CHAPTER ONE

Zoonotic Potential of Emerging Paramyxoviruses: Knowns and Unknowns

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Contents

Abstract

The risk of spillover of enzootic paramyxoviruses and the susceptibility of recipient human and domestic animal populations are defined by a broad collection of ecological

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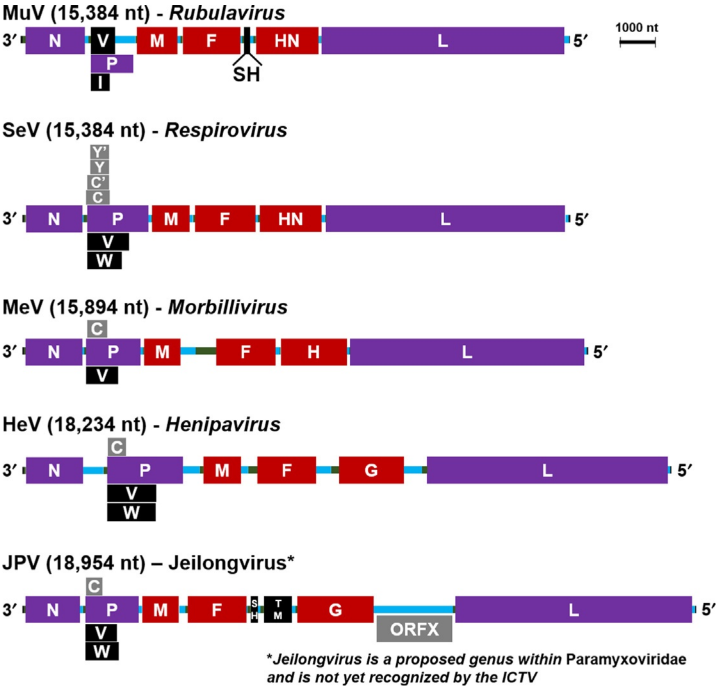
and molecular factors that interact in ways that are not yet fully understood. Nipah and Hendra viruses were the first highly lethal zoonotic paramyxoviruses discovered in modern times, but other paramyxoviruses from multiple genera are present in bats and other reservoirs that have unknown potential to spillover into humans. We outline our current understanding of paramyxovirus reservoir hosts and the ecological factors that may drive spillover, and we explore the molecular barriers to spillover that emergent paramyxoviruses may encounter. By outlining what is known about enzootic paramyxovirus receptor usage, mechanisms of innate immune evasion, and other host-specific interactions, we highlight the breadth of unexplored avenues that may be important in understanding paramyxovirus emergence.

ABBREVIATIONS

BPIV-3 bovine parainfluenza virus 3
CDV canine distemper virus
(HPIV)-1, -2, -3, and -4 human parainfluenza virus
MuV mumps virus
MeV measles virus
PIV-5 parainfluenza virus 5
PPRV peste-des-petits-ruminants virus
RPV rinderpest virus
SV-41 simian virus 41

1. INTRODUCTION

The paramyxovirus family comprises numerous viruses that collectively have a very broad host range, infecting vertebrates from fish to mammals, with transmission primarily via the respiratory route (Lamb and Parks, 2006). At the molecular level, paramyxoviruses are enveloped, negative strand, nonsegmented RNA viruses, with six open reading frames (ORFs) encoding the structural genes. N (nucleocapsid), encapsidates genomic, and antigenomic viral RNA, while L (polymerase) and P (phosphoprotein) form the RNA-dependent RNA polymerase to transcribe viral messenger RNAs, and coordinate with N to amplify the genome; together these comprise the viral replicase (Fig. 1, purple). M (matrix) coordinates virion assembly and budding, while the F (fusion) and G/H/HN (attachment) glycoproteins decorate the surface of the virion and are responsible for entry into the host cell; together with the replicase, these proteins (Fig. 1, red) form the virion structure. In most cases, paramyxoviruses also use an alternative start codon and RNA editing to generate two to four additional accessory proteins from



*Jeilongvirus is a proposed genus within Paramyxoviridae and is not yet recognized by the ICTV

