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A Systematic Review

Unpacking the Pox: A Systematic Review of Chickenpox in Pakistan

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ABSTRACT

Background: Chickenpox, caused by the varicella-zoster virus (VZV), remains an underreported and understudied public health concern in Pakistan, especially in the wake of recent outbreaks and the emergence of novel genotypes. Despite global efforts toward varicella control, Pakistan lacks comprehensive data on epidemiological trends, diagnostic practices, and viral strain diversity, hindering effective disease management and vaccination strategies. **Objective**: This systematic review aimed to evaluate the epidemiological patterns, clinical characteristics, diagnostic approaches, and molecular strain variations of chickenpox in Pakistan from 2004 to 2025, with a focus on identifying diagnostic gaps and implications of emerging genotypes for public health and vaccine planning. **Methods**: A systematic review was conducted following PRISMA guidelines. A total of eight eligible observational and cross-sectional studies were selected from an initial pool of 18 records after applying defined inclusion and exclusion criteria. Studies were retrieved from databases such as PubMed, PakMediNet, and Google Scholar, focusing on English-language articles related to chickenpox in Pakistan. Diagnostic methods included clinical evaluation, ELISA, complement fixation tests, and PCR. The primary outcomes assessed were complication prevalence, strain identification, and diagnostic accuracy. Ethical considerations followed the Helsinki Declaration where applicable. Descriptive statistics and comparative analyses were extracted; SPSS software was noted as the primary tool in eligible studies. **Results**: Key findings included 58.8% VZV positivity via complement fixation tests in Punjab, 30% thrombocytopenia prevalence in Khyber Pakhtunkhwa, and the first-time identification of the M4 genotype in 66.7% of outbreak cases in Islamabad and Punjab post-COVID-19. The mean pediatric age was 5.3 years with seasonal clustering, while adults aged 15–50 exhibited more severe complications including ARDS (0.078%). PCR proved to be a superior diagnostic method, and acyclovir treatment showed improved outcomes in severe cases. **Conclusion**: Chickenpox in Pakistan exhibits significant regional and demographic disparities, with emerging genotypes such as M4 posing challenges for existing diagnostic and vaccination strategies. Enhanced genomic surveillance, standardization of diagnostic protocols, and selective immunization programs are essential for reducing morbidity and controlling future outbreaks, especially among high-risk groups.

Keywords: Chickenpox, Varicella-Zoster Virus, Epidemiology, Genomic Surveillance, Diagnostic Techniques, Pakistan, Public Health

INTRODUCTION

Chickenpox, caused by the varicella-zoster virus (VZV), continues to pose a significant public health burden in Pakistan, especially in the context of recurrent outbreaks and complications in adult and immunocompromised populations. The disease, characterized by a vesicular rash, fever, and malaise, is typically self-limiting in children but may lead to severe complications such as pneumonia, acute respiratory distress syndrome (ARDS), and thrombocytopenia in adults (1). In recent years, regional outbreaks—such as the widespread episode in Chitral during 2023 that affected

hundreds—have underscored systemic weaknesses in disease monitoring and response strategies in high-density or underserved areas (2). Similar challenges have been observed in Faisalabad, where outbreaks have resulted in notable morbidity and strained local healthcare services, highlighting the urgent need for reliable surveillance systems and preventive frameworks including vaccination (3).

Despite the global burden of varicella being well documented, there is a paucity of localized epidemiological data from low- and middle-income countries like Pakistan. A seroepidemiological survey conducted across various age groups in the country found that only 41.8% of individuals up to 30 years old had immunity to VZV, indicating a large susceptible population (5). This low seroprevalence, coupled with insufficient integration of the varicella vaccine into Pakistan's Expanded Programme on Immunization (EPI), increases the likelihood of outbreaks among children, adolescents, and institutionalized adults. The absence of routine varicella immunization, unlike in many high-income countries where childhood vaccination has significantly curtailed disease incidence, means that Pakistan remains vulnerable to both endemic transmission and imported outbreaks (22). Consequently, children continue to contract the disease at school and household levels, with older unvaccinated cohorts at risk of developing more severe complications (17).

