Modelling the time-varying transmission of wild poliovirus in Pakistan

Abstract

The efforts to eradicate the wild poliovirus since 1988 have successfully reduced its global prevalence by 99%. However, as of 2023, Pakistan and Afghanistan remain the only two endemic countries facing continual virus transmission. In this study, an ordinary differential equations-based deterministic model was developed to assess the persistence of wild poliovirus type 1 (WPV1) in Pakistan. The model considered both human-human and environment-human virus transmission through sewage contamination represented by time-dependent transmission rates. The model was calibrated by fitting the reported data of WPV1 cases from 2017 to 2022 in Pakistan. Our analysis identified the unvaccinated asymptomatic population to be the major contributor to disease persistence and the estimated value of the basic reproduction number through the next-generation matrix method was 1.61 while the effective reproduction number of 0.12 indicated the efficacy of current intervention strategies. The model showed a better predictive ability than the usual constant transmission rate models. The results suggest that endemic virus transmission will continue in Pakistan subject to the current higher vaccination rates. The numerical simulations considering the reduction in the virus-shedding rate by the asymptomatic infectious population through targeted vaccinations indicated an 85% reduction in the number of future cases in Pakistan. The model can be further utilized to guide eradication efforts for the targeted allocation of preemptive measures through the incorporation of spatial data of routine surveillance and vaccination coverage in the country.

Keywords: Dynamic modeling, polio eradication, transmission ecology, risk analysis, biomathematics, vaccination, environmental surveillance

Introduction

Poliomyelitis (Polio) is a highly contagious, potentially debilitating, and incurable disease caused by the poliovirus. The virus primarily affects children under the age of five years and can invade the central nervous system, resulting in permanent paralysis [1]. Transmission occurs through either the fecal-oral or oral-oral route [2]. In the early 20th century, polio was the most feared pathogen in industrialized nations until the development of a vaccine in the 1950s [3]. Since the launch of the Global Polio Eradication Initiative (GPEI) by the World Health Organization (WHO) in 1988, wild poliovirus infections have reduced significantly across the globe. Mass immunization against the virus has led to the complete eradication of poliovirus serotypes 2 and 3, leaving only two endemic countries, Pakistan and Afghanistan, still affected by wild poliovirus type 1 (WPV1) transmission [4,5]. This ongoing circulation of the virus not only poses a threat to the health of residents in these countries but also hinders vaccination efforts in polio-free regions [6].

Intensified immunization efforts have reduced the incidence of wild poliovirus cases in Pakistan; however, the country faces several challenges in effectively implementing eradication policies. These challenges include geopolitical instability, government negligence, lack of efficient public health infrastructure, and general misconceptions regarding polio vaccines [7]. Moreover, the neighboring country; Afghanistan is also battling constant virus transmission which also poses an immense threat to eradication efforts in Pakistan as the two countries are considered to be one epidemiological block due to the highly porous border and extensive population migrations [8]. Thus, it has been considered that if Pakistan achieves eradication Afghanistan will soon follow and the world will eventually achieve a milestone of global polio eradication.

Mathematical models have long assisted policymakers in identifying improved vaccination strategies and optimizing surveillance [9]. In this study, we developed a deterministic mathematical model based on ordinary differential equations (ODEs) to evaluate wild poliovirus transmission in Pakistan. This model considers both human-human and environment-human transmission of the virus through the primary fecal-oral route owing to sewage water contamination [10]. This route is also the focus of environmental surveillance efforts to detect the silent circulation of the virus [11]. Another significant aspect of this study is the incorporation of different types of time-dependent transmission rates to reflect the epidemiological characteristics of polio infections in the country. These transmission rates change in response to various intervention measures and human behavior during different periods. By incorporating these features, our model can improve its predictive accuracy and

enhance our understanding of the periodic polio outbreaks in Pakistan. Thus it will lead to an effective resource allocation to interrupt the transmission and achieve eradication.

Methods

A mathematical model is adapted to understand the transmission dynamics of WPV1 in Pakistan. Our modelling strategy is inspired by the approach used by Yang and Wang (2021) to model COVID-19 transmission in Hamilton County, Tennessee, United States. In our model, the target population is divided into four classes: susceptible individuals 'S', exposed individuals 'E', reported wild poliovirus cases 'I', and recovered individuals 'R', while compartment 'W' represents the poliovirus in sewage water. The original model divided the host population into five classes, including hospitalized individuals, with the sixth compartment representing the concentration of coronavirus aerosols in the environment. Furthermore, the model assumed that the entire target population was susceptible to COVID-19, as the vaccine had not yet been introduced. Therefore, because the entire target population is susceptible, no scaling of the disease data was necessary. In contrast, our model includes children up to the age of five years who did not receive OPV during the annual National Immunization Days (NIDs) from 2017-2022 as the susceptible population [13]. **Figure 2** shows the NIDs conducted in Pakistan during this period along with the percentage of children who were missed by each campaign. This percentage was increasing till 2019 which led to a surge in cases see **Figure 1** and with the reduction of these missed children the reported cases dropped to a single case in the year 2021. The 'E' compartment represents the number of asymptomatic infections. We assumed that 70% of poliovirus infections would be asymptomatic [1]. The total number of WPV1 cases reported in the country during the targeted years is shown in **Figure 1**. Data scaling was performed to provide the model with a more balanced landscape for training, leading to improved efficiency and predictive ability [14].