Fig. 1 Paramyxovirus genome structures. Depicted here are scaled genomes in 3′ to 5′ orientation of representative virus species for each of the mammalian-targeting paramyxovirus genera. JPV is included to represent the putative Jeilongvirus genus. Protein gene products are the larger lettered blocks. The replicase is colored *purple*, while the remaining proteins found in the virion are colored *red*. Nonstructural accessory proteins are *black* (V, W, I, SH, and TM) or *gray* (C, Y, and ORFX); *gray* proteins are produced from alternate start codons of a given mRNA. RNA regions are thinner, unlettered horizontal segments: 3′ leader and 5′ trailer regions are *black*, while the 5′ UTR of each mRNA is colored *green*, and the 3′ UTR of each mRNA is colored *blue*. The scale bar indicates 1000 nucleotides.

the phosphoprotein gene (Fig. 1, gray and black; Table 1). Some, but not all, paramyxoviruses have additional ORFs for nonstructural proteins (e.g., mumps virus—MuV; or Jeilongvirus—JPV, in Fig. 1). Collectively, the functions of the various nonstructural accessory proteins are incompletely understood, although many have been implicated in manipulating host immune responses (discussed later). An interesting and defining feature of paramyxovirus genome organization is conformity to the "rule of six": as a consequence of the mode of genome encapsidation by the nucleoprotein,

Table 1 Paramyxovirus Accessory Proteins of Interest

		P[a]	V[a]	W/D/I[a]	C[b]	SH
Respirovirus	***SeV***	100% (568)	100% (384)	100% (318)	100% (204)[c]	–[d]
	HPIV-1	54.4% (568)	–	–	70.1% (204)[c]	–
	PPIV-1	42.1% (574)	33.9% (375)[e]	29.3% (334)[e]	57.4% (204)[e]	–
	CPIV-3	27.0% (626)	24.0% (428)[e]	20.2% (397)[e]	33.3% (201)[e]	–
	HPIV-3	24.8% (602)	–	22.5% (373)	34.3% (199)	–
	BPIV-3	24.3% (596)	23.4% (412)	20.6% (367)	33.3% (201)	–
Henipavirus	***HeV***	100% (707)	100% (457)	100% (448)	100% (166)	–
	NiV	66.2% (709)	58.8% (456)	58.4% (450)	83.1% (166)	–
	KV	28.2% (870)	27.9% (621)[e]	–	34.0% (162)[e]	–
	CedV	25.1% (737)	–	–	28.8% (177)[e]	–
	MojV	18.2% (695)	20.0% (464)[e]	16.7% (435)[e]	25.5% (267)[e]	–
Rubulavirus	***MuV***	100% (390)	100% (224)	100% (170)	–	100% (57)
	BMV	81.8% (390)	79.5% (224)	–	–	35.1% (57)
	PIV-5	35.4% (392)	38.7% (221)	–	–	14.0% (44)
	HPIV-2	35.3% (395)	33.9% (225)	–	–	–
	SV-41	33.0% (395)	30.8% (225)	–	–	–
	MapV	31.2% (391)	29.2% (251)	14.7% (201)[e]	–	–
	PorV	30.2% (404)	25.0% (249)	7.1% (174)[e]	–	–
	HPIV-4	24.9% (399)	20.9% (229)	–	–	–
Morbillivirus	***MeV***	100% (507)	100% (300)	–	100% (186)	–
	RPV	61.0% (507)	60.2% (299)	–	57.6% (177)	–
	CeMV	47.4% (506)	41.1% (303)	–	40.7% (177)	–
	PPRV	46.2% (509)	27.9% (298)	–	41.8% (177)	–
	CDV	43.6% (507)	37.1% (300)	–	45.4% (174)	–
	PDV	43.2% (507)	34.1% (299)	–	41.4% (174)	–
Jeilongvirus	***JPV***	100% (499)	100% (292)	100% (310)	100% (152)[e]	100% (76)
	BeiV	45.2% (496)	43.2% (292)	39.4% (313)	6.7% (160)[e]	29.2% (69)
	TlmV	44.4% (496)	43.2% (292)	40.7% (310)[e]	38.2% (153)[e]	27.8% (76)

[a] Rubulavirus V proteins are the primary transcripts, with P/I proteins being produced through mRNA editing. For all other genera, P proteins are the primary transcript, with V/W/D proteins produced through mRNA editing. Unedited P/V transcripts are indicated by underline.

[b] C proteins are produced from alternate start codons of the P ORF and are translated in a different open reading frame.

