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REVIEW

Management of neonatal central nervous system viral infections: Knowledge gaps and research priorities

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Abstract

Congenital CMV, enteroviruses, human parechovirus and herpes simplex virus are all common causes of severe central nervous system (CNS) infection in neonates. The introduction of screening (i.e. newborn hearing screening programme), integration of molecular syndromic testing (i.e. multiplex polymerase chain reaction assays) and increase in sexually transmitted infections (i.e. anogenital herpes) have contributed to increases in each of these infections over the last decade. However, therapeutic options are highly limited in part due to the lack of epidemiological data informing trials. This review will describe our current understanding of the clinical burden and epidemiology of these severe neonatal CNS infections, outline the novel antiviral and vaccines in the pipeline and suggest future research studies which could help develop new therapeutics.

KEYWORDS
antiviral, CMV, enterovirus, herpes simplex virus, parechovirus, vaccine

1 | INTRODUCTION

Viral infections affecting the central nervous system (CNS), namely congenital cytomegalovirus (cCMV), enteroviruses (EV), human parechovirus (HPeV) and herpes simplex viruses (HSV) cause significant morbidity and occasional mortality in neonates. In England, the introduction of the NHSP (newborn hearing screening programme) in 2007 led to a 55% increase in detection of neonates with cCMV.[1] Increased use of sensitive molecular tools, such as multiplex PCR (polymerase chain reaction) in neonates with suspected meningitis has led to a sevenfold increase in the detected incidence of all causes of viral meningitis.[2] Furthermore, there has been an increasing burden of disease; over the last decade, surveillance studies in the USA, U.K and Australia have all shown a year-on-year increase in maternal anogenital HSV and subsequent increase in neonatal HSV disease.[1,3,4] However, therapeutic interventions to treat and prevent neonatal viral infections are highly limited due to a paucity of epidemiological data to inform therapeutic trials.

This review will provide an overview of the current epidemiology, available treatment modalities and novel agents being trialled in neonates with cCMV, EV, HPeV and HSV. We highlight specific studies that could be conducted to inform the therapeutic pipeline for these poorly understood infections.

2 | METHODS

Literature databases PubMed and ClinicalTrials.gov were searched using terms ['neonatal', 'neonate' or 'paediatric'] alongside the following interchangeable terms: ['cytomegalovirus' or 'cCMV'] or

Abbreviations: cCMV, congenital cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; ECMO, extracorporeal membrane oxygenation; EV, enterovirus; HLH, hemophagocytic lymphohistiocytosis; HPeV, human parechovirus; HSCT, haematopoietic stem cell transplantation; HSV, herpes simplex virus; IVIG, intravenous immune globulin; LMIC, low middle income countries; NHSP, newborn hearing screening programme; PCR, polymerase chain reaction; RCT, randomised controlled trial.

['enterovirus' or 'enteroviral' or 'coxsackie'] or ['parechovirus' or 'hPeV'] or ['HSV' or 'herpes']. Relevant clinical trials, case reports/series, trials and systematic/narrative reviews were identified, with references in each also analysed for relevance.

2.1 | Congenital cytomegalovirus

2.1.1 | Current epidemiology

In the adult population, cytomegalovirus (CMV) is a highly prevalent human herpes viral infection, with worldwide seroprevalence varying from 45% to 100%.[5] Although usually presenting with non-specific mild symptoms of malaise, headache, fever and potential transaminitis in immunocompetent individuals, it can present with significant morbidity in those who are immunosuppressed or in CMV-naïve transplant recipients.

Maternal CMV infection is acquired due to exposure to individuals shedding CMV in bodily fluids. A majority of mothers have been exposed to CMV in early childhood or adolescence. However, sources of primary exposure are via toddlers through saliva (i.e. sharing food/utensils) or urine (i.e. diaper changes). Primary maternal infection affects 1%–4% of pregnancies and rates of transplacental/intrapartum transmission from seronegative and seropositive women to foetus are 32% and 1.4% respectively.[6] Congenital infection can be a result of both primary infection or infection in mothers with preconceptual immunity.[7] Infection most commonly occurs via vertical transmission, through transplacental translocation.

cCMV is symptomatic (i.e. causes overt disease) in 12% of infected neonates worldwide and is the most common cause of non-genetic sensorineural hearing loss (SNHL).[8] Of neonates with symptomatic disease, 35% present with SNHL.[9] cCMV may cause neurodevelopmental impairment (including cerebral palsy, epilepsy, autistic spectrum disorder and feed intolerance) and affected infants require a range of educational, medical and psychological support. In the UK, the annual direct (incurred by the public sector) and indirect (societal) costs of managing affected infants is estimated to be £732 million.[10]

Maternal CMV seropositivity is significantly higher in lower/middle income countries (LMIC) (Iran, Benin and India: 95%–97%) than high income countries (Ireland, Canada and Germany: 44%–59%).[11,12] cCMV affects 0.3%–0.7% live births in developed countries.[13] In LMIC settings, women are likely to be seropositive due to increased rates of transmission in denser populations, higher number of children per household and reduced access to sanitation. The incidence of cCMV in LMICs is poorly understood due to lack of routine data, population-based screening studies and inconsistent clinical definitions/testing. However, small single centre/regional studies estimate the incidence at 1.2% in rural North India,[14] 5.8% in Jakarta[15] and 2.6% in Mozambique,[16] correlating with the higher transmission rates in LMIC settings.

The global burden of cCMV occurs most commonly in seropositive pregnant women. However, research trials, public health messaging and clinical concern often focus on hygiene strategies to prevent infection in seronegative women (i.e. careful hand hygiene after diaper changes, avoiding kissing toddlers on the lips, not sharing food/utensils) which are the mainstay in preventing acquisition. These measures reduced primary infection from 7.6% to 1.2% in a study of 646 CMV seronegative pregnant women.[17] This focus should broaden through ensuring enrolment of seropositive women into research studies in order to optimise understanding of how to minimise the risk of re-activation/re-infection and prevent transmission to the foetus.

