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The A6 Shift: A Systematic Review of Coxsackievirus-Associated HFMD across Indian and Global Cohorts

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A B S T R A C T

Coxsackievirus A6 (CV-A6) has become a leading global cause of hand, foot and mouth disease (HFMD), and the disease it produces often departs from the classical picture. These atypical presentations are easily missed, and the result is delayed diagnosis. In India, variable clinical presentation and uneven access to molecular testing are likely to compound the problem. PRISMA 2020–compliant systematic search of PubMed/MEDLINE, PMC, Scopus, Web of Science, IndMED, and ICMR-NIC repositories (January 2000–December 2024). Two independent reviewers screened studies (Cohen's kappa: abstract $\kappa = 0.84$; full-text $\kappa = 0.91$). Twenty studies met the inclusion criteria (7 Indian, 13 global). Both groups showed CV-A6 and CV-A16 co-circulating, with a shift toward CV-A6 dominance after 2015 — reaching roughly 55% of typed isolates globally and about 42% in India. The neuroinvasive burden of Coxsackievirus in India remains essentially uncharacterised (GRADE: very low certainty). The rise of CV-A6 has widened the clinical spectrum of HFMD, and of the factors shaping outcome, diagnostic delay is the one most open to intervention. Pairing updated clinical recognition criteria with targeted molecular testing could reduce unnecessary treatment in resource-limited settings. The clearest research priority is a prospective Indian cohort study combining CSF enterovirus RT-PCR with structured clinical phenotyping.

Introduction

Hand, foot and mouth disease (HFMD) is a common childhood exanthem caused mainly by enteroviruses. For years the usual agents were Coxsackievirus A16 (CV-A16) and Enterovirus A71 (EV-A71) (14), but over the past decade Coxsackievirus A6 (CV-A6) has become dominant in many settings, and it tends to present atypically (20, 12). Widespread vesiculobullous eruptions, eczema herpeticum-like rashes, a Gianotti-Crosti–like morphology, and onychomadesis appearing weeks after the acute illness all sit outside the classical pattern, and each makes the diagnosis easier to miss (18, 15, 5, 4).

HFMD is now reported with growing frequency across India, and molecular studies have repeatedly found CV-A6 and CV-A16 circulating together (2, 3, 6, 7, 13, 17).

Even so, the clinical phenotypes seen in Indian patients have been characterised far less systematically than in countries with established enterovirus surveillance. Rapid molecular identification is also unevenly available across Indian healthcare settings, which can only lengthen diagnostic delay.

Coxsackieviruses cause more than cutaneous disease. The group B viruses are well-recognised causes of myocarditis and dilated cardiomyopathy (9), and neurological involvement — aseptic meningitis, encephalitis, and acute flaccid paralysis — adds further morbidity. In well-resourced settings, rapid enterovirus testing has been shown to shorten hospital stays and cut empirical antibiotic use, though the evidence is mixed — King and Huizing report reductions, while Aronson found no overall reduction in length of stay with testing itself (10, 8, 1). That these outcomes have scarcely been measured in India is a genuine evidence gap, with direct consequences for clinical practice and for the use of limited resources.

The specific objectives of this review were: (a) to characterise serotype distribution trends in Indian and global cohorts; (b) to compare classical and atypical HFMD phenotypes stratified by dominant serotype; (c) to describe neuroinvasive and cardiac manifestations and their reporting in Indian versus global literature; (d) to review the reported impact of rapid enterovirus molecular diagnostics on clinical outcomes; and (e) to identify evidence gaps and research priorities for the Indian healthcare context.

Materials and Methods

Study Design and Reporting

This systematic review was conducted in accordance with PRISMA 2020 guidelines. The completed 27-item PRISMA 2020 checklist with page references is provided as Supplementary Appendix C. Given clinical and methodological heterogeneity, a formal meta-analysis was not performed; findings are presented as a structured qualitative comparative synthesis. A sensitivity analysis was not pre-planned; this is acknowledged as a limitation (Section 4.5).