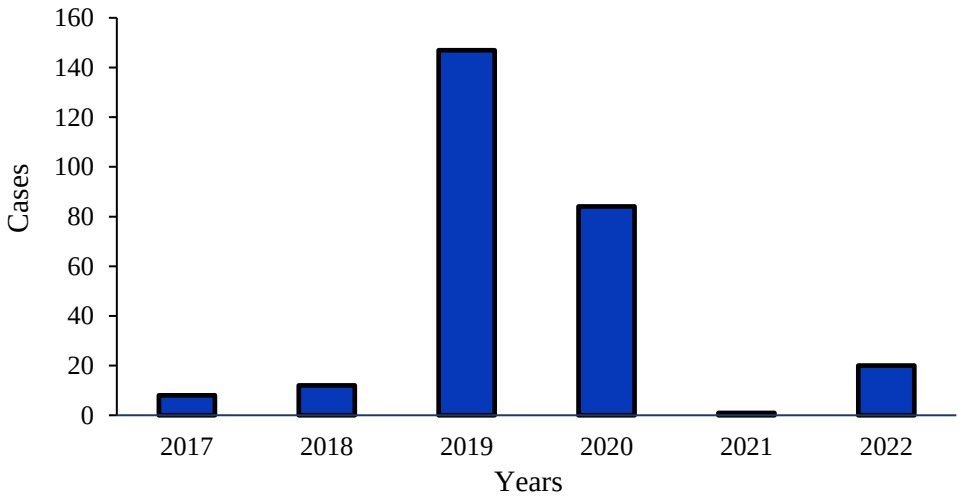


Fig 1. Reported WPV1 cases in Pakistan from 2017-2022.

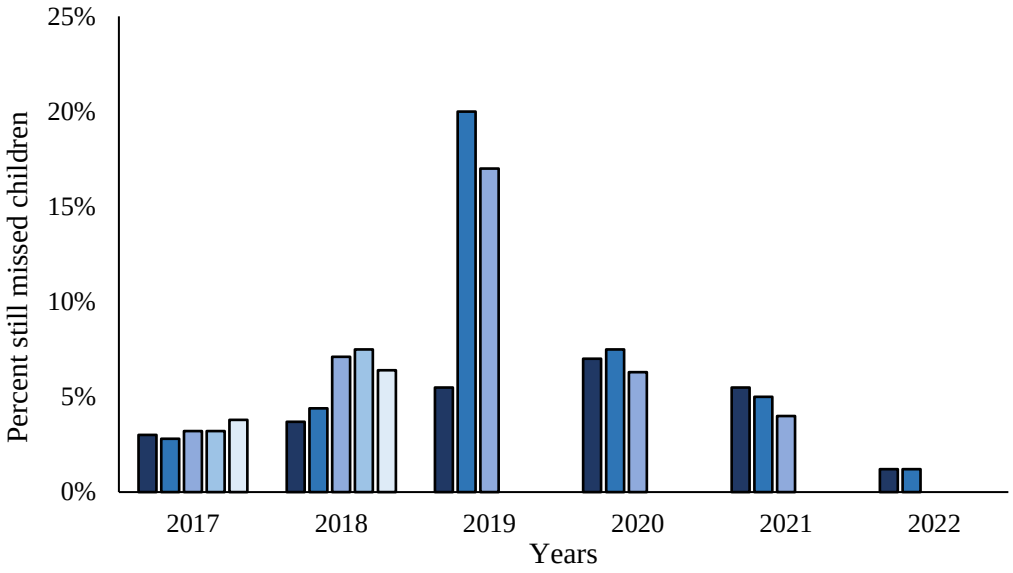


Fig 2. National Immunization Activities occurred from 2017-2022 in Pakistan. The number of columns are representing the number of campaigns of every year and their height is indicating the proportion of missed children by each campaign [15–19]

The following set of ordinary differential equations represents our model:

$$\frac{dS}{dt} = \Lambda - \beta_E (I, t)\, SE - \beta_I (I, t)\, SI - \beta_W (I, t)\, SW - \mu S$$

$$\frac{dE}{dt} = \beta_E (I, t)\, SE + \beta_I (I, t)\, SI + \beta_W (I, t)\, SW - (\alpha + \gamma_1 + \mu)\, E$$

$$\frac{dI}{dt} = \alpha (1-p)\, E - (q + \gamma_2 + \mu)\, I$$

$$\frac{dR}{dt} = \gamma_1 E + \gamma_2 I - \mu R$$

$$\frac{dW}{dt} = \xi_1 E + \xi_2 I - \sigma W$$

Where the 'Λ' is a parameter for population inflow, μ = death rate, α = average incubation period of poliovirus, 'p' represents the proportion of asymptomatic population who develop paralysis, q = rate of infected persons who develop paralysis, σ is the removal rate of poliovirus from the environment; γ_1 and γ_2 are the rates of recovery of asymptomatic and symptomatic persons and ξ_1 and ξ_2 are the rates of contributing virus to the environment by the exposed and infected population respectively. These parameter values were obtained from a literature search and are listed in **Table 1**. The schematic representation of the model is given in **Figure 3**.