2.1.2 | Current treatments

Educational interventions in pregnant women to prevent acquisition during the antenatal period are limited and inconsistently delivered. A double-blind placebo-controlled randomised controlled trial (RCT) of 45 pregnant women receiving valaciclovir reduced the rate of vertical transmission in early pregnancy (11% vs. 30%). The primary endpoint in this study was evidence of infection in amniotic fluid and data additionally analysed any evidence of symptomatic neonatal infection (pregnancies not carried to term due to non-CMV reasons were excluded) and demonstrated 7% (3/44) incidence in neonates/infants in the valaciclovir arm versus 16% (7/43) in the placebo group.[18] CMV-specific Human Immunoglobulin has not been shown to prevent cCMV in an RCT of 123 pregnant women with primary infection.[19]

Only two RCTs have evaluated the safety and efficacy of antiviral treatment in neonates (Table 1). Each trial took a decade to complete and in combination recruited fewer than 200 neonates, with limited follow-up. Kimberlin et al. demonstrated that 6 weeks of IV ganciclovir (6 mg/kg administered twice daily) in neonates younger than 30 days with CNS disease resulted in improved audiological outcomes at 12-month follow up. Almost two thirds of those receiving ganciclovir had neutrophil counts <0.5.[20] A second RCT (2015), commencing 6 months versus 6 weeks of oral valganciclovir in symptomatic infants in the first month of life, resulted in modest audiological improvement and better expressive and receptive language at 2 years follow-up.[9] However, a fifth of babies receiving valganciclovir developed significant neutropenia.

A phase II, open-label trial to evaluate valganciclovir (16 mg/kg/dose BD for 4 months), as prevention for SNHL in 229 asymptomatic neonates (non-randomised, single group assignment), is expected to complete in 2024.[36] No other phase II/III studies have evaluated the efficacy of treating asymptomatic neonates. Pharmacokinetic data of 24 neonates a dose of 16 mg/kg achieved area under the curve over 12 h target of 27 mg $\times$ h/L,[23] but there are a lack of pharmacokinetic/pharmacodynamic data to inform dosing in preterm neonates. This is particularly important as cCMV is associated with preterm delivery. The national screening committee in the UK cited that the absence of an approved highly efficacious and well-tolerated antiviral treatment is a significant obstacle to population-based screening.[37] No countries have implemented an antenatal or postnatal universal screening programme.

TABLE 1 Current widely used treatments for severe neonatal CNS infections

	Current treatments	Toxicity	Efficacy	PK/PD data	Duration of treatment
CMV	IV ganciclovir	29 of 46 ganciclovir treated neonates (63%) developed neutropenia <0.5[20]	Reduction in sensorineural hearing loss (16% [4/25] worsening vs. 41% [7/17] in controls at 6 months; 21% [5/24] vs. 68% [13/19] at 12 months). Improved neurodevelopmental outcomes in study of 100 neonates (Denver developmental test scores 4.46 vs. 7.51 in controls at 6 months; 10.06 vs. 17.14 at 12 months)[20,21]	Analysis of neonatal samples post infusion demonstrated clearance (volume of fluid completely cleared of drug of) 0.428 L/h[22]	6 weeks[20,21]
	PO valganciclovir	21% (10/47)—neutropenia <0.5. Slight non-significant increases in ALT and AST in treatment group[9]	Improved total ear hearing outcomes at 12 months (73% [58/79] vs. 57% [44//77] improved or normal in the 6 months vs. 6 weeks treatment) and 24 months (77% [54/70] vs. 64% [37/58]), and improved Bayley Scale for neurodevelopmental scoring at 24 months[9]	16 mg/kg PO valganciclovir equivalent plasma concentration to IV ganciclovir[23]	6 months
EV	Limited evidence: use of IVIG	IVIG administration in neonates is largely safe. Rare side effects include thrombosis (1%–18%), anaphylaxis (theoretical risk), apnoea (case reports), arrhythmias (case reports) and necrotising enterocolitis (odds ratio 4.53 in haemolytic patients compared to controls)[24]	IVIG with neutralisation titre >1:800 was associated with higher neutralisation titres and more rapid reduction viraemia/viruria[25]	-	IVIG within first 72 h associated with favourable prognosis (odds ratio 14.7)[26]
HPeV	Limited evidence: use of IVIG	As above	In vitro & case reports IVIG has been shown to provide potent in vitro antiviral activity,[27] and indeed was used in the treatment of a patient with dilated cardiomyopathy.[28] A cohort study of 108 febrile neonates <60 days of which 4 were RT-PCR positive for HPeV showed for all 4 who received IVIG starting at day 1–4 demonstrated improvements in clinical presentation of rash, diarrhoea, apnoea and seizures (data on durations for individual HPeV-infected cohort was not included)[29]	-	Limited data

(Continues)

TABLE 1 (Continued)

	Current treatments	Toxicity	Efficacy	PK/PD data	Duration of treatment
HSV	IV high-dose aciclovir (60 mg/kg/day split into TDS dosing)	6 (21%) of 29 neonates receiving high-dose aciclovir experienced transient neutropenia, which all spontaneously improved.[30] Renal toxicity (5.6% of 1017) neonates[31]	Use of standard-dose aciclovir reduced 1-year mortality from disseminated disease to 61% from 85% with no therapy; and from CNS disease to 14% from 35%.[32] Higher dosing versus standard dosing for CNS and disseminated disease: odd ratio 3.3 for survival and 6.6 for normal neurodevelopmental outcome at 12 months[30]	Elimination half-life is 3 h for neonates 36–41 weeks, 6.55 h for neonates 30–35 weeks and 10.2 h for <30 weeks.[33] Limited data for CNS pharmacokinetics in neonates—in adults, valaciclovir 1000 mg administration peaked at 2 days and was minimal at 20 days	14 days for skin/eyes/mouth, 21 days for disseminated disease and CNS depending on nature of disease dissemination; also require 6 months of PO aciclovir as suppressive treatment
	Followed by PO aciclovir	Transient, self-resolving neutropenia in infants receiving aciclovir suppressive therapy[34]	Neonates with CNS involvement had significantly higher neurodevelopmental outcome scores at 12 months compared to placebo[34]	Half-life decreased during first 30 days of life from 10 to 15 h to 2.5 h[35]	6 months

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; EV, enterovirus; HPeV, human parechovirus; HSV, herpes simplex virus; IVIG, intravenous immune globulin.

2.1.3 | Novel treatments

Other viral agents in trials to treat CMV infection include nucleoside analogues and DNA polymerase inhibitors, with paediatric studies largely limited to cohort studies.

Cidofovir, a nucleoside analogue, has been used to treat CMV retinitis.[38] However a cohort study of 5 neonates with adenoviral infection demonstrated renal toxicity in 80%, requiring continuous renal replacement therapy or ECMO.[39] Brincidofovir (lipid conjugate form of cidofovir) has been evaluated in three Phase II/III studies of haematopoietic stem cell or solid organ recipients in adults and children (230, 48 and 232 participants respectively) with CMV, HSV, adenovirus, vaccinia and variolavirus infections. This demonstrated 80% of participants had improved renal function when switched from either cidofovir or foscarnet to brincidofovir.[40]

Foscarnet (60 mg/kg/day), a DNA polymerase inhibitor, has been shown in case reports of immunocompetent neonates to show resolution of liver CMV infection. Further reports of foscarnet, using 100 mg/kg/day dosing, have been associated with clinical improvement in infants with CMV-driven haemophagocytic lymphohistiocytosis and no significant side effects.[41,42]

Letermovir inhibits the terminase complex and can be administered intravenously or orally. It is also less myelosuppressive and nephrotoxic than valganciclovir. Letermovir is being more commonly used as prophylaxis against CMV in HSCT recipients in adults and currently being investigated in a phase 2b trial in children post HSCT (NCT03940586). However, no trials have yet been conducted in neonates.

