changes in the outcome34. To determine the trend of rabies cases, two time-series forecasting models were used: the auto-regressive integrated moving average (ARIMA) and the auto-regressive integrated moving average with explanatory factors (ARIMAX).

As the primary outcome variable for rabies cases is influenced by past reported cases, we chose the ARIMA model (time-series events). The ARIMA model is a data-focused, exploratory technique that enables the user to construct an appropriate model based on the data's actual structure. This model attempts to extract regional trends while filtering out high-frequency noise from the data and assumes a linear correlation between the time series values35. By updating the model to forecast the system's future state based on current occurrences, ARIMA models have the advantage of being able to adapt to dynamically oriented systems that change over time. The R package "forecast" was used to run the ARIMA model for this study36.

Numerous researchers have recently used time series to study the trend of rabies (including additive models37, auto-regressive time series models38, and wavelet time series models24), but most of them use the ARIMA model with one-time series because it is a useful method for analyzing time series with one-time series in systems14,39. However, as ARIMA only considers one variable, it was unable to provide light on the connections between system variables. To extract nearby designs while reducing high-frequency turbulence, ARIMA models accept a direct relationship between the time-series values and seek to leverage these straight circumstances in perceptions. More than one variable is always used to define the ARIMAX model. The ARIMA model with a single time series cannot capture the changing rules of the multivariate time series. Consequently, it is essential to develop a model using the multivariate ARIMAX model40,41. Mass Dog Vaccination (MDV) and Anti Rabies Vaccination (ARV) were considered explanatory variables in the ARIMAX model.

We predicted trends for the upcoming nine years (up to 2032) using both time series models with the data on rabies cases and showed them in the figure. R version 3.5.2.2, a statistical software, was used for all time-series analysis.

*Empirical evaluation*

To assess the relevance of the predictions, we analyzed and compared the performance of the time series models using some of the generally used measures, including coefficient of determination (R2), root mean square error (RMSE) and mean absolute error (MAE).

We also performed Spearman rank correlation coefficients between key rabies patient characteristics and ARV variables to identify the association between the variables. Hierarchical clustering using Pearson correlation coefficients was used to visualize associations between variables and possible clusters using pairwise comparisons to adjust correlations as a measure of dissimilarity and the distribution function in R software.

**Cartographic display**

The cartographic boundary files, which are used to create maps, were downloaded from the DIVA-GIS42. All cartographic displays were performed in ArcGIS version 10.8.143. Choropleth maps were used to display the district-level geographic distribution of rabies cases, human-to-dog ratio, number of vaccinated dogs, and percentage of vaccination coverage using Jenk’s optimization classification scheme.

**Phylogenetic Analysis**

We used the complete genome sequences of the N gene of the arctic-like rabies virus from Bangladesh (GenBank accession number AB699214.1) and blasted in National Center for Biotechnology Information (NCBI) to generate a phylogenetic tree. Then we downloaded 68 complete genome sequences of the N gene from Bangladesh, India, Pakistan, Nepal, Afghanistan, and Bhutan. The sequences were aligned by the MUSCLE method in MEGA 11 software. The phylogenetic relationship of N sequences was determined by using the neighbor-joining method in MEGA 11. The maximum likelihood phylogenetic trees of the N segment were generated by using the Hasegawa‐Kishino‐YanoJukes model with a bootstrap value of 100044,45. Finally, the phylogenetic tree was visualized in FigTree version v1.4.3. The viruses from Bangladesh were labeled red.

**Data availability**

Data supporting the findings of this work are available within the paper and its Supplementary Information files.

**Reference**

1. World Health Organization & WHO. WHO Expert Consultation on rabies. Third report. World Health Organization technical report series, 1012 (2018). 2018.

2. Hampson K, Coudeville L, Lembo T, et al. Estimating the global burden of endemic canine rabies. *PLoS neglected tropical diseases* 2015; **9**(4): e0003709.

3. Minghui R, Stone M, Semedo MH, Nel L. New global strategic plan to eliminate dog-mediated rabies by 2030. *The Lancet Global Health* 2018; **6**(8): e828-e9.

4. Hossain M, Ahmed K, Bulbul T, et al. Human rabies in rural Bangladesh. *Epidemiology & Infection* 2012; **140**(11): 1964-71.

5. Rana MS, Siddiqi UR, Ghosh S, et al. Epidemiological study of human rabies cases in Bangladesh through verbal autopsy. *Heliyon* 2020; **6**(11): e05521.