[c] SeV and HPIV-1 produce additional alternate start codon proteins in the same reading frame as C, named C′, Y1, and Y2. They share the majority of their sequence with C, but with slightly longer (C′) or shorter (Y1, Y2) N termini.

[d] – = not present or not expressed.

[e] Putative.

Percent amino acid identity (progressive pairwise alignment, calculated with default settings of ClustalW in MEGA7.0) to each genus' type species (*italics, underlined*) is given; boxes are shaded proportional to percentage, and protein sizes are given in amino acids (brackets).

genomes must be a multiple of six nucleotides in length in order for efficient paramyxovirus replication (Kolakofsky et al., 1998, 2005).

Mammalian paramyxoviruses are currently classified into four genera—Morbillivirus, Rubulavirus, *Respirovirus*, and *Henipavirus*—each of which contain both human-tropic and animal-tropic viruses (Afonso et al., 2016). However, many recently identified paramyxoviruses fall outside these existing genera and may represent additional clusters of closely related mammalian paramyxoviruses (Fig. 2) (Magoffin et al., 2007; Wilkinson et al., 2014). Because there is no evidence that reptilian, piscine, or avian paramyxoviruses

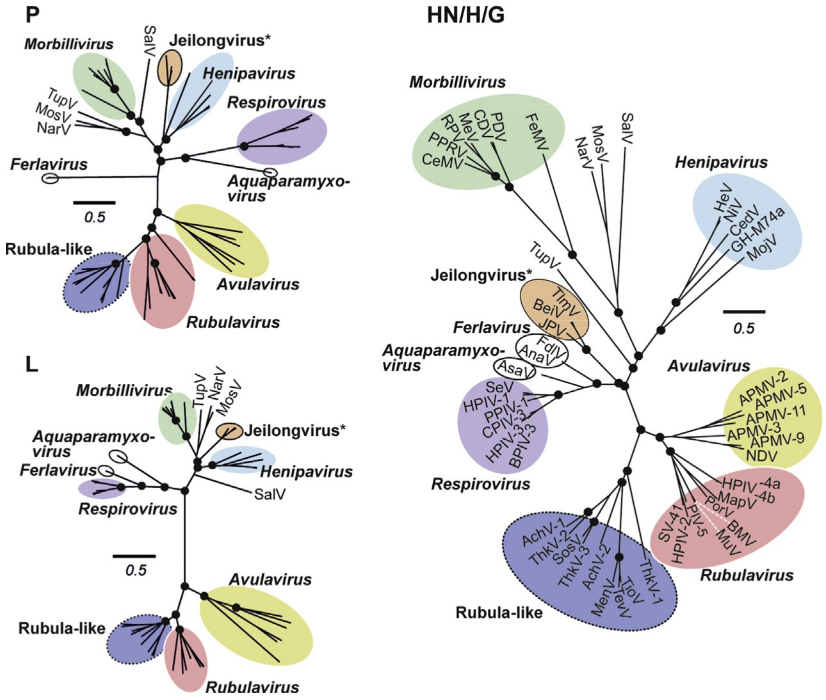


Fig. 2 Paramyxovirus attachment proteins demonstrate great diversity within and among genera. Maximum likelihood phylogenetic trees of P, L, and attachment (HN/H/G) protein sequences of Paramyxoviridae. *Circles* encompass phylogenetic groupings best characterized as genera. *Jeilongvirus is a proposed genus that has not yet been recognized by the ICTV. Rubula-like viruses have genetic similarities to recognized members of *Rubulavirus*, but consistently group separately, and so are encircled in a *dotted line*. Unclassified but fully sequenced Paramyxoviruses are individually labeled in each tree. Scale bar indicates 0.5 amino acid substitutions per site, and trees are scaled such that the scale bar is the same in all trees. *Black circles* at nodes represent >75% support from 500 bootstrap replicates. All analyses were performed in MEGA 6 using a complete deletion option and a WAG substitution model.

pose a major health threat to humans, this review will focus on discovery and understanding of the mammalian paramyxoviruses.