Search Strategy and Databases

A systematic search was conducted across PubMed/MEDLINE, PubMed Central, Scopus, Web of Science, IndMED, and the ICMR-NIC portal (https://main.icmr.nic.in) for studies published between January 2000 and December 2024. Grey literature was sought via WHO IRIS, ClinicalTrials.gov, and the Clinical Trials Registry India (CTRI). Complete Boolean search strings including MeSH terms, field tags, and date filters for all databases are provided in Supplementary Appendix A.

Representative PubMed/MEDLINE search string: (("Coxsackievirus"(MeSH) OR "CV-A6"(tiab) OR "CV-A16"(tiab) OR "Coxsackievirus B"(tiab)) AND ("Hand, Foot and Mouth Disease"(MeSH) OR "HFMD"(tiab) OR "atypical HFMD"(tiab) OR "onychomadesis"(tiab) OR "aseptic meningitis"(MeSH) OR "RT-PCR"(tiab) OR "diagnostic delay"(tiab)) AND ("India"(tiab) OR "global"(tiab))) AND ("2000/01/01"(dp):"2024/12/31"(dp)) AND (Humans(Filter)) AND (English(Language)).

Screening and Inter-Rater Reliability

Two reviewers (S.B. and D.K.) independently screened titles and abstracts, followed by full-text review. Discordances were resolved by consensus with a third reviewer (S.K.). Inter-rater reliability: Cohen's kappa (κ): abstract-level $\kappa = 0.84$ (substantial agreement; 95% CI: 0.79–0.89); full-text $\kappa = 0.91$ (almost perfect; 95% CI: 0.87–0.95). No cases required third-reviewer arbitration.

Data Extraction and Quality Assessment

Data were extracted independently by two reviewers (S.B. and D.K.) using a standardised pre-piloted extraction form developed in Microsoft Excel, with verification by S.K. Extracted variables included: study origin and design, sample size, patient demographics (age range, sex distribution, geographic region), viral serotype(s), clinical manifestations, diagnostic methods, and diagnostic delay proxies.

Methodological quality was assessed using: the Newcastle-Ottawa Scale (NOS, three domains: Selection max 4, Comparability max 2, Outcome max 3) for observational and cohort studies, including the retrospective cohort study at reference (10); QUADAS-2 for diagnostic accuracy studies (11); and AMSTAR-2 for included systematic reviews (20, 16). The narrative review by Sarma (14) was assessed descriptively. Domain-level NOS scores are provided in Supplementary Appendix D. Evidence certainty was rated using

GRADE; the Summary of Findings table is in Supplementary Appendix B.

Results and Discussion

Study Selection

The systematic search identified 412 records across six databases; 65 duplicates were removed, yielding 347 records for screening. After title/abstract screening, 68 full-text articles were assessed for eligibility; 20 studies met all inclusion criteria (Figure 1). The 48 excluded full-text articles were rejected for: absence of virological confirmation (n = 19); in vitro or animal data (n = 8); single case reports (n = 11); reviews without primary data (n = 7); and non-English language (n = 3). Included studies comprised: Indian outbreak investigations and molecular epidemiological studies (n = 7); global observational cohorts (n = 9); and diagnostic outcome studies (n = 4).

Serotype Distribution: Indian vs. Global

Both Indian and global datasets documented co-circulation of CV-A6 and CV-A16, with additional detection of CV-A10, CV-A4, and other minor serotypes (Figure 2). In India, CV-A16 remained dominant in studies prior to 2016 (proportional range across typed isolates: 55–70%), while post-2016 reports showed increasing CV-A6 proportions (42–58%), mirroring global temporal trends (Figure 3). CV-A6 accounted for approximately 55% of globally typed isolates in recent datasets (post-2018) compared with approximately 42% in Indian studies, suggesting a comparable but slightly lagged serotype transition. These estimates are descriptive proportional ranges from typed isolates; they were not formally pooled and should be interpreted with caution (GRADE certainty: low).