2.1.4 | Vaccines in development

Vaccination offers the main public health strategy to controlling cCMV. A variety of approaches are being developed including attenuated whole virus vaccines, protein subunit vaccines and mRNA vaccines. Glycoprotein B (gB) and pp65 provide immunodominant targets in association with CMV-directed T cell responses.

A phase II placebo-controlled, RCT of a CMV gB/MF59 adjuvanted vaccine showed a significant reduction of maternal primary infections in women in the adjuvanted vaccine arm (18/225 [8%]) versus placebo (31/216 [14%]).[7] In a further RCT of 120 CMV seropositive women versus 30 women receiving placebo, there were boosted antibody and CD4+ responses in the treatment group (mean titres of 146 vs. 39 [day 28], 111 versus 40 [day 180], 90 vs. 33 [day 360]).[43] A vaccine containing both CMV gB and pp65 protein to elicit a broader array of immune responses is currently being trialled in a phase II study of renal transplant recipients.[44]

Messenger RNA (mRNA) vaccines act through delivering mRNA sequences coding for pathogen-specific proteins into host cells that then express the proteins encoded by these sequences. Candidate mRNA vaccines (mRNA-1647 encoding antigens gB and the pentameric complex, and mRNA-1443 encoding antigens for pp65) have been shown to elicit neutralising antibodies in mice and primate models[45] and have completed phase I trials.[46] Now in phase II trials of healthy adult cohorts, the mRNA-1647[47] candidate encodes gB protein and subunits of the CMV pentamer complex required for viral cell entry. Phase III trials in women of childbearing age are currently recruiting.[48]

The induction of anti-CMV neutralising antibodies as well as cytotoxic T cell responses by a live-attenuated 'Towne' CMV strain led to a trial of chimaeric Towne/non-attenuated Toledo vaccine candidate in a phase I study in CMV-seronegative men. These isolates have been formulated by passaging, resulting in mutations in the 'ULb' genome region containing sequences spanning open reading frames, resulting in attenuation. This candidate was well-tolerated and yielded detectable, yet low, levels of neutralising antibodies, and CD8+ T cell responses.[49]

The V160 vaccine is a highly passaged replication-defective CMV virus gH/gL/pUL128-131, a natural surface pentameric complex promoting infectivity in epithelial and endothelial cells. Phase I trials in seronegative recipients, demonstrated that it was well-tolerated and resulted in a significant increase in antibody titres that persisted to 18 months, as well as CD8+ effector, effector memory and memory B cell responses.[50]

Other multivalent vaccines are being trialled in HSCT recipients including the triplex vaccine combination of pp65/IE1-exon4/IE2-exon5 peptide vaccines which underwent phase II trials in CMV positive HSCT recipients—pp65 and IE1 were chosen as are immunodominant CMV antigenic targets associated with recognition by human CD4+ and CD8+ T cells and associated reduction in viraemia.[51] This was well-tolerated and reduced reactivation-related viraemia.[52] Phase I/II studies are also underway in paediatric populations undergoing HSCT.[53] A further City of Hope peptide vaccine (HLA A*0201/pp65) is also being trialled in phase II studies.[54]

2.2 | Enteroviruses

2.2.1 | Current epidemiology

There are over 110 genetically distinct EV, classified into four major species: A (including EV71, Coxsackie A6/16—which cause hand, foot and mouth disease), B (including echoviruses, Coxsackie B3 causing a variety of presentations including gastrointestinal or myocarditis/pericarditis), C (including poliovirus 1–3, presenting with myelitis) and D (including EV68, associated with acute flaccid myelitis). Our understanding of circulating EV types is limited and based predominantly on passive surveillance from regional or national repositories. Transmission occurs from exposure to infected stool or eye/nasal/oral fluid, or vertical intrapartum acquisition. Most neonatal EV infections are asymptomatic. However, EV is the commonest cause of neonatal meningitis and can cause coagulopathy, hepatitis, myocarditis, with some fatalities. Some serotypes, EV-71 and EV-68, have been identified as causes of acute flaccid paralysis in a small proportion of infection.

A case series of 668 EV-infected infants <90 days old showed that fever (85%), irritability (66%) and reduced feeding (54%) were the commonest presenting features and 11% of cases required intensive care admission.[2] In these infants, sequelae at 12 months (0.6%) were rare.[2] However, our understanding of long-term enteroviral sequelae is limited, with only four studies having attempted to investigate the neurodevelopmental outcomes of infants and children with non-EV71 meningitis.[55–58]

A Korean study of 802 children with EV meningitis showed only 63% of neonates had cerebrospinal fluid (CSF) pleocytosis.[59] This emphasises the importance of syndromic testing of EV in CSF of neonates with suspected meningitis. A retrospective cohort study of 345 EV positive infants <6 months old showed that a positive test was associated with reduced lengths of stay (51.6 vs. 74.1 h) and discontinuation of empirical antibiotics (65.4% vs. 48.5%).[60]

It could be anticipated that the reported rates of EV meningitis will continue to rise as multiplex PCR assays, such as the BioFire FilmArray, become increasingly integrated across paediatric clinical services. However, the clinical impact of these newer diagnostic assays is still being understood.

2.2.2 | Current treatments

Developing antivirals against EV has not been a priority for the pharmaceutical industry and there are no licenced treatments for EV infections. Yearly hand, foot and mouth disease outbreaks in South East Asia reflect a significant EV71 burden.[61] However, potential revenue from marketing EV71 antivirals may be limited in these resource-deprived settings. The manufacturing of antivirals against EV needs to account for their high mutation rate. The need for multiple drug agents to act on different viral targets to minimise resistance and limited cross genotypic activity further increases the challenge to successfully trial new antivirals.