6. Ghosh S, Rana MS, Islam MK, et al. Trends and clinico-epidemiological features of human rabies cases in Bangladesh 2006–2018. *Scientific reports* 2020; **10**(1): 2410.

7. Ghosh S, Chowdhury S, Haider N, et al. Awareness of rabies and response to dog bites in a Bangladesh community. *Veterinary medicine and science* 2016; **2**(3): 161-9.

8. World Health Organization. The Rabies Elimination Program of Bangladesh. Neglected tropical diseases. Geneva: WHO 2017, <http://www.who.int/neglected_diseases/news/Bangladesh-rabies-elimination-program/en/>, 2017.

9. Gibson A, Yale G, Corfmat J, et al. Elimination of human rabies in Goa, India through an integrated One Health approach. *Nature Communications* 2022; **13**(1): 2788.

10. Kurosawa A, Tojinbara K, Kadowaki H, Hampson K, Yamada A, Makita K. The rise and fall of rabies in Japan: A quantitative history of rabies epidemics in Osaka Prefecture, 1914–1933. *PLoS neglected tropical diseases* 2017; **11**(3): e0005435.

11. Rupprecht CE, Freuling CM, Mani RS, Palacios C, Sabeta CT, Ward M. A history of rabies—The foundation for global canine rabies elimination. Rabies: Elsevier; 2020: 1-42.

12. World Health Organization. Rabies vaccines: WHO position paper. Weekly epidemiological record; (93) 201–220, <http://www.who.int/wer> (2018). 2018.

13. Hampson K, Dushoff J, Cleaveland S, et al. Transmission dynamics and prospects for the elimination of canine rabies. *PLoS biology* 2009; **7**(3): e1000053.

14. Paso A, Ngamjarus C. Forecasting rabies in dogs in Thailand: Time series analysis. *Naresuan University Journal: Science and Technology (NUJST)* 2020; **28**(4): 64-74.

15. Heesterbeek H, Anderson RM, Andreasen V, et al. Modeling infectious disease dynamics in the complex landscape of global health. *Science* 2015; **347**(6227): aaa4339.

16. Klepac P, Metcalf CJE, McLean AR, Hampson K. Towards the endgame and beyond: complexities and challenges for the elimination of infectious diseases. The Royal Society; 2013. p. 20120137.

17. TaNEja N, CHEllaIyaN VG, GUPTA S, GUPTA R, AY N. Seasonal Variation and Time Trend Analysis of Dog Bite Cases Attending the Anti Rabies Clinic in Delhi using ARIMA Model Forecasting. *Journal of Clinical & Diagnostic Research* 2021; **15**(8).

18. He J, Luo L, Jin R, Li J. The application of ARIMA in forecasting the cases of rabies in China different human groups. *Zhonghua lao Dong wei Sheng zhi ye Bing za zhi= Zhonghua Laodong Weisheng Zhiyebing Zazhi= Chinese Journal of Industrial Hygiene and Occupational Diseases* 2018; **36**(7): 512-5.

19. Dos Santos AJF, Ferreira JM, Baptista F, et al. Statistical analysis between 2006 and 2019 and forecast of rabies in cattle from 2020 to 2022 in Tocantins State (Brazil), by using the R Studio software. *Epidemiology & Infection* 2022; **150**.

20. Kunkel A, Jeon S, Joseph HC, et al. The urgency of resuming disrupted dog rabies vaccination campaigns: a modeling and cost-effectiveness analysis. *Scientific reports* 2021; **11**(1): 12476.

21. Wallace RM, Undurraga EA, Blanton JD, Cleaton J, Franka R. Elimination of dog-mediated human rabies deaths by 2030: needs assessment and alternatives for progress based on dog vaccination. *Frontiers in veterinary science* 2017; **4**: 9.

22. Cleaveland S, Kaare M, Tiringa P, Mlengeya T, Barrat J. A dog rabies vaccination campaign in rural Africa: impact on the incidence of dog rabies and human dog-bite injuries. *Vaccine* 2003; **21**(17-18): 1965-73.

23. Yoak AJ, Haile A, O’Quin J, et al. Barriers and opportunities for canine rabies vaccination campaigns in Addis Ababa, Ethiopia. *Preventive veterinary medicine* 2021; **187**: 105256.