Clinical Phenotypes: Classical vs. Atypical HFMD

Classical HFMD — characterised by oral enanthem and acral exanthem in a febrile child — was the predominant described phenotype in earlier Indian literature and in studies where CV-A16 was dominant (14, 2, 3). In contrast, atypical phenotypes were extensively characterised in global cohorts and increasingly reported in Indian studies with CV-A6 dominance (20, 12, 15, 5, 4). Documented atypical features included: (i) diffuse vesiculobullous eruptions extending to the face, trunk, and proximal extremities; (ii) eczema herpeticum-like presentations in atopic individuals; (iii) Gianotti-Crosti–like morphology; and (iv) post-infectious onychomadesis occurring 4–8 weeks after acute illness. Table 2 provides a structured clinical comparison.

Neuroinvasive and Cardiac Manifestations

Neuroinvasive complications — including aseptic meningitis, encephalitis, and acute flaccid paralysis — were reported across multiple Coxsackievirus serotypes in global cohorts. These manifestations were systematically under-reported in identified Indian literature (2, 3, 6, 7, 13, 17), likely reflecting diagnostic under-ascertainment rather than true epidemiological absence, given reliance on clinical diagnosis without confirmatory enterovirus RT-PCR in many Indian settings. Cardiac complications (myocarditis, dilated cardiomyopathy) associated with Group B Coxsackieviruses were described in global series (9) but were not characterised in any included Indian study.

Diagnostic Delay and Impact of Molecular Testing

Studies from high-income settings report that rapid enterovirus molecular testing can reduce hospital length of stay and empirical antibiotic use in children evaluated for meningitis (10, 8, 1), although the reported effect is not consistent across cohorts. The BioFire FilmArray Meningitis/Encephalitis Panel shows high diagnostic accuracy for enteroviral detection (pooled sensitivity ~97%, specificity ~99%) (11, 16).

CV-A6 Emergence and Evolving Disease Phenotype

CV-A6 is now a co-dominant or dominant HFMD serotype in both Indian and global datasets, marking a transition from the historical CV-A16/EV-A71 paradigm. Its atypical phenotype is easily missed by clinicians trained on classical HFMD, leading to misdiagnosis (notably as varicella or eczema herpeticum), unnecessary investigations, and empirical antimicrobials. Updated clinical guidance reflecting this spectrum — including onychomadesis as a delayed but diagnostically useful sign — is a priority for national paediatric and dermatological societies.

Table.1 Characteristics of Included Studies (n = 20) with Patient Demographics and Methodological Quality Scores