We know from early written accounts of disease that some paramyxoviruses, such as measles virus (MeV), have circulated in human populations and caused substantial morbidity and mortality for centuries (Furuse et al., 2010). However, in just the last several decades, the repeated zoonotic outbreaks of the highly lethal Hendra virus (HeV) and Nipah virus (NiV) have alerted us to the threat of emergence of as-yet-unknown paramyxoviruses into human populations from wildlife reservoirs. Fully sequenced novel enzootic paramyxoviruses are catalogued in Table 2, and their wildlife reservoir(s) are indicated, where they have been identified. In this review, we will not only discuss our current knowledge of emergent paramyxoviruses, but also look more broadly at whether divergent paramyxoviruses circulating in wildlife reservoirs also warrant increased attention as having zoonotic potential. In addition, we will discuss what we know, as well as what we cannot yet predict, in terms of the factors anticipated to contribute to the likelihood of emergence of highly pathogenic zoonotic paramyxoviruses.

2. KNOWN HIGHLY LETHAL EMERGENT PARAMYXOVIRUSES: NIPAH VIRUS AND HENDRA VIRUS

NiV and HeV (both species in the *Henipavirus* genus) are highly virulent emerging zoonotic paramyxoviruses that circulate in *Pteropus* species of bats (Halpin et al., 2011), and have caused numerous outbreaks of respiratory and neurological disease in humans and domesticated mammals over the last several decades (reviewed in Eaton et al., 2006). Remarkably high case fatality rates, their repeated reemergence, and the absence of any vaccines or therapeutics approved for use in humans have led to their classification as pathogens that require biosafety level 4 containment facilities for handling. They are further designated "Category C" priority pathogens by the National Institute of Allergy and Infectious Diseases (NIAID) Biodefense Research Agenda, reflecting their potentially devastating impact if used as bioterrorism agents (NIAID and NIH, 2016). Moreover, in December 2015, NiV was included in the World Health Organization (WHO) list of the seven pathogens it deems most require urgent research and development in order to mitigate potential public health emergencies (WHO, 2015).

Table 2 Distribution, Classification, and Origins of Fully Sequenced Enzootic and Emergent Paramyxoviruses

Virus	**Abbrev.**	**Proposed Genus**	**Geographical Distribution**	**Animal Source(s) (Order)**	**Spillover Hosts**	**Evidence**	**References**
Achimota virus 1	AchV-1; AchPV1	Rubula-like[a]	Accra, Ghana Dar es Salaam, Tanzania São Tomé and Principe Annobón, Equatorial Guinea	*Eidolon helvum* (Chiroptera)	Humans	Serology	Baker et al. (2013)
Achimota virus 2	AchV-2; AchPV2	Rubula-like[a]	Accra, Ghana Dar es Salaam/ Muheza, Tanzania São Tomé and Principe	*Eidolon helvum* (Chiroptera)			Baker et al. (2013)
Bat Mumps virus	BMV; BMuV	Rubulavirus	Democratic Republic of Congo	*Epomophorus spp.* (Chiroptera)			Drexler et al. (2012)
Beilong virus	BeiV; BeiPV	Jeilongvirus[b]	Laboratory animal cell line—Beijing, China Hong Kong, China La Réunion, France (Indian Ocean)	*Rattus norwegicus, rattus;* (Rodentia)			Li et al. (2006), Wilkinson et al. (2014), and Woo et al. (2012b)

Continued

Table 2 Distribution, Classification, and Origins of Fully Sequenced Enzootic and Emergent Paramyxoviruses—cont'd

Virus	Abbrev.	Proposed Genus	Geographical Distribution	Animal Source(s) (Order)	Spillover Hosts	Evidence	References
Cedar henipavirus	CedV	Henipavirus	Queensland/ Victoria, Australia	*Pteropus alecto, poliocephalus* (Chiroptera)			Burroughs et al. (2016) and Marsh et al. (2012)
Cetacean morbillivirus	CeMV; DMV; PWMV;	Morbillivirus	Worldwide	Dolphins, porpoises; toothed and baleen whales (Cetacea)			Van Bressem et al. (2014)[c]
Caprine parainfluenza virus 3	CPIV-3	Respirovirus	Jiangsu/Anhui, China	*Capra aegagrus hircus* (Artiodactyla)	Goats[d]	Virus, Serology	Li et al. (2014)
Feline morbillivirus	FeMV; FMoV	Morbilli-like[a]	China Japan United States	*Felis cattus* (Carnivora)	Cats[d]	Virus, Serology	Furuya et al. (2014), Sakaguchi et al. (2014), Sharp et al. (2016), and Woo et al. (2012a)
Ghanaian bat henipavirus	GH-M74a KV; GhV;	Henipavirus	Ghana Cameroon	*Eidolon helvum* (Chiroptera)	Humans	Serology	Drexler et al. (2012) and Pernet et al. (2014b)
Hendra virus	HeV	Henipavirus	New South Wales/ Northern Territory/ Western Australia/ Queensland, Australia Papua New Guinea	*Pteropus alecto, conspicillatus*; other fruit bat *spp.* (Chiroptera)	Horses, humans, dogs	Virus, Serology	Field (2016)[c] and Field et al. (2013)
J paramyxovirus	JPV	Jeilongvirus[b]	Queensland, Australia	*Mus musculus* (Rodentia)	Humans, pigs, cows	Serology	Drexler et al. (2012), Jun et al. (1977), and Mesina et al. (1974)