Molecular investigations have begun to shed light on the diversity and evolution of VZV strains circulating in the country. Traditionally, the genotypes M1 and M2 have dominated in tropical and subtropical regions (21). However, recent genomic surveillance has identified the emergence of the M4 genotype in Pakistan for the first time in 2024, following the COVID-19 pandemic (6). This novel genotype has been associated with greater clinical severity and increased incidence during outbreaks, suggesting potential vaccine escape mechanisms or altered virulence traits. These findings mark a shift in the genotypic landscape of VZV in Pakistan and warrant urgent attention from both virologists and policymakers. As the current varicella vaccine in use (Oka strain) is developed against classical genotypes, there are growing concerns that M4 and other emerging strains may compromise vaccine efficacy in the future (6, 16).

The diagnostic landscape for chickenpox in Pakistan remains highly variable. While clinical diagnosis has historically been the standard due to limited laboratory infrastructure, newer studies have incorporated serological techniques such as enzyme-linked immunosorbent assay (ELISA) and complement fixation tests, and more recently, molecular diagnostics like polymerase chain reaction (PCR) and genotyping (20). However, laboratory confirmation remains inconsistent across healthcare settings, particularly in rural areas. The lack of standardized diagnostic protocols undermines effective outbreak tracking and strain identification. Enhanced diagnostic capacity is essential not only for clinical management but also for understanding epidemiological trends and planning immunization strategies.

Despite sporadic studies and outbreak investigations, comprehensive synthesis of data on chickenpox in Pakistan remains limited. Current literature does not adequately cover the geographic, clinical, diagnostic, and genomic aspects of the disease. There is a notable underrepresentation of data from provinces such as Balochistan and rural Sindh, creating blind spots in national surveillance. Furthermore, pediatric populations and age-associated disease burden trends have not been thoroughly investigated, though preliminary findings suggest seasonal clustering and potential under-diagnosis in younger age groups (1, 11). These gaps hinder the development of robust health policies and impede the formulation of region-specific vaccine strategies.

Given these limitations, this study aims to conduct a systematic review of the literature on chickenpox in Pakistan from 2004 to 2025, with an emphasis on epidemiological trends, clinical outcomes, diagnostic practices, and genomic characterization of circulating VZV strains. By compiling and analyzing peer-reviewed data from multiple provinces and settings, this review seeks to fill critical knowledge gaps and offer evidence-based recommendations for improving surveillance, diagnosis, and prevention of chickenpox in Pakistan. The central research question guiding this review is: What are the epidemiological, clinical, diagnostic, and genomic patterns of chickenpox in Pakistan, and how can this information inform national public health interventions?

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to synthesize available literature on chickenpox (varicella-zoster virus, VZV) in Pakistan published between 2004 and April 2025. The primary objective was to examine the epidemiological distribution, clinical characteristics, diagnostic methodologies, and genomic trends of chickenpox in the country.

A comprehensive electronic search was conducted using databases such as PubMed, Google Scholar, PakMediNet, and other indexed national medical journal repositories. Search terms included combinations and variations of the following keywords: "chickenpox", "varicella-zoster virus", "VZV", "Pakistan", "epidemiology", "clinical outcomes", "diagnosis", "molecular genotyping", and "outbreaks". Filters were applied to include only English-language, peer-reviewed or indexed journal articles published from January 2004 to April 2025. Grey literature, non-peer-reviewed editorials, and institutional reports were excluded.

The initial database search yielded 18 studies. Duplicates were identified and removed, leaving 17 unique records for title and abstract screening. Of these, five studies were excluded based on predefined exclusion criteria. Specifically, these excluded studies consisted of a parental perception survey, a numerical modeling study on disease transmission without clinical correlation, a study on vaccine-preventable diseases lacking chickenpox-specific data, a general population survey unrelated to chickenpox epidemiology, and a single-patient case report with no population-level insights. This screening process resulted in eight full-text articles being assessed for retrieval and eligibility. An additional four studies were excluded at the full-text review stage due to irrelevance to the core parameters of the review. These parameters required included studies to

report on at least one of the following: epidemiologic trends, clinical outcomes, diagnostic practices, or genomic findings related to VZV in Pakistan. Therefore, only studies that provided empirical data on these aspects were retained for final inclusion.