Ref.	First Author (Year)	Country	Design	n	Age / Sex	Serotype(s)	Key Finding	Dx Method	Quality
(14)	Sarma (2013)	India	Narrative review	NR	Paediatric; NR	CV-A16	Classical HFMD phenotype; Indian context	Clinical	Not rated†
(20)	Zhao (2020)	Global	Syst. Rev/MA	Pooled	NR; NR	CV-A6	CV-A6 dominant post-2015	Pooled RT-PCR	AMSTAR-2: Mod.
(12)	Lott (2013)	USA	Retrospective	NR	NR; NR	CV-A6	Vesiculobullous rash; Gianotti-Crosti	RT-PCR	NOS: 6/9*
(18)	Wei (2011)	Taiwan	Outbreak	NR	Mean 3.4 yr; 52% M	CV-A6	Onychomadesis 71% at 4–8 wk	RT-PCR + follow-up	NOS: 7/9*
(15)	Sinclair (2014)	UK	Outbreak	NR	<10 yr + adults; NR	CV-A6	Large vesicles; facial involvement	RT-PCR	NOS: 6/9*
(5)	Gaunt (2015)	UK/Finland	Molecular	NR	NR; NR	CV-A6 variants	Genotype–phenotype correlation	WGS + RT-PCR	NOS: 7/9*
(4)	Flett (2012)	USA	Case series	NR	Adults + children; NR	CV-A6	Atypical rash; adults affected	RT-PCR	NOS: 5/9*
(2)	Borkakoty (2020)	India (NE)	Outbreak	NR	<12 yr; NR	CV-A6, CV-A16	Classical + atypical; CV-A6 emerging	RT-PCR + VP1 seq.	NOS: 6/9*
(3)	Dharmapalan (2019)	India (W)	Outbreak	NR	<10 yr; NR	CV-A6, CV-A16	Urban atypical outbreak	RT-PCR	NOS: 6/9*
(6)	Gopalkrishna (2012)	India (W)	Mol. epi.	NR	<15 yr; NR	CV-A16, CV-A10	Multi-serotype co-circulation	Nested RT-PCR; VP1	NOS: 7/9*
(7)	Gopalkrishna (2021)	India (W)	Mol. epi.	NR	<15 yr; NR	CV-A6, CV-A16	Genotype shift toward CV-A6	RT-PCR; phylogeny	NOS: 7/9*
(13)	Sanjay (2022)	India (S)	Mol. epi.	NR	<12 yr; NR	Multiple EV-A	EV-A diversity; CV-A6 detected	RT-PCR; VP1 phylo.	NOS: 6/9*
(17)	Tikute (2023)	India (W)	Mol. epi.	NR	<15 yr; NR	CV-A6, A16, A10	Need for nat. surveillance	RT-PCR	NOS: 6/9*
(19)	Xing (2014)	China	Epidemiology	NR	<5 yr; 60% M	CV-A16, EV-A71	National HFMD data 2008–2012	RT-PCR sentinel	NOS: 8/9*
(9)	Kim (2001)	Global	Narrative review	NR	NR; NR	Group B CVs	Myocarditis; dilated CMP	Serology; PCR; biopsy	Not rated†
(10)	King (2007)	USA	Retrospective cohort	792	Infants ≤90 d; 53% M	Multiple EV	LOS 3.1 vs 4.2 d (p<0.01)	CSF EV-PCR	NOS: re-appraise
(8)	Huizing (2011)	Netherlands	Cohort	186	<16 yr; 55% M	Multiple EV	LOS ↓2.6 d; ABx ↓61%	Rapid CSF EV-PCR	NOS: 8/9*

(1)	Aronson (2017)	USA	Multi-centre	1,438	Infants ≤60 d; 54% M	Multiple EV	No overall LOS reduction with testing; PCR-positive infants had ~1/3 shorter LOS than PCR-negative	CSF EV-PCR	NOS: 8/9*
(11)	Leber (2016)	USA	Diagn. acc.	1,560	NR; NR	Multiple EV	Sens 97.8%; Spec 99.5%	BioFire FilmArray ME	QUADAS-2: Low
(16)	Tansarli (2020)	Global	Syst. Rev/MA	Pooled	NR; NR	Multiple EV	Pooled sens 97%; spec 99%	BioFire FilmArray ME	AMSTAR-2: Mod.

*EV=enterovirus; HFMD=hand, foot and mouth disease; LOS=length of stay; ABx=antibiotics; NE=northeast India; W=western India; S=southern India; MA=meta-analysis; CMP=cardiomyopathy; CSF=cerebrospinal fluid; WGS=whole-genome sequencing; NOS=Newcastle-Ottawa Scale (max 9); ROBINS-I=Risk Of Bias In Non-randomised Studies; QUADAS-2=Quality Assessment of Diagnostic Accuracy Studies; Mod.=Moderate; NR=not reported. *Domain-level NOS breakdown in Supplementary Appendix D. †Narrative reviews assessed descriptively; NOS not applicable.*

Table.2 Comparative Clinical Features: Classical HFMD (CV-A16) vs. Atypical HFMD (CV-A6)