Hypogammaglobulinaemia is associated with risk of enteroviral disease.[62] The use of intravenous immunoglobulin (IVIG) therapeutically in enteroviral disease was initially supported by a randomised trial of 16 neonates.[25] In this trial, 750 mg/kg IVIG administered to nine infected infants increased serum neutralisation titres, and doses at neutralisation titres > or equal to 1:800 to the patients' viral isolates were associated with significantly higher increases in serum neutralising titres and reduced blood and urine viral load. Clinical outcomes of fever, duration of symptoms and residual symptoms at discharge were the same. IVIG was well-tolerated with possible adverse effects of fever, tachycardia and tachypnoea in three infants.[25] Another trial in 41 neonates <1 month with severe EV infection (hepatitis, coagulopathy, thrombocytopaenia, myocarditis or meningitis) showed odds of survival 14.7 higher in those receiving IVIG within the first 72 h of presentation.[26] In adult enteroviral cases, a systematic review of IVIG in prospective trial/case series/reports demonstrates association with possible survival advantage in immunosuppressed patients with rare incidence of serious adverse events.[62]

2.2.3 | Novel treatments

The EV capsid shell is flanked by four structural proteins and contains a hydrophobic pocket that can be targeted with capsid inhibitors, preventing receptor binding and uncoating of the virion particles following cell entry. A number of drug candidates target the capsid, including pleconaril, pocapavir and suramin (Table 2).

TABLE 2 Novel antivirals in therapeutic pipeline for severe neonatal CNS infections

	Novel antivirals	Mode of action	Stage of development	Results thus far
CMV	Cidofovir Foscarnet Filociclovir (cyclopropovir) CRISPR/Cas9—genome-editing TAL effector nuclease (TALEN) plasmids—Plasmids containing restriction endonucleases with a propensity to cleave specific DNA sequences	Nucleoside analogue DNA polymerase inhibitor Nucleoside analogue catalysed by viral enzyme pUL97 which inhibits viral DNA polymerase Genome-editing technology that originated as an archaeal bacterial defence mechanism consisting a Cas9 protein, which has helicase and nuclease activity, allowing the system to cleave specific foreign RNA sequences following guiding by a small guide RNA (sgRNA) sequence Plasmids containing restriction endonucleases with a propensity to cleave specific DNA sequences	It is being trialled in the lipid conjugate form CMX001 in a current phase II/III study for adults and children with CMV, HSV, adenovirus, vaccinia and variolavirus infections[63] Trialled in a cohort of 107 AIDS neonatal patients[64] at IV 60 mg/kg for 2 weeks and compared to a group of 127 patients given IV ganciclovir for 5 mg/kg for 2 weeks[64] Phase I, double-blind, randomised placebo-controlled trial of 24 CMV-naïve patients[65] In vitro studies[66] Mouse models[67]	A cohort study in neonatal adenoviral infection demonstrated renal toxicity and little efficacy.[39] Awaiting phase II/III data Median survival of 12.6 months compared to 8.6 months, with equivalent rates of progression of retinitis[64] Generally well tolerated but one participant developed renal dysfunction[65] Cleaving HCMV UL122/123 gene for lytic replication/reactivation prevented 90% gene expression in fibroblasts.[68] In other studies cleaving non-essential genes were targeted causes framshifts in essential genes Transfection into mouse models resulted in inhibition of murine CMV replication reduced titres by 60%–75% and 25% at days 3 and 5 compared to controls and reduced transcription of CMV genes in murine organs by 10–100-fold[67]
EV	Capsid inhibitors Pleconaril NLD-22 Pocapavir. (V-073) Suramin Peptidomimetics for example, 3Cpro inhibitors for example, rupintrivir,[69] AG7404, DC07090[70] 3Dpol inhibitors[70] gemcitabine, NITD008, ribavirin, amiloride 2C inhibitors for example, fluoxetine analogues Monoclonal antibodies NA11F12 4 Engineered bispecfic antibody Bs(scFv)4-IgG-1 OSBP inhibitors: itraconazole	Bind to the hydrophobic pocket of the viral capsid in viral protein 1 As above As above As above, narrower spectrum Binding of the viral capsid of EV-A71 3Cpro inhibitors: 3Dpol in conjugation with proteins 3Cpro and 3AB, which are involved in viral priming, and 2C with ATP-dependent helicase activity and acts as a ATP-independent RNA chaperone[70] 3C inhibitor—inhibits viral priming 2C inhibitor—inhibits viral priming Viral neutralisation Viral neutralisation Binding to OSBP (factor in molecular translocation involved in EV replication)	Randomised placebo-controlled trial[71] In vitro[72] Case reports[73,74] Currently being trialled in phase 1[75,76] In vitro[69] In vitro In vitro[77] Mouse models[78] In vitro[79] In vitro[80]	Improved survival and shorter times to negative culture in neonates presenting with enteroviral sepsis Promising antiviral activity in vitro at present Successful use even in cases with fulminant neonatal myocarditis Dose-dependent reduction in virions in rhabdomyosarcoma cell lines, blocking viral attachment to cells EV inhibition in cell lines EV inhibition in cell lines EV inhibition in cell lines Dose- and time-dependent cross-neutralisation activity against lethal-dose infection in murine models against Coxsackie A 16[78] Cross-reactivity against EV71 and CA16 in mice with complete therapeutic efficacy against these infections in mice[79] Inhibits EV replication in cell lines by binding to OSBP[80]

TABLE 2 (Continued)

	Novel antivirals	Mode of action	Stage of development	Results thus far
Parechovirus	IVIG Monoclonal antibodies[81]	Viral neutralisation Viral neutralisation	In vitro & case reports[27,28] Molecular studies[81]	IVIG has been shown to provide potent in vitro antiviral activity,[27] and indeed was used in the treatment of a patient with dilated cardiomyopathy[28] Antibodies AM18 and AM28 bind to epitopes on VP1, preventing integrin binding to the viral capsid, and VP0/VP3, blocking RNA uncoating, respectively[81]
HSV	Brincidofovir/CMX001 (a lipophilic derivative of cidofovir without nephrotoxicity) Pritelivir Amenamevir CRISPR/Cas9 Small interfering RNA (siRNA)	Nucleoside analogue Viral helicase/primase inhibitor Viral helicase/primase inhibitor Cleave latent HSV neuronal infection Cleave latent HSV neuronal infection	Currently being evaluated from clinical trial[63] Phase II studies[82,83] Phase II/III studies[84,85] In vitro[86] In vitro[87]	Awaited Reduce viral shedding in HSV2-seropositive individuals with annually recurrent genital herpes, over 28 days compared to oral valaciclovir.[82] A further open-label, multi-centre randomised phase II trial ongoing[83] 3 days course reduced median lesion duration by 20.2 h compared to placebo[84] equivalent days to cessation of new lesion formation, complete crusting and virus disappearance as valaciclovir[85] Successfully carried out in human cell culture models,[86] although delivery of the technology remains a major hurdle Sequences targeting the UL-29 HSV sequences reduced HSV replication and stimulated increased innate immune cytokine responses[87]

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; EV, enterovirus; HSV, herpes simplex virus; IVIG, intravenous immune globulin.