Table 1. Model parameter values for poliomyelitis

Parameters	**Values**	**References**

Incubation period(α)	12 days	[20]
Population size(N)	40000000	[18]
Natural Birth & Death rate(μ)	160	[21]
Environmental Removal Rate of virus(σ)	0.12/d	[22]
Virus shedding rate by infected persons(ξ2)	0.025/ml/person/day	[23]
Virus shedding rate by exposed persons(ξ1)	0.45/ml/person/day	[24]
Recovery rate of exposed individuals(γ1)	1/10/d	[20]
Recovery rate of infected individuals(γ2)	1/14/d	[25]
Rate of paralysis in exposed individuals(p)	1.5%	[26]
Rate of paralysis in infected individuals(q)	<1%	[26]

The incubation period of the poliovirus was considered to range from 3-21 days, in this study, the average value of $1/\alpha = 12$ days is considered [20]. The recovery period from polio depends on different factors, including the severity of infection and immune status of infected individual. The model includes the recovery period of the exposed and infected population. In cases of recovery from an asymptomatic state, the population usually shows no symptoms. The time period for this recovery was considered to be 7-14 days and in this model, an average recovery period of 10 days is considered for those 70% of infections that go unnoticed, which gives $\gamma_1 = 1/10$ per day [20]. Because it is a paralytic disease, in such cases, there is no recovery, but rather a permanent disability or death. However, those who experience milder symptoms can recover within 1-2 weeks, so a complete recovery period of 14 days is considered, which gives $\gamma_1 = 1/14$ per day [25]. Evaluation of the poliovirus removal rate from the environment showed a time period of 3 hours which led to 90% removal of the virus from the environment. Therefore, the virus removal rate from the environment is taken as $\sigma = 0.12$ per day [22]. Population immigration and emigration rates across the country are considered equivalent; thus, the rate of influx of the at-risk population was $\Lambda = \mu N$, where N is the magnitude of the target population. The natural birth and death rates of the population are considered equal to μ [12]. The shedding rate of wild poliovirus by the asymptomatic population [24] and infected individuals [23] is taken from the literature. The rate of paralysis in asymptomatic infections is $p = 1.5\%$ and that among infected individuals is $q = 1\%$ [26]

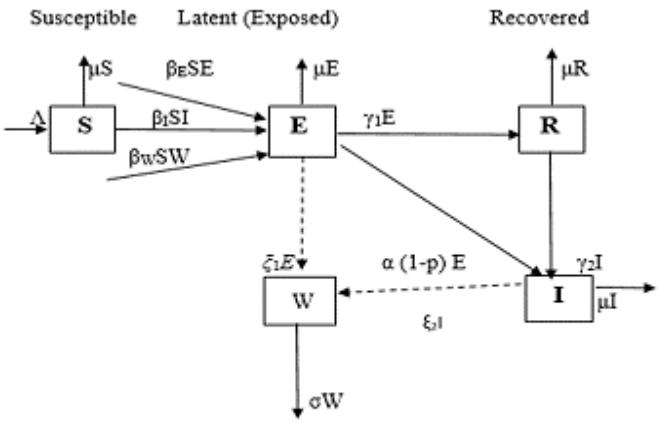


Figure 3. A SEIRW model adapted for poliovirus transmission in Pakistan incorporating the effect of a virus-contaminated environment on the spread of the disease.

The model incorporates multiple transmission routes each of which is associated with non-linear incidence. The functions $\beta_E(I, t)$ and $\beta_I(I, t)$ indicate the direct, human-human transmission rates between asymptomatic and susceptible populations and between infected and susceptible populations, respectively. The $\beta_W(I, t)$ function depicts the environment-human transmission rate. The model considers the chance of the infected (both latent and clinical) population coming into contact with other individuals which could lead to the shedding of the poliovirus into the environment by those individuals. Our assumption is based on the fact that in densely populated areas with poor sanitation facilities and an under-immunized or zero-dose population, the presence of poliovirus in the environment can pose a significant threat to the susceptible population [27]. The values of the transmission rate parameters are obtained by fitting the model to the reported data. The considered time domain is divided into two 3-year time periods. These have distinct time intervals: $[T_1, T_2]$ and $[T_2, T]$ and for some positive constants, $T_1 < T_2 < T$. The first period from 2017 to 2019 is considered the period of increased vaccine resistance **Figure 2**, which eventually led to a surge in polio cases in Pakistan in 2019. We assumed that the disease transmission rate increased monotonically during the first period. The second period from 2020-2022, on the other hand, was a period of increment in vaccination rates **Figure 2** and reduced exposure of the susceptible population to infectious individuals due to the nationwide lockdown to contain the COVID-19 pandemic. Thus, the transmission saw a major decline during this period and is assumed to no longer increase monotonically. The separate transmission rates for each of these periods are then developed to represent their unique properties.

- **Period 1**: Here, we considered that all the transmission rates are increasing with the time 't' during this transitional interval and are described as

$\beta_E(I, t) = \beta_{E0} f(t)$, $\beta_I(I, t) = \beta_{I0} f(t)$, $\beta_W(I, t) = \beta_{W0} f(t)$

$f(t) = 1+d(t-T_1)$ with $T_1 \leq t \leq T_2$.