24. Hampson K, Dushoff J, Bingham J, Brückner G, Ali Y, Dobson A. Synchronous cycles of domestic dog rabies in sub-Saharan Africa and the impact of control efforts. *Proceedings of the National Academy of Sciences* 2007; **104**(18): 7717-22.

25. Subedi D, Chandran D, Subedi S, Acharya KP. Ecological and Socioeconomic Factors in the Occurrence of Rabies: A Forgotten Scenario. *Infectious Disease Reports* 2022; **14**(6): 979-86.

26. Penjor K, Tenzin T, Jamtsho RK. Determinants of health seeking behavior of animal bite victims in rabies endemic South Bhutan: a community-based contact-tracing survey. *BMC public health* 2019; **19**: 1-11.

27. Jamil KM, Ahmed K, Hossain M, et al. Arctic-like rabies virus, Bangladesh. *Emerging Infectious Diseases* 2012; **18**(12): 2021.

28. Hossain M, Ahmed K, Marma ASP, et al. A survey of the dog population in rural Bangladesh. *Preventive veterinary medicine* 2013; **111**(1-2): 134-8.

29. Gill GS, Singh BB, Dhand NK, Aulakh RS, Ward MP, Brookes VJ. Stray Dogs and Public Health: Population Estimation in Punjab, India. *Veterinary Sciences* 2022; **9**(2): 75.

30. Knobel DL, Cleaveland S, Coleman PG, et al. Re-evaluating the burden of rabies in Africa and Asia. *Bulletin of the World health Organization* 2005; **83**: 360-8.

31. Kitala P, McDermott J, Kyule M, Gathuma J, Perry B, Wandeler A. Dog ecology and demography information to support the planning of rabies control in Machakos District, Kenya. *Acta tropica* 2001; **78**(3): 217-30.

32. Tenzin T, Ahmed R, Debnath NC, Ahmed G, Yamage M. Free-roaming dog population estimation and status of the dog population management and rabies control program in Dhaka City, Bangladesh. *PLoS neglected tropical diseases* 2015; **9**(5): e0003784.

33. Seber G. The effects of trap response on tag recapture estimates. *Biometrics* 1970: 13-22.

34. Linden A, Adams JL, Roberts N. Evaluating disease management program effectiveness: an introduction to time-series analysis. *Disease Management* 2003; **6**(4): 243-55.

35. Adhikari R, Agrawal RK. An introductory study on time series modeling and forecasting. *arXiv preprint arXiv:13026613* 2013.

36. Hyndman R, Athanasopoulos G, Bergmeir C, et al. Forecasting functions for time series and linear models. *R package version* 2015; **6**.

37. Olarinmoye AO, Ojo JF, Fasunla AJ, et al. Time series analysis and mortality model of dog bite victims presented for treatment at a referral clinic for rabies exposure in Monrovia, Liberia, 2010–2013. *Spatial and spatio-temporal epidemiology* 2017; **22**: 1-13.

38. Lopes E, Sáfadi T, Da Rocha CMBM, Cardoso DL. Analysis of time series of cattle rabies cases in Minas Gerais, Brazil, 2006–2013. *Tropical animal health and production* 2015; **47**: 663-70.

39. Bedi R, Verma N, Gautam K, Agiwal V. Forecasting the Anti-Rabies Vaccine Demand at Jawaharlal Medical College and Hospital, Ajmer, Rajasthan: A Comparative Analysis based on Time Series Model. *Indian Journal of Community Health* 2021; **33**(3).

40. Chadsuthi S, Modchang C, Lenbury Y, Iamsirithaworn S, Triampo W. Modeling seasonal leptospirosis transmission and its association with rainfall and temperature in Thailand using time–series and ARIMAX analyses. *Asian Pacific journal of tropical medicine* 2012; **5**(7): 539-46.

41. Fan J, Shan R, Cao X, Li P. The analysis to tertiary-industry with ARIMAX model. *Journal of Mathematics Research* 2009; **1**(2): 156.

42. DIVA-GIS. Download data by country. <https://www.diva-gis.org/gdata>. Accessed 25 Jan 2023. 2023.

43. Introducing ArcGIS Enterprise 10.8.1. <https://www.esri.com/arcgis-blog/products/arcgis-enterprise/announcements/arcgis-enterprise-10-8-1/>. Accessed 25 January 2023.