Pleconaril inhibits the uncoating of viral RNA and progeny virions during EV replication. Pleconaril has also been shown to have good oral bioavailability. In a double-blind placebo controlled RCT, infants up to 12 months with suspected EV meningitis were randomised to receive pleconaril (5 mg/kg/dose) orally three times daily for 7 days or placebo. Twelve subjects received pleconaril and 8 received placebo. There were no differences in symptoms or length of hospital stay in either group. Overall, 10/12 (83%) in the pleconaril group and 6/9 (75%) in the placebo group had adverse events, most commonly diarrhoea, rash and fever. The lack of clear evidence of efficacy led to early termination of the trial by the pharmaceutical sponsor.[88] Pleconaril is currently not licenced by the Food and Drug Administration, and has substantial drug interactions as a CYP3A4 inducer.

Pocapavir, a viral capsid inhibitor, has also shown efficacy against EV infection. It has been used with favourable outcomes in a case of enteroviral sepsis, with significantly improved myocardial output and coagulopathy, although these were improving prior to commencement of drug.[89] Two isolated case reports of neonates with fulminant neonatal myocarditis have demonstrated viral clearance and recovery within 2 weeks without adverse effects—currently this investigational drug has been only available in these limited number of cases as emergency treatment.[73,74] Emergency investigational new drug approval from the Food and Drug Administration, parental consent, and placental enteroviral typing and pocapavir susceptibility testing were required prior to the use of the first case.[89] A further capsid binder, suramin, which inhibits EV-A71 is being trialled in a Phase I study in 36 healthy adults.[75]

RNA replication in EV is carried out by the viral RNA-dependent RNA polymerase $3D^{pol}$ in conjunction with proteins $3C^{pro}$ and 3AB involved in viral priming, and 2C which has helicase/chaperone activity. $3C^{pro}$ inhibitors (e.g. rupintrivir),[69] $3D^{pol}$ inhibitors (including nucleoside and non-nucleoside analogues) and 2C inhibitors (e.g. fluoxetine) have been trialled in murine models, demonstrating reduction in Coxsackie viral titres after intraperitoneal administration,[90] but in human cohort studies of enteroviral D68 acute flaccid paralysis was not associated with poorer neurological outcomes.[91]

2.2.4 | Vaccines in development

Vaccine development is an active area of research, with greatest global efforts focussed on EV71 as the most problematic and virulent serotype. EV71 epidemics in 2009 and 2010 led to over a million cases, with thousands of hospitalisations and mortality in the hundreds.[92] Development of a vaccine candidate with durable and efficacious immunogenicity may provide a reduction in incidence of these endemic viruses and thus reduce cases of primary maternal infection. This research field is in its early stages with limited vaccine candidate options at present, consisting of inactivated, multivalent and experimental Virus-Like Particle (VLP) vaccines.

The inactivated one-dose Human Diploid cell, KMB-17 Cell EV vaccine has been licenced in China and has recently undergone phase IV trials in children aged 6–71 months against hand, foot and mouth disease, with previous reported efficacy of 97%.[93] Furthermore, the inactivated, vero cell-based EV71 Sinovac vaccine showed non-inferior immunogenicity in infants 3–5 years to those aged 6–35 months.[94] A phase I bivalent vaccine IN-B001 for EV71/CV16 is currently being trialled in healthy adults.[95] The use of such polyvalent approaches offers promise in overcoming the heterogeneity of enteroviral types.

An inactivated EV 71 vaccine (INV21) was safe in healthy adults in a phase I double-blind study.[96] Meanwhile another human diploid-cell–based inactivated EV71 C4 genotype vaccine showed 97.1% efficacy in healthy children for EV71-related hand, foot and mouth disease.[97]

A recent multivalent candidate has been the combination of recombinant Coxsackie B1 nanoparticles/Norovirus VLPs/Rotavirus oligomeric rVP6, which generated IgG1 and IgG2a antibodies and broad T cell responses in mice.[98] Experimental VLP vaccines are currently being trialled in and have been shown to protect mice from lethal infection against different EV's including EV71.[99]

2.3 | Human parechoviruses

2.3.1 | Current epidemiology

HPeVs are a genus of viruses within the family Picornaviridae, alongside the Enterovirus genus. These are non-enveloped RNA viruses, of which there are 18 circulating HPeVs. Seasonal outbreak monitoring for parechoviral disease is an important public health measure, as has been demonstrated in Australia, where there have been recent notable outbreaks in 2013–2014, 2015–2016 and 2017, with >200 cases of hospitalised HPeV infection in young infants.[100] All three epidemics in Australia have now shown to have been primarily attributed to the novel recombinant HPeV3,[100] with viral phylogenetic analysis of a cohort of 33 hospitalised infants in the third epidemic demonstrating significant stability of the HPeV3 indicating need for further therapeutics and vaccines.[101]

HPeVs are associated with frequent and significant illness in neonates and young infants. HPeV3 is the second most common cause of viral meningitis in neonates. In the UK, surveillance data showed that 23% (8/35) of cases required intensive care.[102] Neonatal HPeV3 encephalitis has been associated with gross motor delay, cerebral palsy and visual impairment and has characteristic deep periventricular white matter changes. A study in 426 post mortem specimens in infants showed that 4% of deaths were associated with HPeV.[103] An Australian study revealed impaired neurodevelopmental outcomes in 11 of 77 infants with HPeV meningitis and a further study demonstrated 5/8 young infants at 12 months with parechovirus encephalitis had neurodevelopmental sequelae[104]: cerebral palsy, gross motor impairment[105]; however these findings have not been consistently replicated. A British Paediatric Surveillance Unit Study demonstrated no sequelae in 35 neonates with HPeV meningitis[2] at 12 months follow up and a Dutch study of 58 children with CNS infection showed no neurodevelopmental outcomes at 24 months' follow-up.[106]

CSF pleocytosis in infants with HPeV meningitis is uncommon, with over 90% of CSF samples in HPeV meningitis containing 0–10 WCC/mm.[2] Routine testing of all CSF samples, irrespective of degree of inflammation, in infants with suspected meningitis should therefore be conducted. As with EV, the lack of active clinical and virological surveillance mechanisms has meant there is a paucity of epidemiological data to inform therapeutic trials.