Each transmission rate initiates from the minimum $t = T_1$ and grows monotonically relative to t with a constant rate d. Parameter d was estimated through model fitting to the disease data.

- **Period 2**: In this period, the transmission rates no longer increase monotonically but take the form

$\beta_E(I, t) = \beta_{E0} f(T_2) g(I)$, $\beta_I(I, t) = \beta_{I0} f(T_2) g(I)$, $\beta_W(I, t) = \beta_{W0} f(T_2) g(I)$,

Here, $f(t) = 1+d(T_2-T_1)$, and $g(I) = 1 - \frac{2}{\pi}\tan^{-1}(c\cdot (I(t) - I(T_2)))$

Where $T_2 < t < T$ and function g(I) represents the variation in transmission rates in relation to I. This variation was due to increased vaccination and reduced exposure rates. The infection prevalence at the beginning of this period, $t = T_2$, was represented by $I(T_2)$. The constant 'c' is used to adjust the magnitude of the difference, and its value is determined through data fitting. In addition, an inverse tangent is used to transfer this difference to a standard interval.

Our modelling strategy considers the time-dependent transmission rates of wild poliovirus in Pakistan. Typically, infectious disease models for poliovirus transmission in one of the last reservoirs of the virus consider only constant transmission scenarios [9]. By considering time-dependent transmission rates, we can enhance the accuracy of model predictions for future disease trajectories in the country. This will also help us develop effective intervention strategies to control viral transmission.

Results

A SEIRW model is developed to study the transmission and spread of WPV1 in Pakistan. The disease pattern was observed during two periods: 2017-2019 and 2020-2022. In the first period, there was a rapid increase in the number of new cases, which can be attributed to a reduction in vaccination rates **Figures 1 & 2**. However, from 2020 to 2022, the number of cases decreased owing to increased vaccination rates and reduced exposure rates resulting from stay-at-home orders implemented to contain the transmission of COVID-19. Transmission rates were formulated for each of these periods, as previously described, to conduct data fitting and model simulations.

Model fitting to WPV1 cases in Pakistan during 2017-2019

Initially, data fitting is conducted for the period of 2017 to 2019 to estimate the values of the three transmission parameters, with two parameters representing human-human transmission and the

other representing environment-human transmission. Based on the demographic and reported data, the initial conditions for this time period were set as (S, E, I, R, W) = (1200000, 0.12, 0.05, 0, 22). The value of poliovirus concentration in the sewage water was obtained as 22 virions/ml [10]. Because our model did not consider developed immunity, the recovered individuals are considered to be equal to zero as an initial value for model calibration **Figure 4**. Data fitting was performed using the estimated parameter values listed in **Table 2**.

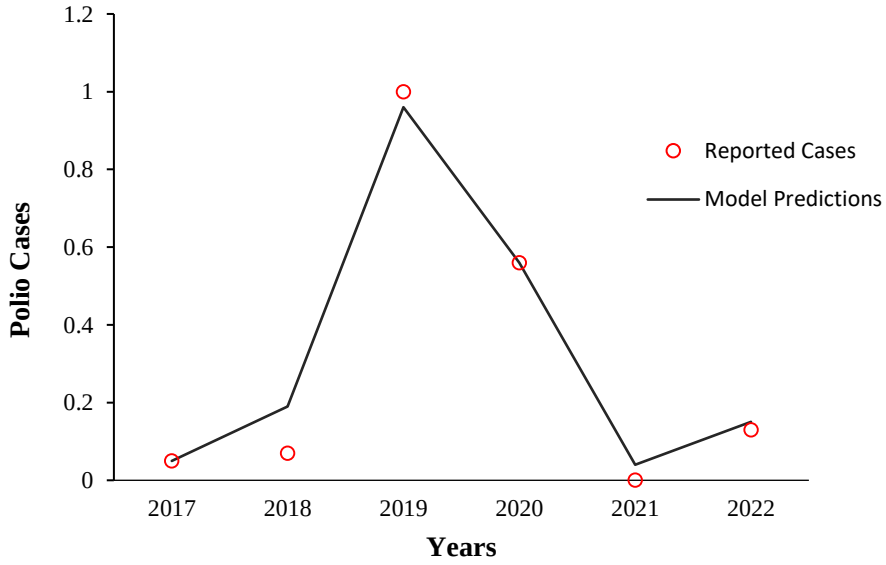


Figure 4. Model fitting results for the reported cases of Polio in Pakistan from 2017-2022.

These results confirmed our assumption that a decrease in vaccination rates led to an increased transmission rate. The estimated parameter values show that asymptomatic individuals pose a significant threat to the susceptible population. Parameter d represents the rate of transmission increment during this time period as a function of t, and its estimated value is presented in **Table 3**. This increase was consistent and steadily rising, so instead of a decline in the epidemic curve, we observed a sharp surge in virus transmission and an increase in cases.

Table 2. WPV1 model parameter values estimated through model calibration.