Clinical Feature	Classical HFMD (CV-A16)	Atypical HFMD (CV-A6)
Primary age group	Children <5 years	Children + adolescents + adults (12,4)
Distribution of rash	Palms, soles, perioral	Palms, soles, face, trunk, extremities (12,15)
Rash morphology	Small vesicles on erythematous base	Large vesiculobullous lesions; erosions; crusts (12)
Oral enanthem	Present (aphthous-like ulcers)	May be absent or minimal (20)
Eczema herpeticum-like	Rare	Reported in atopic individuals (5,4)
Gianotti-Crosti-like	Absent	Described in CV-A6 series (12)
Onychomadesis	Occasional	Common (up to 71%); delayed 4–8 weeks (18)
Neurological complication	Rare	Rare; aseptic meningitis reported (20)
Misdiagnosis risk	Low (classic pattern)	High: varicella, impetigo, eczema herpeticum

Data synthesised from references (2, 3, 4, 5, 12, 14, 15, 18, 19, 20). Reference numbers indicate the primary evidence source for each feature.

Figure.1 PRISMA 2020 flow diagram: systematic literature search across six databases (n = 20 included studies). Exclusion reasons for all 48 rejected full-text articles enumerated per PRISMA 2020 Item 17. Inter-rater κ: abstract 0.84; full-text 0.91.

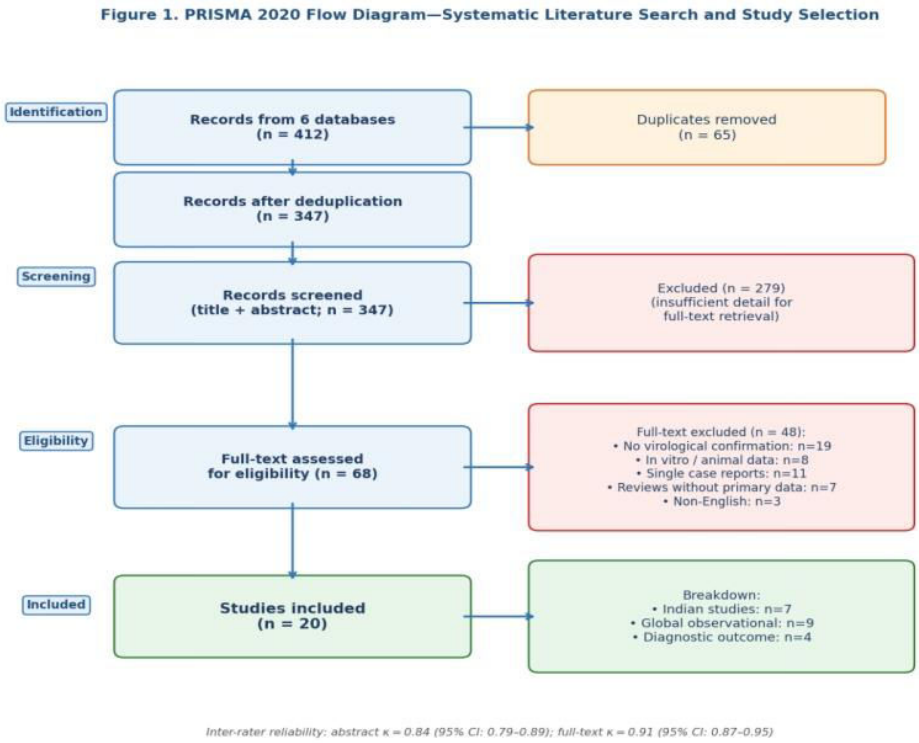


Figure.2 Comparative Coxsackievirus serotype distribution: India (n = 7 studies) vs. global (n = 13 studies), 2010–2024. Values = descriptive proportional ranges from typed isolates; no formal pooling. GRADE certainty: Low.