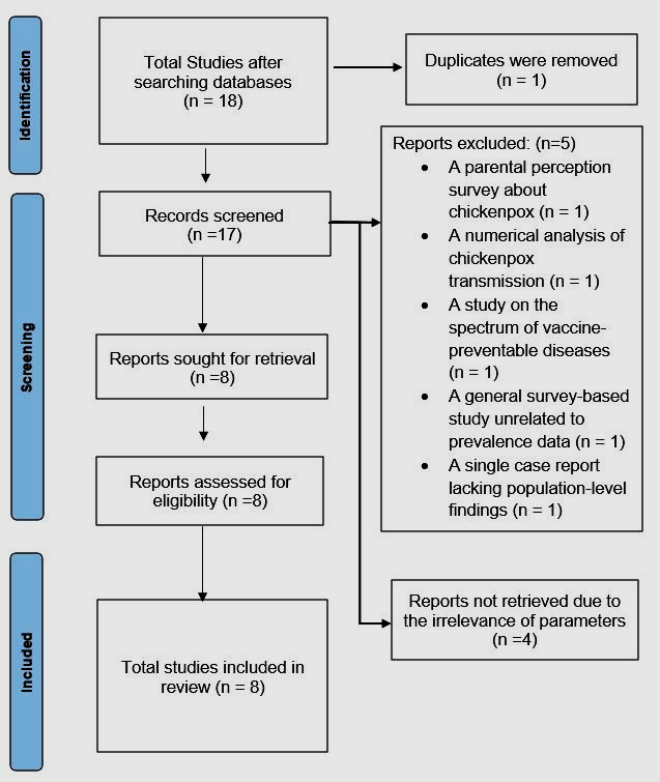

Figure 1 A PRISMA flow

The final review included eight studies that met all eligibility criteria. These studies represented diverse methodological designs including cross-sectional surveys, observational hospital-based surveillance, outbreak investigations, and retrospective chart reviews.

Only research conducted within Pakistan's geographic boundaries was considered, and all included studies focused on human populations affected by VZV. Studies with a primary focus on other vaccine-preventable diseases were excluded unless they disaggregated and reported chickenpox-specific data. Laboratory-confirmed data using serological (ELISA, complement fixation tests) or molecular (PCR, genotyping) methods were favored but not mandatory for inclusion if substantial clinical or epidemiological data were available.

RESULTS

Following the PRISMA-based selection process, 18 studies were initially identified. After removal of one duplicate, 17 records were screened by title and abstract. Of these, five were excluded due to irrelevance to the research objectives. Four additional studies were excluded upon full-text review as they did not meet inclusion criteria regarding chickenpox-specific epidemiologic, diagnostic, or genomic data. Ultimately, eight studies were included for final synthesis. The study selection process is summarized in the PRISMA diagram (Figure 1).

The included studies displayed considerable geographical skewness, with a predominant concentration in Punjab (5 out of 8 studies), followed by Khyber Pakhtunkhwa (KPK), Islamabad, and Sindh. No studies from Balochistan were found, highlighting a significant regional gap. Punjab-based data included an outbreak of 102 cases in a military training center in Attock, where 58.8% tested positive for varicella-zoster virus via complement fixation tests (8). Faisalabad data identified a 0.078% prevalence of ARDS among adult varicella patients, suggesting a link between severe disease and comorbidities (9). Adult chickenpox cases constituted 30% of reported infections in another KPK-based study, indicating higher susceptibility and morbidity in this demographic (10).

Pediatric data were limited, with only one detailed study conducted in Islamabad reporting a mean patient age of 5.3 years (1). This study observed significant clustering during the summer season, with both primary and secondary cases among children suggesting underdiagnosis and underreporting in the pediatric age group. In rural Sindh, a survey of 223 clinically diagnosed patients across nine union councils in Taluka Khipro showed a high burden in agrarian and low-income communities, indicating that socioeconomic and environmental factors may influence disease distribution (11).

A large dataset from Rawalpindi involving over 10,000 patients revealed that herpes zoster prevalence increased with age, with a peak in the 81–102 years age group (14.06%), demonstrating the aging population's vulnerability (12). These results emphasize the need for age-stratified surveillance and preventive interventions, particularly in older adults and institutionalized populations. A comprehensive summary of complications across key studies is provided in Table 3.