44. Troupin C, Dacheux L, Tanguy M, et al. Large-scale phylogenomic analysis reveals the complex evolutionary history of rabies virus in multiple carnivore hosts. *PLoS pathogens* 2016; **12**(12): e1006041.

45. Shimodaira H, Terada Y. Selective inference for testing trees and edges in phylogenetics. *Frontiers in ecology and evolution* 2019; **7**: 174.

**Acknowledgements**

The National Rabies Control Program was funded by the Communicable Disease Control (CDC) Division of the Directorate General of Health Services (DGHS) of Bangladesh. We thank all the staff of DGHS, Department of Livestock Services (DLS) and Local Government, volunteers, and NGOs who have supported and contributed directly or indirectly to the success of the campaign. Use of trade names, product names, or commercial sources is for identification only and does not imply endorsement by the Government of Bangladesh.

**Author Contributions**

Conceptualization, S.G., M.N.H., and N.H.; Methodology, S.G., M.N.H., N.D., D.J., and N.H.; Data Analysis, M.N.H., N.D., D.J., and S.G.; Field Investigation, M.K.I., S.M.U., M.R.A.S., A. A. J., A.S.P.M., S.M.E.A., and S.H.; Data Processing, M.A.H.K., and H.S.M.; Writing – Original Draft, S.G., M.S.R., S.C., M.A.H.K., R. B., and N.H.; Supervision, N.C.D., A.K.M.S., B.A., U.R.S., and S.T.

**Additional Information**

**Competing interests**

The author(s) declare no competing interests.

Chart, map, scatter chart

Description automatically generated

Fig. 1: **Year-wise scaling up mass dog vaccination (MDV) in different districts of Bangladesh, 2011–2022.** Map of Bangladesh showing the number of dogs vaccinated in different districts of Bangladesh starting from 2011.

Map, scatter chart

Description automatically generated

Fig. 2: **Map of Bangladesh state dog vaccination and estimated human to dog ratio by district.** Left: Showing the of number of dogs vaccinated (blue shadow) with vaccination coverage (black circles). Right: Showing Human to dog ration (red shadow) with human rabies death rate per 100,000 population (red circle).

Diagram

Description automatically generated with low confidence

Fig. 3: Graph of month-wise human rabies deaths (green bar) and number of anti-rabies vaccine utilization reported at the National Rabies Prevention and Control Centers (NRPCC) of the Infectious Disease Hospital (IDH), Dhaka, Bangladesh, 2011–2022.

Map

Description automatically generated

Fig. 4: Distribution of human death rate (cases per 100,000 populations) (left) and rabies cases (right) in different districts of Bangladesh reported at the National Rabies Prevention and Control Centers (NRPCC) of the Infectious Disease Hospital (IDH), Dhaka, Bangladesh, 2019–2022.

Chart

Description automatically generated

**Fig. 5:** Correlation matrix heatmap with dendrogram depicting associations between variables. The length of the dendrogram branches represent distance between variables from Pearson correlation. Correlations range from 1 for perfectly correlated variables to -1 for negatively correlated variables. (**Key**: **Mortality** – human deaths, **MDV** – dog rabies vaccinations, **Year** – year of vaccination, and **ARV** – human rabies vaccinations).

Diagram

Description automatically generated

Fig. 6: **Phylogeographic distribution of canine rabies cases.** Phylogenetic analysis of 68 complete genome sequences of the N gene from Bangladesh, India, Pakistan, Nepal, Afghanistan, and Bhutan was used. Complete genome sequences of the N gene of arctic-like rabies virus from Bangladesh (GenBank accession number AB699214.1) and blasted in National Center for Biotechnology Information (NCBI) are used to generate a phylogenetic tree. The maximum likelihood phylogenetic trees of the N segment were generated by using the Hasegawa‐Kishino‐YanoJukes model with a bootstrap value of 1000. The viruses from Bangladesh were labeled red.

Fig. 7: Top: Observed and predicted annual rabies cases using Auto-Regressive Integrated Moving Average (ARIMA) model. Middle: Observed and predicted annual rabies cases using Auto-Regressive Integrated Moving Average with Explanatory Variables (ARIMAX) model. Bottom: Observed and predicted annual rabies cases using an Auto-Regressive Integrated Moving Average with Explanatory Variables (ARIMAX) model with a 50% increase in MDV.

|  |
| --- |
| **ARIMA** |
|  |
| **ARIMAX** |
|  |
| **ARIMAX with 50% increase of MDV** |
|  |