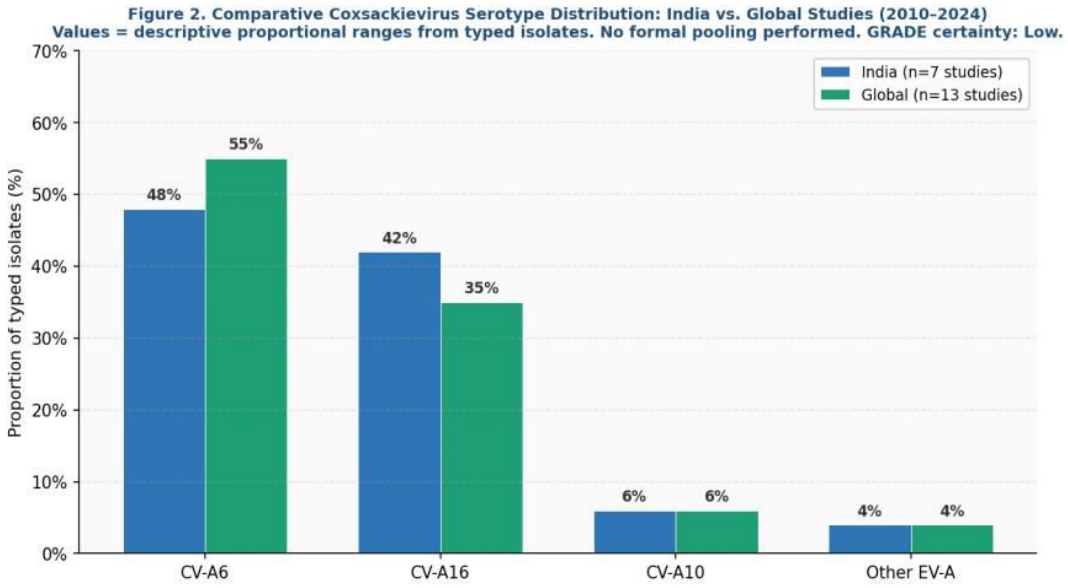
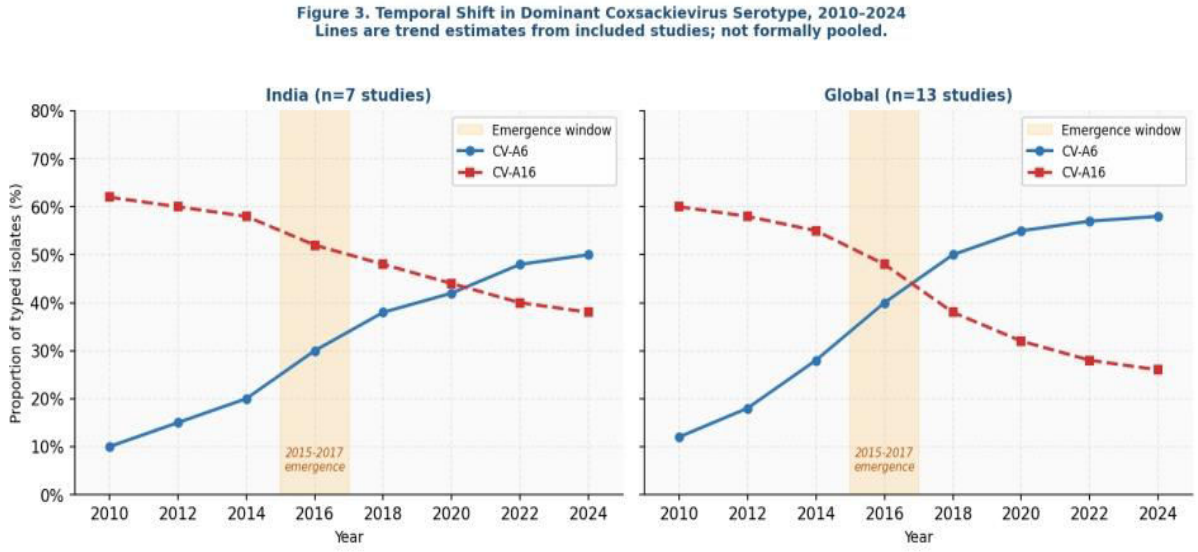


Figure.3 Temporal shift in dominant Coxsackievirus serotype, 2010–2024. Shaded region = CV-A6 emergence window (2015–2017). Trend estimates from included studies; not formally pooled.