Mapuera virus	MapV	Rubulavirus	Para, Brazil	*Sturnira lilium* (Chiroptera)			Karabatsos (1985)
Menangle virus	MenV	Rubula-like[a]	New South Wales/Queensland, Australia Papua New Guinea	*Dobsonia magna; Pteropus alecto, conspicillatus, poliocephalus, scapulatus* (Chiroptera)	Pigs, humans	Virus, Serology	Barr et al. (2012), Breed et al. (2010), Chant et al. (1998), and Philbey et al. (1998)
Mojiang virus	MojV	Henipavirus	Yunnan Province, China	*Rattus flavipectus* (Rodentia)	Humans	Association[e]	Wu et al. (2014)
Mossman virus	MosV	Morbilli-like[a]	Queensland, Australia	*Rattus leucopus, fuscipes* (Rodentia)			Campbell et al. (1977)
Nariva virus	NarV	Morbilli-like[a]	Bush Bush Island, Trinidad	*Zygodontomys brevicauda brevicauda* (Rodentia)			Tikasingh et al. (1966)
Nipah virus	NiV	Henipavirus	Bangladesh Ghana West Bengal, India Malaysia Papua New Guinea Singapore Thailand Philippines	*Pteropus spp.*; *Eidolon helvum, Dobsonia magna* (Chiroptera)	Pigs, humans, horses, dogs, goats, cows, cats	Virus, Serology	Luby and Gurley (2015)[c], Breed et al. (2010), Ching et al. (2015), Chowdhury et al. (2014), Hayman et al. (2008), and Wacharapluesadee et al. (2005)

Continued

Table 2 Distribution, Classification, and Origins of Fully Sequenced Enzootic and Emergent Paramyxoviruses—cont'd

Virus	Abbrev.	Proposed Genus	Geographical Distribution	Animal Source(s) (Order)	Spillover Hosts	Evidence	References
Phocine distemper virus	PDV	Morbillivirus	Worldwide	Seals, sea lions, sea otters, walruses (Carnivora)			Duignan et al. (2014)[c]
Porcine rubulavirus	PorV; LPMV-PorPV; PPBED	Rubulavirus	Guanajuato/Jalisco/Michoacan/Estado de Mexico, Mexico	*Sus scrofa* (Artiodactyla) *Rhogeessa parvula major,* (Chiroptera)	Pigs, humans	Virus, Serology	Cuevas-Romero et al. (2015)[c], Rivera-Benitez et al. (2014) and Salas-Rojas et al. (2004)
Porcine parainfluenza virus 1	PPIV-1	Respirovirus	Hong Kong, China Illinois/Nebraska/Oklahoma, USA	*Sus scrofa* (Artiodactyla)	Pigs	Virus	Lau et al. (2013) and Palinski et al. (2016)
Salem virus	SalV	Morbilli-like[a]	Massachusetts, USA	*Equus caballus* (Perissodactyla)	Horses[d]	Virus, Serology	Renshaw et al. (2000)
Sosuga virus	SosV	Rubula-like[a]	South Sudan Uganda	*Homo sapiens* (Primates) *Rousettus aegypticus* (Chiroptera)	Humans	Virus	Albariño et al. (2014) and Amman et al. (2015)
Teviot paramyxovirus	TevV	Rubula-like[a]	Queensland/Victoria, Australia	*Pteropus alecto, poliocephalus* (Chiroptera)			Barr et al. (2015) and Burroughs et al. (2015)
Tuhoko virus 1	ThkV-1	Rubula-like[a]	Guangdong, China	*Rousettus leschenaulti* (Chiroptera)			Lau et al. (2010)