2.3.2 | Current treatments

There are no licenced antiviral drugs for HPeV. IVIG has been shown to provide dose-dependent antiviral activity, with HPeV3 RNA intracellular levels decreasing from 4.71×10^7 to 2.83×10^3 copies/μl in vitro.[27] An uncontrolled case series of four febrile RT-PCR HPeV3 positive neonates <60 days, who received IVIG starting at day 1–4 of illness, showed some improvements in clinical presentation of rash, diarrhoea, apnoea and seizures.[29]

2.3.3 | Novel treatments

No current antivirals are in phase II/III trials under ClinicalTrials.gov as searched/accessed on 3 July 2022. Unlike EV, HPeVs are intrinsically resistant to the capsid binders due to a shallower capsid pocket, impeding the fit of molecular binding. A Finnish group demonstrated use of monoclonal antibodies as therapeutic candidates—molecular mapping showed antibodies AM18 and AM28

targeted to viral capsid (epitopes of RGD motif and amino acids from loops of VP0/VP3 respectively) preventing integrin binding to the viral capsid and blocking RNA uncoating respectively.[81]

2.3.4 | Vaccines in development

No vaccine candidates are being investigated in Phase I/II/III studies at present under ClinicalTrials.gov as of search/access date 3 July 2022.

2.4 | Herpes simplex virus

2.4.1 | Current epidemiology

HSV-1 and HSV-2 are double-stranded DNA viruses within the *Herpesviridae* family and transmitted by direct (orolabial mucosa) and sexual contact. HSV-2 causes the majority of cases of genital herpes, although HSV-1 has also emerged as a major cause of genital herpes infections. Following initial epithelial infection, the virus migrates towards local neuronal ganglia, establishing latency with the potential for reactivation.

We use the term 'neonatal' to include all cases of possible transmission of HSV (i.e. encompasses intrauterine, intrapartum and perinatal transmission). Between 2010 and 2015, there were 14,257 reported worldwide cases of neonatal herpes of which 2/3 were thought to be due to HSV-2 and 1/3 due to HSV-1.[107] The reported incidence of neonatal HSV is rare in HIC: 17.6 per 100,000 infants (UK),[1] 1.6 per 100,000 (Switzerland), 3.2 per 100,000 (Netherlands) and 8.5 per 100,000 (Israel) and 5–33 per 100,000 (US)[108] although higher in LMICs such as Kenya (33 per 100,000 births per year). The estimates based on HSV-1 and HSV-2 incidences amongst women have suggested that neonatal infection occurs at 0.0031%–0.0072% live births respectively; greatest incidence is in the Americas for HSV-1 (0.0126%) and Africa for HSV-2 (0.0153%).[107]

Primary maternal infection in particular, as well as outbreaks of recurrent herpes ulceration, are associated with neonatal infection via vaginal delivery. The risk of transmission from mother to neonate is highest in primary genital herpes (25%–60%) and much lower (approximately 5%) to mothers with recurrent genital infection.[109] HSV maternal seropositivity is highly variable with documented prevalence of 63% for HSV-1 and 22% for HSV-2 (US),[110] 62.5%/8.3% (Germany),[111] 95.7%/40.1% (Brazil)[111] and 32% for HSV-2 (Kenya).[112]

In the UK, the last published prospective study of HSV in neonates was performed between 1986 and 1991 and showed an incidence of 0.5 per 100,000 live births.[113] In 2013, a UK study of laboratory confirmed HSV meningo-encephalitis cases showed an apparent four-fold increased incidence of 2.2 per 100,000 live births, which was attributed by the authors to be due to the introduction of PCR leading to higher diagnostic rates.[114] A longitudinal study of routine collected patient records showed that the rate of neonates diagnosed in hospital with HSV increased nearly four-fold between 1999—2016.[1] This corresponds with a 22% increase in diagnosis of new episodes of genital HSV in England between 2008—2017.[115] The increase in reported cases of neonatal HSV therefore highlights the importance of safe and effective treatments to manage this catastrophic disease.

Neonatal disease has 3 distinct phenotypes: skin/eye/mouth (SEM) (45%), CNS (30%) and disseminated disease (25%).[109] Typically, SEM and disseminated disease occurs at 2 weeks and CNS disease at 3 weeks of life.[109] Approximately half of neonates with SEM have recurrent cutaneous lesions without suppressive treatment.[109] A fifth of neonates with disseminated disease have neurologic sequelae at 1 year and with 70% of those with CNS disease have permanent neurologic impairment.[34]

2.4.2 | Current treatments

The mainstay of treatment in HSV infection involves aciclovir, with other nucleoside analogue options, which all target the thymidine kinase enzyme (Table 1).

Aciclovir, famciclovir and valaciclovir are nucleoside analogues that target thymidine kinase. Parenteral aciclovir has been the first-line agent in management of neonatal HSV. This has been based on two RCTs that each took a decade to recruit. The first RCT in 210 neonates comparing vidarabine (neonatal cases of: 28 disseminated, 31 SEM, 36 CNS) and aciclovir (18 disseminated, 54 SEM, 35 CNS) and demonstrated equivalent tolerability and efficacy of aciclovir, although with notable disproportions of disease phenotypes between arms.[32] A further RCT (41 disseminated, 28 CNS, 10 SEM) in neonates used 60 mg/kg/day dosing compared to 45 mg/kg/day dosing and showed 3.3× greater odds of survival in the disseminated groups; odds were similar in CNS groups.[30] Aciclovir is usually divided as thrice-daily dosing for 14 days, or 21 days if disease is disseminated or with CNS involvement. Renal toxicity (5.6% (57/1017) in neonates in one retrospective US cohort study from 2011 to 2015 occurred more often in those with intensive care stay or mechanical ventilation[31] and neutropenia (21% of 29 neonates; all spontaneously resolved[30]) but these significant side effects require careful monitoring.

A suppressive course of oral aciclovir for 6 months follows the initial intravenous treatment course for neonatal HSV. This is based on a single phase III RCT of 74 neonates with CNS (45) or SEM disease (29) of which 6 and 3 neonates respectively did not complete the 6 months course; follow-up demonstrated 6 months of oral aciclovir reduced disease recurrence at 12 months (approximately 35% less for CNS disease and 30% less for SEM disease).[34] Neonates with CNS infection that had Bayley neurodevelopmental assessments undertaken and randomised to the aciclovir arm also had improved developmental outcomes at 12 months—69% (11/16) versus 33% (4/12); no differences were seen for SEM disease.[34] A study of 5-year duration is currently underway to investigate the safety and pharmacokinetics of enteral valaciclovir in 10 neonates 2–12 weeks in age and 34+ gestation with confirmed HSV.[116]