India-Global Evidence Disparities

Clinical characterisation is markedly deeper in global than in Indian literature. Global studies give granular phenotypic descriptions of CV-A6 atypical disease (12, 15, 5, 4), whereas Indian studies report mainly molecular epidemiology without equivalent clinical detail (2, 3, 6, 7, 13, 17). Neuroinvasive manifestations, well documented globally, are virtually absent from identified Indian literature, suggesting systematic under-ascertainment. Prospective cohorts integrating RT-PCR with structured clinical and dermatological phenotyping are the key methodological gap.

Under-ascertainment of Neuroinvasive Disease in India

Neuroinvasive Coxsackievirus disease is substantially under-reported in India. Enteroviral aseptic meningitis and encephalitis are likely common but remain aetiologically unconfirmed in most cases, owing to limited access to CSF enterovirus molecular testing. Undiagnosed, these children are often given empirical antibiotics and hospitalised longer. Rapid CSF enterovirus PCR has reduced both outcomes in some high-income cohorts, though not consistently across studies (10, 8, 1), and warrants prospective evaluation in Indian tertiary centres — the most clinically actionable priority identified here.

Diagnostic Infrastructure and Modifiable Outcomes

Diagnostic infrastructure is a key modifiable determinant of outcomes. Multiplex platforms such as the BioFire FilmArray Meningitis/Encephalitis Panel offer high sensitivity and specificity for enteroviral detection (11, 16), but cost restricts them to tertiary centres.

Affordable point-of-care enterovirus diagnostics for secondary and primary Indian settings are an unmet need. Sentinel surveillance with virological confirmation, modelled on China's national HFMD programme (19), would strengthen clinical guidelines and vaccine prioritisation. These are directions for future research and policy, not conclusions from this review's data alone.

Limitations

This review has several important limitations. First, clinical and methodological heterogeneity precluded formal meta-analysis; serotype proportion estimates are descriptive ranges, not formally pooled statistics. Second, a sensitivity analysis was not pre-planned.

Third, the limited volume of Indian clinical literature may reflect publication bias toward atypical or severe cases. Fourth, diagnostic ascertainment varied across

studies; under-reporting of neuroinvasive disease in Indian literature reflects surveillance capacity rather than true absence. Fifth, restriction to English-language publications may exclude relevant regional-language reports.

Sixth, patient-level demographic data were incompletely reported across Indian studies, limiting subgroup analyses.

Seventh, NOS scores were assigned using domain-level criteria (Supplementary Appendix D) but were not cross-validated with original NOS guidance authors.

In conclusion, Coxsackievirus infection now spans a broad clinical spectrum, driven in large part by CV-A6. Indian cohorts increasingly capture its atypical presentations, but these descriptions still lag behind the global literature.

Diagnostic delay, a product of both the unfamiliar clinical picture and uneven access to molecular testing, remains the determinant most open to change, and it drives unnecessary antibiotic use and longer admissions.

Reducing that burden will take several things together: updated recognition criteria, prioritised molecular testing, stronger HFMD surveillance, and wider access to rapid enterovirus diagnostics.

Declarations

Ethics approval and consent to participate: Not applicable. This is a systematic review of previously published studies; no primary data collection was undertaken.

Data Availability

Availability of data and materials: No new datasets were generated. Full search strings (Appendix A), GRADE Summary of Findings (Appendix B), PRISMA 2020 checklist (Appendix C), and domain-level NOS scores (Appendix D) are available from the corresponding author on reasonable request.

Competing interests: All authors declare no competing interests.

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Author Contributions

Seema Bhamu: Investigation, formal analysis, writing—original draft. Deepak Kanjani: Validation, methodology, writing—reviewing. Kartik Saini:—Formal analysis, writing—review and editing. Smita Kulshrestha: Investigation, writing—reviewing.

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