Tuhoko virus 2	ThkV-2	Rubula-like[a]	Guangdong, China	*Rousettus leschenaulti* (Chiroptera)			Lau et al. (2010)
Tuhoko virus 3	ThkV-3	Rubula-like[a]	Guangdong, China	*Rousettus leschenaulti* (Chiroptera)			Lau et al. (2010)
Tioman virus	TioV	Rubula-like[a]	Tioman Island, Malaysia	*Pteropus sppnn* (Chiroptera)	Humans, pigs	Virus, Serology	Breed et al. (2010), Chua et al. (2001), Iehlé et al. (2007), Yadav et al. (2016), and Yaiw et al. (2007, 2008)
			Madagascar				
			Papua New Guinea				
			Assam, India				
Tailam paramyxovirus	TlmV	Jeilongvirus[b]	Hong Kong, China	*Rattus andamanensis* (Rodentia)			Woo et al. (2011)
Tupaia paramyxovirus	TupV; TPMV	Morbilli-like[a]	Bangkok, Thailand	*Tupaia belangeri* (Scandentia)			Tidona et al. (1999)

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[a] Unclassified, but phylogenetically similar to the indicated genus.

[b] Proposed genus (Li et al., 2006).

[c] Review article.

[d] Reservoir and spillover host are same species.

[e] Temporal and geographical association, no molecular or immunological evidence.

2.1 Hendra Virus

Chronologically, the first zoonotic HeV outbreak occurred in Mackay, Australia in August 1995, resulting in the deaths of two horses and a farm worker (Hooper et al., 1996; Rogers et al., 1996). However, HeV infection was only retrospectively identified as the etiology of these cases, following a larger outbreak almost 1000 km away in the Brisbane suburb Hendra, Australia, approximately one month later. In this second outbreak, 21 horses and two further people presented with severe disease, and a novel zoonotic paramyxovirus was identified as causative (Murray et al., 1995). This highly lethal emerging virus was initially classified as a morbillivirus, but further characterization, as well as the subsequent emergence of NiV (see later), a phylogenetically and antigenically related paramyxovirus (Chua et al., 2000), led to reclassification of HeV as the type species in a novel paramyxovirus genus *Henipavirus*, which also includes NiV (Mayo, 2002; Wang et al., 2000; see also Fig. 2, "L" bottom left). In the decades following the initial emergence of HeV, it has continued to cause annual spillovers and outbreaks in horses and closely associated humans (Field, 2016).

2.2 Nipah Virus

The first documented outbreak of NiV began in September 1998 in Peninsular Malaysia, with respiratory illness in pigs (Mohd Nor et al., 2000), and severe, frequently fatal, febrile illness in humans (Chua et al., 2000). The outbreak continued for over six months, and as a result of the transport of infected pigs, spread to more distant regions of Malaysia, and to Singapore, cumulatively causing 265 human cases of encephalitis and 105 fatalities (Chua et al., 2000; Paton et al., 1999). Following this initial outbreak, NiV reemerged separately in Bangladesh (Arankalle et al., 2011; Hsu et al., 2004; Rahman and Chakraborty, 2012), and in Siliguri, India (Chadha et al., 2006), both during 2001. NiV has subsequently reemerged almost every year in Bangladesh, with frequent outbreaks also documented in India (Islam et al., 2016; Kulkarni et al., 2013; Luby et al., 2009). These outbreaks differ from the first—Malaysian—NiV outbreak in that transmission appears to occur directly from the bat reservoir to humans, primarily via consumption of date palm sap contaminated with urine or saliva from infected bats (Islam et al., 2016; Luby et al., 2006; Openshaw et al., 2016; Rahman et al., 2012). Furthermore, there is clear evidence of secondary human-to-human transmission during outbreaks (Hegde et al., 2016; Homaira et al., 2010; Sazzad et al., 2013), raising serious concern that NiV has the capacity to cause a devastating pandemic (Luby, 2013).