Table 1. Geographic Distribution of Chickenpox Studies and Key Findings in Pakistan

Key Study	Province	Sample Size	Notable Findings
(8, 9)	Punjab	102, 27	58.8% VZV positivity via CFT; 0.078% prevalence of ARDS in hospitalized adult cases
(10, 13)	Khyber Pakhtunkhwa	270, 200	30% of adult cases had thrombocytopenia; 90.5% presented with mild disease
(1, 6)	Islamabad	243, 267	Mean pediatric age: 5.3 years; first detection of VZV M4 genotype post-COVID-19
(12)	Rawalpindi, Punjab	10,169	Age-associated increase in herpes zoster; highest prevalence in the 81–102 year group

Table 2. Summary of Studies on Chickenpox in Pakistan (2004–2025)

Authors	Year	Province(s)	Study Area	Design	Duration	Months	Sample Size	Statistical Methods	M/F Ratio	Diagnostic Method(s)	Treatment	Age (Years)	Virus Type / Strain
(14)	2004	Punjab	PAF Hospital Sargodha, Military Hospital Rawalpindi	Observational Descriptive	2 weeks	0.5	60	Student t-test	6.5	Clinical	Supportive care	15–50	VZV
(13)	2006	Sindh & KPK	Military Hospital Malir (Karachi), CMH Abbottabad	Cross-Sectional Analytical	May 2003 – Jun 2004	14	200	Descriptive analysis	10.76	Clinical	Acyclovir	15–40	VZV
(10)	2006	KPK	CMH Attock	Observational Descriptive	Jul 2003 – Jun 2004	12	270	Descriptive analysis	89.0	Clinical	Acyclovir	15–40	VZV
(8)	2016	Punjab	Military Training Center, Attock	Cross-Sectional	Nov 2007 – Jan 2008	3	102	Descriptive analysis	∞ (undefined)	CFT, ELISA, Direct Immunofluorescence	Supportive care	16–35	VZV
(9)	2018	Punjab	Allied Hospital, Faisalabad	Cross-Sectional Descriptive	Jan 2017 – Sep 2017	9	27	Descriptive analysis	5.75	Clinical and Radiological	Ventilatory support, conservative therapy	≥16	VZV
(1)	2022	Islamabad	Federal General Hospital, Pediatric Department	Prospective Observational	Jan 2018 – Dec 2019	24	81	Independent t-test, Chi-square	0.88	Clinical	Supportive care (Symptomatic)	5.31 ± 3.3	VZV
(6)	2024	Islamabad & Punjab	PIMS, BBH Rawalpindi, Allied Hospital, NIH	Observational, Surveillance & Outbreak Investigation	Mar 2019 – Dec 2022	45	267	Chi-square test, Odds ratios	1.62	Molecular (PCR, Genotyping)	Supportive care	1–25, >25	M4

CFT = Complement Fixation Test, ELISA = Enzyme-Linked Immunosorbent Assay, CMH = Combined Military Hospital, M/F = Male to Female ratio, PCR = Polymerase Chain Reaction, NIH = National Institute of Health, PIMS = Pakistan Institute of Medical Sciences, BBH = Benazir Bhutto Hospital, KPK = Khyber Pakhtunkhwa.

Adult patients (aged 15–50 years) were the primary focus in most studies, particularly those reporting complications. In a cross-sectional study from KPK, thrombocytopenia was observed in 30% of adult varicella cases, confirming a significant hematological complication (10). Another study from Punjab linked ARDS with varicella pneumonia, although its prevalence remained low (0.078%) and was mainly seen in adults with underlying respiratory conditions (9). A prospective pediatric study reported that most children exhibited typical mild symptoms and recovered with supportive care (1), yet data on pediatric complications remain sparse.

Notably, a 2024 multicenter study documented the emergence of the M4 genotype, which was associated with severe disease in 66.7% of cases (6). This strain was not linked to any specific age group, although more severe outcomes were observed in patients over 25 years of age. Gender distribution across studies generally reflected male predominance, which may be attributed to greater institutional access or care-seeking behavior, rather than biologic susceptibility. Diagnostic practices varied widely across included studies. Earlier investigations relied heavily on clinical diagnosis supplemented by serological methods such as complement fixation tests and ELISA. In a military outbreak investigation, complement fixation testing showed a detection rate of 58.8%, compared to 29.4% for ELISA, reflecting variability in diagnostic sensitivity (8). Despite these tools, many rural and under-resourced areas continued to rely exclusively on syndromic diagnosis by local clinicians (11).

In contrast, more recent studies have shifted toward molecular diagnostics. A pivotal 2024 study employed PCR and genotyping techniques to characterize circulating strains, revealing the presence of the M4 genotype in 66.7% of samples across Islamabad and Punjab (6). PCR targeting the ORF22 gene enabled precise identification and phylogenetic analysis of this genotype, positioning molecular testing as the gold standard for future diagnostic and surveillance efforts. However, the implementation of PCR remains limited to tertiary centers, with most healthcare facilities lacking standardized protocols or equipment.