Estimated Parameters		Values	95% Confidence Interval
Human-Human transmission rates	Transmission rate from exposed to susceptible population (β_E)	$3x10^{-6}\ person^{-1}year^{-1}$	$2.05x10^{-6} – 3.99x10^{-6}$
	Transmission rate from infected to susceptible population (β_I)	$2x10^{-6}person^{-1}year^{-1}$	$1.07x10^{-6} – 3.92\ x10^{-6}$
Environment-Human transmission rate	Transmission rate from environment to susceptible population (β_W)	$1.5x10^{-6}person^{-1}year^{-1}$	$1.04x10^{-6} – 2.94x10^{-6}$

During this period, the transmission of the system was non-autonomous because it depended on the time. In mathematical terms, a system of ordinary differential equations that relies on time as its independent variable is referred to as a non-autonomous system. The rate of transmission, represented by the parameter d increased over time, denoted by t. Because we assume that the increase in transmission during this period was due to a decrease in vaccination rates, the system can be classified as non-autonomous. Consequently, the basic reproduction number (R_0) for this time domain cannot be calculated [28]. For a non-autonomous system where there is no delay between exposure and the appearance of clinical cases, the reproduction number can be calculated by excluding the latent infection period [29]. However, this approach cannot be applied to polio infections.

Model fitting to WPV1 cases in Pakistan during 2020-2022

During the period 2020-2022, there was a more stable spread of infection as transmission no longer increased monotonically. This was a result of higher vaccination rates and decreased exposure of

vulnerable populations to infectious individuals due to stay-at-home orders issued during the COVID-19 pandemic. The data fitting results are shown in **Figure 4** and **Table 3** displays the estimated value of parameter c for this specific time frame. This parameter was used to add an extra dimension and transform the previous system of non-autonomous ODEs into an autonomous system. As a result, the transmission rates of poliovirus during this period were no longer dependent on time, but instead on the prevalence of polio infections in the population. The system is assumed to be time-independent. Transmission now varies based on the contact rates between susceptible and infectious populations, as well as the number of individuals in both groups. Model calibration during this time period revealed that transmission was significantly reduced due to a decrease in contacts and the number of at-risk individuals as immunization rates increased.

Table 3. WPV1 model Parameter values estimated through model calibrations

Parameters	**Values**	**95% Confidence Interval**
Rate of increase in transmission rate during the period of 2017-2019 **(d)** (Period 1)	0.385/year	0.304 – 0.495
Adjustment Parameter **(c)** (Period 2)	0.8/person	0.02 – 0.97

Here, in-sample validation is used for the re-substitution validation method, where the goodness of fit is measured and compared using the root mean square error (RMSE) for our assumption of time-dependent transmission rates while for the model of COVID-19 transmission, normalized root mean square error (NRMSE) was used [12]. The formula for RMSE has been given as

$$\text{RMSE} = \sqrt{\frac{\sum_{i=1}^{N}(\text{Predicted}_i - \text{Actual}_i)^2}{N}}$$

The 'N' represents the number of total data points in the data set. The RMSE value is 0.05, indicating good model accuracy and validating our assumption of time-dependent transmission rates compared with other models that consider constant transmission scenarios. Yang and Wang, (2021) also tested the validity of the constant transmission rate scenario for COVID-19 transmission and found it to be less accurate than the assumption of a time-dependent transmission rate. On the other hand, we did not consider the model fitting results for the constant transmission rate for the entire period of 2017-2022. However, upon testing the validity of this assumption using the RMSE, the

obtained value is 0.44. This makes the constant transmission rate scenario less fitting than the time-dependent transmission rates for the two time periods.

Reproduction number (R_0)

The basic reproduction number (R_0) is the average number of secondary infections caused by an initially infected person over their lifetime when the entire population is susceptible. If $R_0 \leq 1$, the pathogen will be cleared from the population. However, if $R_0 > 1$, the pathogen can spread throughout a susceptible population. R_0 is a crucial parameter for estimating the ability of a pathogen to spread and cause an outbreak. This provides valuable insights into the efforts required to control the disease, such as prompt case identification, quarantine measures, and physical distancing to prevent contact between susceptible and infected individuals.

In our developed model, the first time period is a non-autonomous time-dependent system, making it challenging to define the reproduction number for this period. The argument here is that non-autonomous disease dynamic systems consider the periodicity of infection occurrences. Therefore, the reproduction number becomes a function of time which can be calculated either by disregarding the recruitment of susceptible individuals in the model, or by overlooking the latent stage of infection.

However, the reproduction numbers of time-averaged systems (autonomous systems) are sufficient to explain the mitigation policies that need to be implemented. Thus, in the second instance, our model is an autonomous dynamic system in which the rate of disease transmission is solely a function of prevalence (I). The reproduction number (R_0) for this period can be calculated as follows.

$\beta_E(I, t) = \beta_E(I)$, $\beta_I(I, t) = \beta_I(I)$ and $\beta_W(I, t) = \beta_W(I)$ for $T_2 \leq t \leq T$.