2.3 Broad Geographic Distribution of Potentially Zoonotic Henipaviruses

Given that documented NiV and HeV outbreaks have so far been relatively restricted in their geographical distribution (South East Asia and Australia, respectively), it is perhaps both surprising and worrisome that in the last several years, survey studies in wildlife and domesticated mammals have revealed evidence of henipa- and henipa-like viruses circulating in animal populations as distantly as West Africa, and perhaps even in the south and central Americas (Drexler et al., 2009, 2012; Hasebe et al., 2012; Hayman et al., 2008, 2011; Iehlé et al., 2007; Pernet et al., 2014b; Reynes et al., 2005; Thanapongtharm et al., 2015). These data highlight the role human and ecological factors must play in determining the probability of zoonotic transmission of henipaviruses from animal reservoirs to human populations, which will be discussed in detail later. However, the recent NiV outbreak in the Philippines, a country previously unaffected by NiV, with evidence of a novel route of exposure—consumption of meat from infected horses—serves to highlight that risk factors and drivers of emergence cannot be expected to remain static (Ching et al., 2015).

Given that NiV and HeV are sufficiently different at the molecular level from other paramyxoviruses to have warranted classification in a novel genus (Fig. 2), and that they are the only paramyxoviruses confirmed to have fatally infected humans in repeated outbreaks, this poses the question: Are henipaviruses unique in their likelihood to spillover from wildlife reservoirs and cause serious human disease? While the answer to this question is currently unknown, it is clearly of important consequence in terms of how we direct our attention and resources when considering the zoonotic potential of viruses in the paramyxovirus family. We propose that there are several lines of evidence suggesting that viruses from multiple paramyxovirus genera, as well as numerous currently unclassified paramyxoviruses, should be considered alongside henipaviruses as having zoonotic potential.

One aspect of this question is whether henipaviruses represent a genus of viruses that are inherently highly pathogenic to humans, should spillover infection occur. This is particularly pertinent when considering the recent dramatic expansion in our knowledge of both the sequence diversity of henipaviruses present in wildlife, and the geographical areas in which henipaviruses exist (Drexler et al., 2012; Hayman et al., 2008; Iehlé et al., 2007; Peel et al., 2013; Pernet et al., 2014b). While there is currently insufficient evidence to determine whether henipaviruses (as compared to other paramyxoviruses) have a higher probability of being highly pathogenic in humans, the recent characterization of Cedar virus (CedV), a henipavirus closely related to NiV and HeV, suggests that high pathogenicity is at least not a universal feature of the Henipavirus genus. CedV was isolated from *Pteropus* species bats, displays some antigenic crossreactivity with both NiV and HeV, and likely uses the same cellular entry receptor (ephrin-B2) (Marsh et al., 2012). However, despite this high degree of relatedness, CedV experimental infection of ferrets and guinea pigs resulted in seroconversion but no overt clinical disease (Marsh et al., 2012), in marked contrast to NiV and HeV, which are highly pathogenic in these model species (Pallister et al., 2009, 2011). Molecular characterization of CedV demonstrated an absence of production of frameshift accessory proteins from the P gene (Table 1; Marsh et al., 2012), which are produced in almost all other paramyxoviruses, and contribute to antagonism of the human type I interferon (IFN) response and to pathogenesis (reviewed in Chambers and Takimoto, 2009), and Lieu et al. (2015) show that relative to NiV and HeV, the CedV P protein is ineffective in counteracting the human IFN signaling pathway. Collectively, these molecular features and limited pathogenesis in nonhuman mammalian species suggest CedV is relatively unlikely to be capable of causing serious disease in humans. Additional suggestive evidence that some henipaviruses may result in relatively innocuous spillover events come from a human serosurvey conducted in Cameroon, in which 1–2% of human serum samples were positive for NiV crossneutralizing antibodies, despite no reports of serious disease in seropositive individuals (Pernet et al., 2014b). Interestingly, NiV seropositivity was found almost exclusively among individuals who reported butchering bats for bushmeat (seroprevalence in this high-risk group was ~4%; Pernet et al., 2014b). This relatively high seroprevalence suggests that close contact with body fluids from bats harboring henipaviruses related to NiV might cause spillover infections in the absence of serious clinical disease more frequently than otherwise believed. It is likely that the divergent clades of henipaviruses harbor a similarly diverse virulence spectrum, and that elucidating the determinants of pathogenicity of henipaviruses as a group requires urgent attention.