Treatment approaches across all studies remained predominantly supportive. Antipyretics, antihistamines, and hydration were widely used for symptom management. Acyclovir was selectively administered in severe adult cases, which showed faster recovery and shorter symptom duration in 90.5% of patients (13). Only critical cases, particularly those with respiratory complications like ARDS, required ventilatory support and intensive care, as noted in Faisalabad's tertiary care setting (9).

Table 3. Complications Reported in Pakistani Studies on Chickenpox

Key Study	Province	Reported Complication	Prevalence (%)
(10)	Khyber Pakhtunkhwa	Thrombocytopenia	30.00
(9)	Punjab	Acute Respiratory Distress Syndrome (ARDS)	0.078
(6)	Punjab / Islamabad	Severe clinical presentation associated with M4 genotype	66.67
(12)	Punjab	Age-associated increase in herpes zoster prevalence in older adults	1.03

One of the most significant findings of this review was the post-COVID-19 emergence of the M4 genotype in Pakistan, first detected in a 2024 hospital-based study (6). This strain was identified through a two-amplicon PCR approach, with subsequent genotyping and phylogenetic analysis confirming its divergence from M1 and M2 genotypes, which had previously dominated the region. Phylogenetic trees demonstrated that the M4 genotype formed a distinct clade, with potential implications for virulence and vaccine escape. Notably, M4 was detected in all age groups, although clinical severity was disproportionately higher in adults. This trend highlights the inadequacy of current vaccine strategies, especially since the Oka-based varicella vaccine—targeted against classical genotypes—may not offer sufficient protection against emerging strains. The study found no significant association between gender and disease severity, although more male cases were reported. These findings underscore the necessity of routine genomic surveillance, regional sequence databases, and integration of molecular diagnostics into national public health infrastructure. Continued monitoring of strain evolution will be critical for timely outbreak detection and for guiding future vaccine policy adaptations.

DISCUSSION

The findings of this systematic review highlight a substantial yet underappreciated burden of chickenpox in Pakistan, with notable regional, age-specific, and genotypic variability. The resurgence of chickenpox cases, particularly in the post-COVID-19 period, appears to be driven by both immunization gaps and evolving viral dynamics. The detection of the novel M4 genotype for the first time in Pakistan in 2024 underscores this evolution, with its presence strongly associated with increased clinical severity, especially among adults. This is consistent with international literature where novel or recombinant VZV strains have been linked to enhanced virulence and outbreak potential (6, 16). The review also confirms prior observations from the Southeast Asian region, which show that while M1 and M2 genotypes dominate globally, emerging clades like M4 may represent region-specific adaptations potentially influenced by immune pressure or vaccine coverage variability (21). The clinical findings reinforce the differential disease burden across age groups. While pediatric cases were generally mild and self-limiting, adult patients exhibited higher complication rates, including thrombocytopenia and varicella pneumonia progressing to ARDS, even in immunocompetent individuals (9, 10, 18). This pattern aligns with data from other low- and middle-income countries (LMICs), where delayed varicella exposure due to shifting population dynamics has resulted in an increasing number of susceptible adults, thereby raising the risk of severe outcomes (22). The low seroprevalence of VZV antibodies in individuals under 30 years of age in Pakistan (5) supports the argument that a large proportion of the population remains

vulnerable, particularly in the absence of a universal vaccination strategy.

Historically, clinical diagnosis has been the cornerstone of case identification in Pakistan. However, the transition toward more accurate diagnostic modalities such as ELISA and PCR, observed in recent years, marks a critical advancement. PCR, in particular, offers superior specificity and sensitivity and has become essential for strain identification and outbreak investigation (6, 20). Despite this progress, limited diagnostic infrastructure and underuse of laboratory confirmation in rural and resource-limited settings continue to hinder timely outbreak detection and strain characterization. These limitations not only restrict the granularity of surveillance data but also delay the implementation of control measures during epidemic events. Comparatively, nations with established PCR-based diagnostic algorithms have achieved more accurate disease mapping and effective targeted immunization efforts, exemplified by the decline in varicella incidence in regions like North America, South Korea, and Saudi Arabia following universal vaccination programs (22).