Here, the standard method for calculating the basic reproduction number, which is the next-generation matrix technique was used

Apparently, the ODE system of equations has a condition for the absence of the disease referred to as the disease-free equilibrium (DFE) at

$X_0 = (S_0, E_0, I_0, R_0, W_0) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$

Here, E, I and W are considered as the infectious elements. Matrices F and V represent new infections and transitions between different disease stages, respectively.

$$F = \begin{bmatrix} \beta_{E0}(0)\,S_0 & \beta_{I0}(0)\,S_0 & \beta_{W0}(0)\,S_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \qquad V = \begin{bmatrix} u_1 & 0 & 0 \\ -\alpha(1-p) & u_2 & 0 \\ -\alpha p & -q & 0 \\ -\xi_1 & -\xi_2 & \sigma \end{bmatrix}$$

Here $u_1 = \alpha + \gamma_1 + \mu$ and $u_2 = q + \gamma_2 + \mu$. Then, R_0 of the given model will be the spectral radius of the next generation matrix FV^{-1} which is

$$R_0 = \rho\,(FV^{-1}) = R_E + R_I + R_W$$

Where

$$R_E = \frac{\beta_E(0)S_0}{u_1} = 1.33$$

$$R_I = \frac{\alpha(1-p)\,\beta_I(0)S_0}{u_1 u_2} = 0.15$$

$$R_W = \frac{\beta_W(0)S_0}{\sigma u1}\left(\xi_1 + \frac{\xi_2\,\alpha(1-p)}{u2}\right) = 0.13$$

It estimates the disease risk during the second period. The first two terms, R_E and R_I represent the role of human-to-human transmission routes from non-clinical and clinical infectious populations respectively. The third term, R_W characterizes the impact of the environment on the human transmission pathway through sewage contamination. Thus, we proceed as follows:

$$R_0 = 1.33 + 0.15 + 0.13 = 1.61$$

The values indicate that exposure to asymptomatic infectious population makes the highest contribution, followed by the infected population, and then the environment makes the lowest contribution. All of these values combined make R_0 almost equal to unity, indicating the persistence of the disease. Although the environment was found to play the least role in virus transmission, the rates were close enough to the rates of infected to susceptible populations, indicating that with low vaccination coverage and poor WASH infrastructure, the wild poliovirus contaminated environment can impact disease propagation.

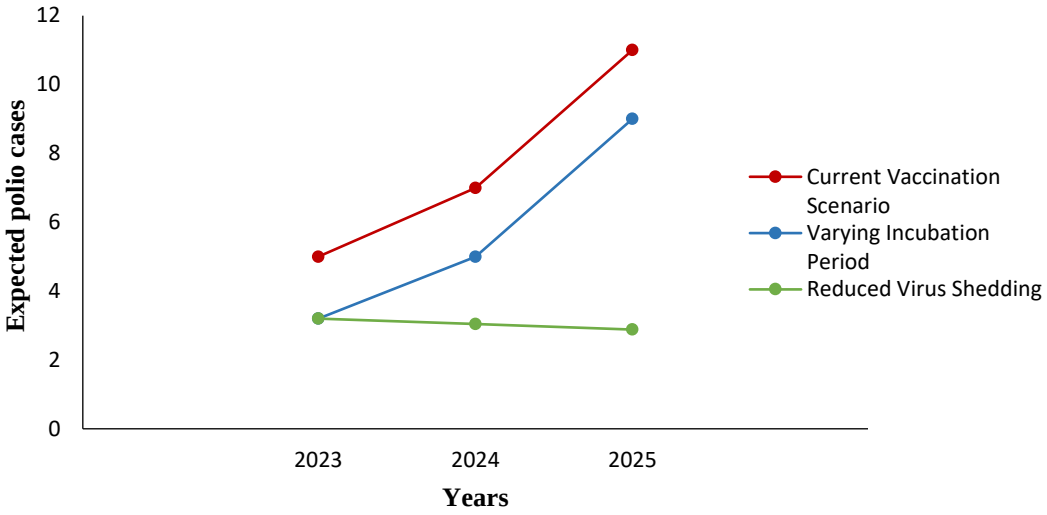
Another important measurement is the effective reproduction number (R_{eff} or R_t), which is the expected number of new infections caused by infectious individuals, to which some individuals in the target population may no longer be susceptible. It is important to reduce this number to below one to control the spread of infection. In our case, our whole population was not susceptible; therefore, we calculated

the effective reproduction number for the second time period using the derived value of the basic reproduction number.

$$R_{eff} = R_0 \left(\frac{S}{N}\right)$$

As a result, a value of 0.12 for the effective reproduction number is obtained, indicating the effectiveness of current intervention strategies in reducing the number of susceptible populations in the country. This is because the value of R_{eff} is directly proportional to the magnitude of susceptible individuals in a target population, and when the number of at-risk individuals is high, the value of R_{eff} is greater than 1. When the susceptible population is lower, the value of R_{eff} is closer to 0, and the disease is contained.

Using the estimated values of the parameters through the model calibration, predictions for the occurrence of future polio cases in Pakistan could be made in the near future. We simulated the developed model considering that the transmission rate no longer increases monotonically. Following the current vaccination scenario and assuming that vaccination rates can keep missing children at the current proportion of nearly 1% every year, the prediction of future transmission scenarios **Figures 5 and 6** indicated that the transmission will remain endemic and that the number of reported cases will be lower than that previous years. The graph depicts that the model has the better predictive ability with the expected polio cases for the year 2023 to be five with the maintained vaccination rate. On the other hand, the vaccination rate dropped in 2023 and reported cases were almost six in the same year closer to the model predictions [30,31]. However, the number of asymptomatic infections remains a problem, as the graph indicates a continuous rise in latent infections as the susceptible population accumulates over the years.