In women with HSV, management of the neonate depends on whether maternal infection is primary or recurrent. In primary infection, skin/mucosal swabs and blood for PCR should be sent at 24 h post-delivery, as well as CSF for HSV PCR, and IV aciclovir should be commenced.[117] In recurrent infection, US guidance from the American Academy of Paediatrics advises that given likelihood of transmission to neonate is low (2%), acyclovir should not be started unless symptomatic; viral skin and mucosal swabs should be taken at 24 h and if negative alongside an asymptomatic neonate, the neonate can be discharged; if positive, the neonate should be treated for 10 days in order to prevent symptomatic infection.[117] However, the British Association for Sexual Health and HIV (BASHH) guidance advises that in recurrent HSV with or without lesions, there is no need to test or treat the neonate.[118]

Foscarnet has some activity in aciclovir-resistant infections with risks of significant nephrotoxicity and metabolic derangement. Two case reports of foscarnet administered at day 18 and day 11 of infection in neonates demonstrated clinical recovery after HSV infection of the larynx in the first case and pneumonitis, hepatitis and DIC following herpes infection, resulting in death in the second.[119] Aciclovir remains the mainstay of treating neonatal HSV. However, resistance through thymidine kinase mutations, could theoretically develop in longer treatment durations. Aciclovir also causes nephrotoxicity, marrow suppression and requires prolonged inpatient hospital stay during the intravenous treatment phase, highlighting the need for novel therapeutics.

2.4.3 | Novel treatments

Given the susceptibility for nucleoside analogue therapy to viral immune evasion via thymidine kinase mutations, there is a pressing need for development of novel agents with alternative mechanisms of action. These include broader acting nucleotide analogues (brincidofovir), pyrophosphate analogues that prevent binding onto DNA polymerase (foscarnet) and viral helicase/primase inhibitors (pritelivir and amenamevir).

Brincidofovir (a lipophilic derivative of cidofovir without nephrotoxicity also known as CMX001) and Pritelivir (helicase primase inhibitor) are drugs being evaluated for acyclic nucleoside resistant viruses. Brincidofovir was recently licenced by the FDA for use in smallpox infections. For HSV, thus far its use has been limited to case reports/series of immunocompromised adult and paediatric patients, where it demonstrated virological response,[120,121] and in HSV prophylaxis of stem cell adult and paediatric transplant recipients where breakthrough was 1.0 per 1000 patient days.[122] It is currently being evaluated in phase II/III trials for adults and children with DNA virus infections including HSV,[63] although its use may be limited due to toxicity profile and concerns of emerging cross-resistance.[123]

Pritelivir (AIC316) and amenamevir (ASP2151) are viral helicase/primase inhibitors and inhibit viral replication by preventing the separation of DNA strands. 100 mg once daily oral pritelivir has been demonstrated in phase II double-blind study to reduce viral shedding in HSV2-seropositive individuals with recurrent genital herpes.[82] A further open-label, multi-centre randomised phase II trial (PRIOH-1) in immunocompromised adults of oral pritelivir versus intravenous foscarnet is ongoing.[83] A 3 days course of amenamevir was demonstrated, in recurrent genital herpes, to reduce median lesion duration by 20.2 h compared to placebo in a randomised trial of 437 adults and was well-tolerated.[84] Further phase III testing of 751 patients treated 72 h after development of rash with 7 days courses of amenamevir 400 mg OD, 200 mg OD and valaciclovir 1000 mg TDS for 7 days showed equivalent times to cessation of new lesion formation, complete crusting and virus disappearance.[85]

2.4.4 | Vaccines in development

The development of HSV vaccination is an active area, with several late phase trials in progress. Several vaccine approaches are in trial including subunit vaccines, multi-epitope and live attenuated vaccines.[124] Of the 80+ proteins encoded by each of the HSV-1 and HSV-2 genomes, 12 glycoproteins are present on the viral envelope and five of which are recognised to interact with cellular receptors and promote viral entry (gB, gC, gD, gH and gL). Other important antigenic targets including the tegument proteins in the viral capsid involved in anchoring viral structure including during proliferation.[124]

Previous HSV vaccine approaches utilised subunit vaccines containing gD (a surface viral protein involved in viral entry) and gB, although these have had limited efficacy—the latter demonstrated only 58% and 20% efficacy for HSV1 and HSV2 respectively in a randomised double-blind study of 8328 seronegative women.[125]

One alternative approach is utilising different epitopes to produce broader T cell responses, including intraviral proteins such as UL25, ICP0 and ICP4 A DNA vaccine containing IL-2, IL-21 and MIP-1alpha elicited specific T cell response and viral elimination in mice.[126] gD with UL25 epitopes inserted into a recombinant adenovirus 5 vector also demonstrated immunogenicity through IFN-dependent T cell responses and reduction in genital lesions in mice.[127]

To overcome the issue of subunit vaccines providing inadequate breadth of epitopes a live attenuated vaccine was developed. VC2 with gK and UL20 deletions prevents axonal translocation of virus and reduces mortality in mice[128] and reduced HSV-2 related neuronal infection in macaques.[129] A trivalent vaccine of gD2/gC2/gE2 containing gC2 and gE2 that are two HSV factors involved in immune evasion through binding to complement 3 and the Fc region of IgG respectively demonstrated immunogenicity in macaques.[130]

2.5 | Future research priorities

We highlight key areas relating to future research priorities for improving the treatment of neonatal viral infections (Table 3). Broadly, few robust epidemiological studies have been carried out for these viral infections in LMICs to ascertain incidence of clinical

TABLE 3 Research priorities to inform the therapeutic pipeline to treat severe neonatal CNS viral infections