The emergence of the M4 genotype in Pakistan, documented in 66.7% of outbreak-associated cases in 2024, presents a potential public health inflection point. This strain's genetic divergence from classical vaccine-targeted genotypes such as the Oka strain raises important questions about vaccine escape and the need for genotype-informed vaccination policies. The current monovalent varicella vaccines may exhibit reduced efficacy against divergent clades, particularly if strain-specific neutralizing epitopes are altered (6, 16). Such shifts necessitate the establishment of VZV genomic surveillance frameworks akin to those used for influenza and SARS-CoV-2, allowing real-time tracking of mutation hotspots and interregional strain migration.

Although the data synthesized in this review offer valuable insights, several limitations must be acknowledged. First, the overall number of studies was small, and regional representation was uneven, with underreporting from provinces such as Balochistan and rural Sindh. This geographic bias limits the generalizability of findings to the national population. Second, the methodological quality varied across studies, with reliance on retrospective or cross-sectional designs, lack of uniform diagnostic criteria, and inconsistent use of molecular tools. Third, many studies did not report stratified outcomes by immunization history, comorbidities, or socioeconomic status, restricting the ability to evaluate risk modifiers comprehensively.

Nonetheless, the review's strength lies in its synthesis of over two decades of clinical, diagnostic, and genomic data on chickenpox in Pakistan, offering a consolidated evidence base for public health action. Importantly, it provides a framework for targeted interventions, including the expansion of diagnostic capabilities, incorporation of PCR-based confirmation in outbreak investigations, and the introduction of sentinel genomic surveillance sites to monitor strain evolution. Furthermore, while universal varicella immunization remains a debated policy in resource-constrained settings, targeted vaccination campaigns—especially for healthcare workers, school-aged children, and adults in high-density institutions—could be a pragmatic first step to reduce transmission and complications (17, 22).

Future research should focus on prospective cohort studies evaluating chickenpox incidence, severity, and vaccine response across different VZV genotypes in Pakistan. Efforts should also be made to sequence viral strains in underrepresented regions and to integrate genotyping data into routine epidemiological reporting. Comparative studies assessing vaccine efficacy against emerging strains such as M4 could inform future modifications to existing vaccines or the development of multivalent formulations. Additionally, integrating varicella surveillance with other vaccine-preventable diseases under the umbrella of national disease control programs could yield synergistic benefits in surveillance efficiency and outbreak response.

A critical appraisal of the existing literature reveals several methodological and evidentiary limitations that constrain the current understanding of chickenpox in Pakistan. Most prior studies employed observational or cross-sectional designs with small sample sizes and limited follow-up, reducing the robustness of causal inferences. Diagnostic methods were inconsistently applied, often relying solely on clinical impressions without laboratory confirmation, thereby limiting diagnostic accuracy and comparability across studies. Moreover, few studies provided granular data on risk stratification by age, comorbidity, or vaccination status, and none explored long-term outcomes or post-infection sequelae. Genomic surveillance, while recently initiated, has not yet achieved sufficient scale or coverage to map interprovincial strain distribution or detect mutation trends in real-time. Despite these gaps, notable progress has been made—particularly the shift from clinical to molecular diagnostics and the first genomic identification of the M4 genotype, which sets the groundwork for future vaccine impact evaluations. However, future research must move beyond isolated outbreak reports toward longitudinal, multicenter studies with standardized protocols for diagnosis, reporting, and strain typing. Such efforts are essential to build a cohesive, evidence-based framework for national surveillance, vaccination policy, and outbreak preparedness.

CONCLUSION

This systematic review of chickenpox in Pakistan from 2004 to 2025 reveals significant epidemiological variability, underdiagnosis, and emerging viral genotypes, notably the M4 strain, which is associated with increased severity and potential vaccine escape. Despite being a vaccine-preventable disease, chickenpox continues to disproportionately affect unvaccinated adults and children in institutional and underserved settings, leading to complications such as thrombocytopenia and ARDS. The findings underscore the need for integrating varicella surveillance into national healthcare infrastructure, enhancing diagnostic capacity through molecular tools, and considering genotype-informed vaccination strategies. Clinically, early recognition and supportive management of severe cases remain essential, while future research must prioritize genomic surveillance, vaccine efficacy studies, and population-level

epidemiology to inform targeted interventions and reduce the disease burden in Pakistan's healthcare system.

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