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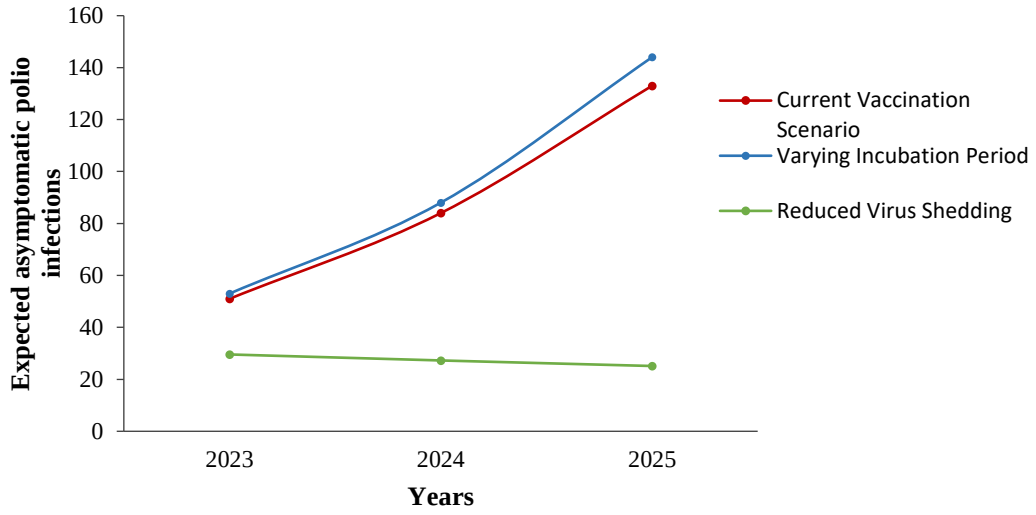
312 **Figure 5.** The expected number of polio cases from 2023-2025 with the ongoing immunization rates
313 and when the incubation period reaches 21 days. The green line depicts the decreasing incidence rate
314 with the reduction in the virus shedding rate of the asymptomatic population.



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316 **Figure 6.** The expected asymptomatic polio infections from 2023-2025 with the ongoing
317 immunization strategies and when the incubation period reaches 21 days. The green line depicts the
318 reduction in asymptomatic infections with reduced virus shedding.

319 **Simulations with varying parameters**

320 The values of the model parameters can vary due to various factors, including environmental
321 conditions, the evolution of population immunity, and changes in population movement patterns across
322 the country. Here, the influence of the incubation period and virus-shedding rate of the asymptomatic
323 population was estimated based on the proportion of reported cases. **Figure 5** indicates that a higher

incubation period leads to a lower number of reported cases. It has been observed that the poliovirus incubation period can range from 7-21 days or even up to 35 days. It also indicates that with an increase in the virus incubation period, the number of latent infections will increase as the virus takes longer to reach the symptomatic phase. Thus, there will be more asymptomatic individuals, posing a threat to the susceptible population. **Figure 6** presents the scenario when the poliovirus incubation period reaches 21 days and the number of latent infections is higher. This increases the threat of silent transmission of poliovirus in the community, as sub-clinical infections are a major source of silent circulation of the virus. The scenario can also be attributed to the failure of vaccination campaigns to achieve the target vaccination coverage [32]. The increase in virus incubation can be attributed to reduced or partial immunization. Incomplete vaccination due to various extrinsic and intrinsic factors can lead to infections with longer incubation periods. This increase in the incubation period and asymptomatic infections, along with the resultant decrease in the number of reported cases, presented a scenario of silent circulation increasing uncertainty in public health measures [33]. This is particularly important in the case of isolated under-vaccinated sub-populations which pose a threat to the entire community. This can also be detected through environmental surveillance. The presence of positive samples indicated silent transmission of poliovirus throughout the country. This situation suggests that more targeted intervention efforts are required to vaccinate under-vaccinated partitioned sub-populations.

Another scenario of reducing the virus-shedding rate in asymptomatic individuals was tested by changing this parameter. A significant decline in the number of asymptomatic infections was observed. In addition, the curve for the proportion of the infected population flattens over time with the reduction of the virus-shedding rate by the sub-clinical infectious population. The shedding rates for the exposed and reported infections were considered equal. **Figures 5** and **6** represent the expected reported cases and latent infections to occur in the next three years, respectively, when the virus-shedding rates of the infected and exposed are equal. This indicates the importance of higher vaccination coverage and the need to consider population movement patterns in targeted immunization campaigns. This will also help reduce the number of positive environmental samples with wild poliovirus in the entire country. The graph suggests that with a reduction in the virus-shedding rate of latent individuals, the number of reported cases of poliovirus will continue to decrease until consistent intervention strategies completely remove the infected individuals from the community. This will ultimately help eradicate the virus from the country.