	Issues	Study suggestions
cCMV		
Understanding pathophysiology	Further evaluation of the phenotypic differences and epidemiology of primary versus non-primary maternal CMV infection in neonates is required Maternal CMV infection may result in placental immune dysfunction and placental insufficiency although the exact mechanisms for this have not been elucidated The role for T cells in CMV immunity was implied from demonstrations that adoptive T cell immunotherapy improved CMV response in allogenic haematopoietic stem cell recipients but has not been fully characterised	Antenatal screening studies to understand pathophysiological cCMV effects on neonates from primary versus non-primary infections and ascertain if clinical, immunological or virological biomarkers predict outcome Immunological studies evaluating placental markers and histopathological effects of maternal CMV non-primary and primary infection at different stages in pregnancy Animal knockout model studies may influence de novo vaccine targets
Identification of infection	To date, epidemiological data have described neonates with symptomatic disease. Our understanding of asymptomatic disease is highly limited There are no robust longitudinal data that describe the natural history of CMV disease	Universal screening studies of cCMV across different populations which enable opportunity to obtain host and virological data Registry that allows prospective longitudinal follow up and opportunity to trial novel interventions
Treatment	Use of therapeutic agents to reduce vertical transmission and investigated in randomised controlled trials Vaccine trials in both seronegative and seropositive women of childbearing age PK/PD data for valganciclovir and ganciclovir is required in neonates aged <32 weeks Trials of valganciclovir only enroled in cases with severe disease Further trials on treatment of asymptomatic neonates and mild symptomatic disease are needed	Further phase II/III trials of anti-CMV agents in pregnancy, especially for cases of non-primary infection Further phase II/III vaccine trials for women of reproductive age who are seropositive and seronegative PK/PD studies of current therapeutic agents especially in neonates <32 weeks Investigation of effects of valganciclovir in isolated SNHL/mild disease and asymptomatic neonates Phase I-III clinical trials of asymptomatic neonates/symptomatic receiving ganciclovir/valganciclovir
EV		
Understanding pathophysiology	Further characterisation of disease subtypes by variation in EV virus type may optimise management	Active enhanced surveillance mechanism. This would be conducted by regional virology laboratories submitting EV positive samples to a reference laboratory for real-time molecular characterisation
Identification of infection	There is a lack of robust neurodevelopmental studies—more data is needed on long-term outcomes of viral meningitis There are no reliable biomarkers which predict neonates who develop severe disease/long term sequalae	Long-term neurodevelopmental outcomes of EV infection are required to assess burden of disease Collect samples for host transcriptomic and immunological profiling during acute illness and convalescence
Treatment	The largest trial of IVIG treatment in neonatal enteroviral sepsis recruited 41 participants[26] Capsid inhibitors have not been utilised in neonatal trials other than case studies at present Combination therapy will be needed to prevent development of drug resistance; for example, consecutively alternating administration of pleconaril/MDL-860/oxoglaucine improved effect of individual administration in coxsackie-B1 infected mice[131]	RCT of IVIG in EV meningitis Phase I neonatal studies are required to evaluate the safety and efficacy of capsid inhibitors Animal and phase I trials of combination therapies of capsid inhibitors with other novel agents could improve therapeutic effect
HPeV		
Understanding pathophysiology	Understanding of host factors involved in RNA replication, protein synthesis and attachment and uncoating (relative to EV little understanding)	Further in vitro molecular work
Identification of infection	No large-scale epidemiological studies have been carried out At present there is a paucity of understanding of neurodevelopmental outcomes and mortality Disease markers of severity for example, urinary beta-2-microglobulin[29]	Surveillance of HPeV in LMIC using syndromic testing of HPeV in neonates with suspected CNS infection Long term neurodevelopmental studies using robust tools for example, Bayley assessment Further identification of disease markers

(Continues)

TABLE 3 (Continued)

	Issues	Study suggestions
Treatment	Development of therapeutic targets to host factors involved in RNA replication, protein synthesis and attachment and uncoating Monoclonal antibodies have been promising therapeutic candidates	Further molecular work is required before in vitro studies Further molecular studies to identify appropriate pathogenic targets
HSV		
Understanding pathophysiology	Understanding burden of viral evasion of suppressive therapy for ongoing viral shedding	Further epidemiological studies are required
Identification of infection	Low proportions of testing—need to evaluate outcomes with improved recognition of possible HSV cases	Large scale cohort studies following increased PCR testing or testing algorithms
Treatment	Viral evasion of maternal suppressive therapy for ongoing viral shedding Development of aciclovir resistance; further studies required within neonatal population of polymerase/helicase/primase inhibitors—foscarnet and cidofovir have been poorly studied in this population Current subunit and live attenuated vaccinations are being trialled in non-pregnant adults alone	Phase I studies of combination therapies to reduce viral shedding Phase I studies in neonatal population An understanding of effect on vaccination on vertical transmission will require phase I trials in pregnant women

Abbreviations: cCMV, congenital cytomegalovirus; CNS, central nervous system; EV, enterovirus; HPeV, human parechovirus; HSV, herpes simplex virus; IVIG, intravenous immune globulin; LMIC, low middle income countries; PCR, polymerase chain reaction; RCT, randomised controlled trial; SNHL, sensorineural hearing loss.

burden, and ongoing epidemiological analysis is required to drive further research on therapies.

In particular, the advent of mRNA vaccine rollout in the COVID pandemic offers a new avenue of vaccine development for this range of viruses. mRNA vaccine technology could potentiate increased output of vaccine manufacture and the breadth of feasible antigenic targets limited by historical expression technologies.[132]

2.5.1 | CMV

Preventing transmission of infection to the foetus is critical. To achieve this, developing a range of vaccine candidates and investing their potential in phase II/III trials is essential. In the meantime, qualitative studies are required to help implement behavioural strategies that minimise acquisition of infection during pregnancy and can be promptly implemented into routine antenatal care. International collaborative epidemiological studies, through universal screening and development of a registry of affected cases, are required to understand the burden of congenital disease and prioritise treatment trials accordingly. Treatment trials of asymptomatic/mildly symptomatic disease are required to determine their efficacy in preventing late onset SHNL.

2.5.2 | Enteroviruses

Improving our understanding of the molecular epidemiology is essential to understand the commonest and most severe forms of EV meningitis. A phase III RCT of IVIG is needed to better understand its effect on clinical outcome. In addition, Phase I/II studies of novel capsid inhibitors should be encouraged. It is likely that combination therapies will be required to prevent development of drug resistance. Further data on long-term neurodevelopmental outcomes of EV meningitis is required to inform the evidence base to manage affected infants after hospital discharge.

2.5.3 | Human parechoviruses

Surveillance studies should be conducted in LMIC in order to gain an understanding for the impact of HPeV in neonates. Improved our knowledge of protein synthesis, molecular cascades and targeting attachment/uncoating will permit development of further drug targets.

2.5.4 | HSV

The issue of aciclovir-resistant infections gives rise to the need for further studies within neonatal populations of foscarnet and cidofovir, as well as novel helicase/primase inhibitors. Given the HSV evasion of suppressive therapy, an evaluation of current vaccine candidates on vertical transmission is needed and will require phase I trials in pregnant women.

3 | CONCLUSIONS

The burden of neonatal viral infections is a significant cause of morbidity and mortality worldwide. However, therapeutic options are

highly limited. Academic institutions, pharmaceutical industry and policymakers should work together to develop the evidence to better treat neonates from this poorly understood group of severe infections.

AUTHOR CONTRIBUTIONS

Seilesh Kadambari conceived the idea for the paper. Movin Abeywickrema wrote the first draft of the manuscript. Movin Abeywickrema, Dominic Kelly and Seilesh Kadambari contributed to the literature review and provided scientific content to each section of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Pubmed at https://pubmed.ncbi.nlm.nih.gov/. These data were derived from the following resources available in the public domain: https://pubmed.ncbi.nlm.nih.gov/.

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