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Peer Review

Review of: "Integrated Determinants of Persistent Wild Poliovirus Transmission in Pakistan and Afghanistan: The Roles of Cross-Border Mobility, Hard-to-Reach Populations, and Micro-Transmission Hotspots, 2010-2025"

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Reviewer Report

Manuscript: Integrated Determinants of Persistent Wild Poliovirus Transmission in Pakistan and Afghanistan: The Roles of Cross-Border Mobility, Hard-to-Reach Populations, and Micro-Transmission Hotspots, 2010–2025

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J7CEFR

Summary

This manuscript presents a scoping review (2010–2025) examining determinants of persistent WPV1 transmission in Pakistan and Afghanistan. It integrates genomic evidence, environmental surveillance, immunity gaps, micro-transmission hotspots, and operational constraints to argue that the two countries function as a single epidemiological block. The topic is of clear global health importance, and the integrative framing is timely and policy-relevant.

The manuscript is well organized and coherent. The four-domain synthesis (cross-border mobility, immunity gaps, localized hotspots, operational constraints) provides a structured and accessible

framework. With further refinement in evidentiary framing and interpretative balance, this review could make a valuable contribution to eradication discourse.

Major Revisions

Clarification of Evidentiary Framing for Quantitative Claims

The manuscript presents several important quantitative findings (e.g., >85% cross-border genetic linkage, 72% bidirectional transmission, 28% importation risk reduction, 2.1–3.4 million children affected annually). These figures are informative and supported by cited literature. However, additional contextual framing would enhance transparency and methodological clarity.

To strengthen interpretability, the authors may consider:

- Indicating the specific study source and time period associated with each key estimate.
- Providing sample sizes or analytic scope where relevant (e.g., number of isolates analyzed in genomic studies).
- Clarifying that these values derive from individual modeling or surveillance studies rather than pooled meta-analytic synthesis, since this is a scoping review without statistical aggregation.
- Presenting ranges where multiple studies report variation across years.
- Adding a brief methodological note acknowledging that surveillance sensitivity, environmental sampling expansion, and genomic sequencing density evolved during 2010–2025 and may influence reported proportions.

These clarifications would avoid any unintended appearance of unwarranted quantitative precision and further strengthen the manuscript's methodological transparency.

Moderation and Contextualization of the cVDPV2 Strategic Claim

The manuscript argues that rapid interruption of WPV1 transmission represents "the single most effective pathway" to resolving the global cVDPV2 emergency. The structural linkage between WPV1 persistence and cVDPV2 vulnerability is convincingly articulated. However, studies already cited in the manuscript suggest that cVDPV2 epidemiology is shaped by multiple interacting determinants.

For example:

- **Kalkowska et al. (Risk Analysis; Refs 18, 19)** demonstrate through modeling that cVDPV2 transmission is strongly influenced by type-2 immunity gaps following the 2016 OPV switch, campaign synchrony, and outbreak response quality.

- **Thompson & Badizadegan (Pathogens 2024; Ref 44)** emphasize population immunity heterogeneity and OPV2 use patterns as key drivers of outbreak risk.
- **Cooper et al. (Lancet Infect Dis 2024; Ref 13)** document significant cVDPV2 transmission in Nigeria in the absence of endemic WPV1 circulation.

These findings do not contradict the manuscript's thesis but indicate that the relationship is multifactorial rather than singular. The authors may therefore consider moderating the phrasing to describe WPV1 interruption as a *critical structural component* or *essential pillar* of resolving the cVDPV2 emergency, rather than the single most effective pathway. Such refinement would maintain strategic emphasis while aligning more closely with the broader modeling and empirical literature.

Discussion of Seroprevalence and Persistent Transmission

The manuscript reports high seroprevalence (>94–95%) in several high-risk districts while also documenting persistent environmental detection and micro-hotspots. The coexistence of high measured immunity and ongoing transmission is an important and analytically rich issue.

The Discussion would benefit from a deeper exploration of possible mechanisms, such as:

- Spatial clustering below herd immunity thresholds
- Mucosal versus systemic immunity dynamics
- Cohort turnover and birth rates
- Sampling limitations in serological surveys

A brief analytical expansion here would strengthen interpretative depth.

Study Quality Appraisal and Evidence Strength

While PRISMA-ScR methodology is appropriately applied, the review would benefit from a short discussion of heterogeneity and evidentiary strength among included studies. Even a narrative acknowledgment of differences in design (modeling vs. genomic vs. surveillance reports), sampling coverage, and potential bias would enhance rigor.

Minor Revisions

- Address minor typographical issues (e.g., spacing inconsistencies).
- Clarify whether weekly WHO/GPEI surveillance updates were systematically archived or selectively reviewed.

- Consider adding a conceptual synthesis figure integrating cross-border mobility, immunity gaps, hotspots, and operational fragility into a single visual framework.

Overall Assessment

This is a thoughtful and policy-relevant synthesis addressing one of the most consequential remaining challenges in global eradication. The integrative framing of Pakistan and Afghanistan as a single epidemiological block is persuasive and well supported by cited genomic and surveillance evidence.

With enhanced methodological clarity, modest moderation of strategic claims, and deeper analytical exploration of key epidemiological paradoxes, the manuscript would be substantially strengthened.

Declarations

Potential competing interests: No potential competing interests to declare.