Discussion

In this study, an ordinary differential equation-based deterministic model was developed for poliovirus persistence in Pakistan. The model applies the concept of time-dependent transmission rates of polio infections. This assumption is usually considered for seasonal infections and takes into consideration the periodicity of the occurrence of a disease [34]. Moreover, the role of poliovirus-contaminated sewage water in the spread of infection was considered. In this model, both direct and indirect transmission routes, considering human-human and environment-human transmission, were incorporated. The period of 2017-2022 was considered for the numerical simulations and model validation. The considered time domain of 6 years was divided into two 3-year time periods: variable transmission rates that increase monotonically with time in Period 1, and variable transmission rates that are shaped by disease prevalence and human behavior in Period 2. The model was applied to the WPV1 case data from Pakistan. The results of the present data fitting approach based on different transmission rates in different time periods show a better performance than that based on the standard approach of using uniform, constant transmission rates throughout the entire time domain.

Martinez-Bakker et al. [35] previously conducted an analysis on the ecology of polio epidemics in the mid-20th century. The findings revealed that prior to the introduction of vaccination, only approximately 6% of infections were officially reported. The primary cause of these epidemics was the rise in birth rates. The study ultimately concluded that for vaccination campaigns to be more effective, it is crucial to consider population demographics and the seasonality of infections. Conversely, our modelling results indicate that as we approach the era of polio eradication, population demographics play an increasingly significant role in the occurrence of polio infections in Pakistan. The authors acknowledge that subclinical infections are more prevalent today than in the pre-vaccine era, which aligns with our current findings. Our model simulations predicted that the virus will continue to transmit in the presence of immunocompromised children. Therefore, it is imperative to monitor the movement patterns of asymptomatic unvaccinated individuals capable of spreading infections throughout the country. The rates of pathogen transmission are determined by two critical factors: the frequency of contact between susceptible and infectious individuals and the duration of contact and immunity within the population [36].

Molodecky et al. [37] performed spatiotemporal analysis of routine surveillance data for wild poliovirus in Pakistan. The findings indicate that movement patterns are not as influential in predicting future polio cases in the country as the virus is mostly restricted to certain areas. However, our results revealed that movement patterns are major contributors to the constant expansion of the virus in Pakistan and can contribute significantly to accurate predictions of future polio cases. This is evident

from the reduction in the number of cases during the COVID-19 lockdown when movement was restricted and transmission was assumed to no longer increase monotonically. Moreover, in 2023 Sindh reported 2 of the total 6 polio cases in Pakistan after almost three years of being case-free suggesting the important role of population movement in the spread of the disease across the country [38].

Browne et al. [39] investigated the impact of routine and supplementary immunization activities, as well as seasonality and environmental transmission, on the effective reproduction number for poliomyelitis. The study concluded that migration rates can significantly affect the overall reproduction number and optimal vaccine strategies. This emphasizes the importance of synchronizing pulse (supplemental) vaccination strategies and suggests that supplementary immunization, considering complete indirect virus transmission through the environment, would be most effective in reducing the reproduction number. Our simulation-based calculation of the effective reproduction number supports the effectiveness of national immunization strategies against poliovirus in Pakistan as it shows a decreasing trend in the incidence of new cases. Furthermore, our study considered both direct and indirect routes of virus transmission and the calculated effective reproduction number suggests that persistent supplementary immunization campaigns, when combined with spatiotemporal analysis of routine surveillance data, will ultimately lead to virus eradication.

The proposed model can be further enhanced by incorporating spatial data on vaccination coverage and environmental surveillance results. This will enable the prediction of future polio infections and the allocation of timely resources across the country to stop the transmission of the virus. However, the study did not consider population demographics [24]. Therefore, the model can be modified to explicitly include the demographics of the entire vulnerable population in Pakistan. Moreover, the shedding rate of the virus in the target population may also be affected by the OPV vaccination status [40]. The model application did not consider the evolution of wild poliovirus in Pakistan over time. Consequently, it may not accurately reflect the infection prevalence in the distant future, as disease features can vary significantly over time. By including such dynamics associated with persistent virus transmission in the country, the modelling results can be improved and intervention strategies can be optimized to achieve eradication.

Conclusion

The transmission of wild poliovirus type 1 is expected to remain low in Pakistan which is subject to high vaccination coverage. The time-dependent transmission rates assumption for poliovirus spread in the country has a better predictive ability than the constant transmission rate models. Our

419 modelling framework can be further enhanced by incorporating spatial data on immunization and
420 routine surveillance to predict future cases in Pakistan and allocate preemptive measures. Furthermore,
421 the model concluded that indirect virus transmission through the fecal-oral route can impact the disease
422 prevalence among under-immunized communities with poor WASH infrastructure across the country.
423 The findings of this predictive model are important for eliminating the spread of wild poliovirus from
424 the remaining endemic countries (Pakistan and Afghanistan) by enhancing the activity of the Global
425 Polio Eradication Initiative.

Ethical Approval

The authors certify that they complied with the Principles of Ethical Publishing Rules.

Consent

The data reported were derived from studies already published and quoted in the reference list. Those papers mentioned informed consent that, depending on the studies, was implied to participate in the study, verbal or written, or a combination of these variants during the follow-up.

Author Contribution:

All authors contributed to the submitted manuscript. Laiba Noor conceived the idea and contributed to data collection and model simulations. Ayesha Shahid contributed to data collection and manuscript preparation. Muhammad Imran Arshad reviewed and supervised the process.

Author Agreement

All authors have seen and approved the final version of the manuscript for submission.

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