3. UNKNOWN ZOONOTIC POTENTIAL OF PARAMYXOVIRUSES

Whether or not we consider additional paramyxoviruses in the henipavirus genus inherently likely to cause serious human disease in the context of spillover, NiV and HeV remain the two major emerging paramyxoviruses that pose a known threat to human health. However, given that three of the four other paramyxovirus genera (*Rubulavirus*, *Morbillivirus*, and *Respirovirus*) include established human pathogens with considerable global health burdens, as well as recently detected vast sequence diversity in wildlife reservoirs (Table 2; Drexler et al., 2012; Kurth et al., 2012; Wilkinson et al., 2014), it is worth exploring whether unknown zoonotic paramyxoviruses from these genera might also pose a significant threat to human populations.

3.1 Diversity of Novel Enzootic Paramyxoviruses

In a landmark study, Drexler et al. (2012) conducted an (RT)-PCR screen to identify potential paramyxoviruses in bat and rodent samples collected from multiple locations around the world, and identified an estimated 66 novel paramyxoviruses. To put this in context, this exceeds the total number of paramyxoviruses in all genera currently listed by the International Committee on Taxonomy of Viruses (ICTV; Afonso et al., 2016; Drexler et al., 2012). Although this large study sampled over 80 bat species, it is worth noting that this represents less than 10% of known Chiropterans and represents only certain geographical locations and moments in time. Thus, in terms of our knowledge of paramyxoviruses in wildlife with unknown capacity for spillover infection and disease, the most dramatic shift this study provided is perhaps an increased awareness of the extent of the unknown unknowns. As well as greatly expanding the known paramyxovirus sequence diversity, the identification of viruses closely related to human MuV (*Rubulavirus*) and canine distemper virus (CDV, *Morbillivirus*) in bats suggests bats host paramyxoviruses from genera beyond just the henipaviruses that may have the potential to switch hosts and cause disease in other mammalian species (Drexler et al., 2012). This and subsequent (RT)-PCR- and sero-surveys for paramyxovirus in wildlife (Mélade et al., 2016; Wilkinson et al., 2014) have also identified many paramyxoviruses that fall within the paramyxovirus family, but variously cluster outside of the currently recognized genera, indicating that older isolates of morbilli-like (Nariva virus, NarV; Mossman virus, MosV) and rubula-like (Menangle virus, MenV; Tioman virus, TioV) paramyxoviruses are not isolated outliers.

The mere presence of—or indeed, simply new knowledge of—diverse paramyxoviruses in wildlife is clearly separable from the propensity for zoonotic transmission to humans, and particularly from the likelihood of causing serious disease or secondary human-to-human transmission, and therefore potential to cause an epidemic. However, efforts to model and understand emerging infectious disease in order to try to predict and respond better to future outbreaks have identified a number of trends and risk factors that allow us to begin to consider the relative threat of the emergence of a zoonotic paramyxovirus of public health concern. Firstly, it is worth noting that there has been a statistically significant increase in outbreaks of emerging infectious disease per se since the 1940s, even correcting for biases due to improvements in detection and reporting (Jones et al., 2008; Smith et al., 2014). The majority of these events is due to zoonotic transmission of viruses, primarily from wildlife reservoirs (Jones et al., 2008; Smith et al., 2014), with human disruption of ecosystems due to changes in land usage shown to be a major driver of such events (Daszak et al., 2001; Myers et al., 2013; Patz et al., 2004). Changes in available technology, such as development of pan-paramyxovirus PCR primers (Tong et al., 2008) and next-generation sequencing, have revolutionized our ability to detect viral genome diversity in wildlife populations, and while such data in isolation reveals little about the likelihood of serious epidemics, it can facilitate attempts to analyze virological factors associated with elevated risk. Phylogenetic analysis comparing various viral families (Kitchen et al., 2011), as well as looking specifically at paramyxoviruses (Mélade et al., 2016), indicate that the dominant driver of viral macroevolution is host switching among different, but relatively related, host species. In fact, comparison with RNA viruses of other families suggests that paramyxoviruses may have relatively high rates and probabilities of transfer to new host species (Kitchen et al., 2011). Moreover, such relative flexibility in host species, in addition to molecular traits of paramyxoviruses such as a nonsegmented genome and nonvector transmission, has also been identified as a positive correlate of likelihood of human-to-human transmission of emerging zoonotic viruses following a spillover event (Anthony et al., 2015; Geoghegan et al., 2016).

3.2 Human Infection by Zoonotic Rubula-Like Viruses

In addition to the theoretical risks of virulent emerging paramyxoviruses (not limited to the henipavirus genus) discussed earlier, there are two case reports of human infections with zoonotic rubula-like viruses (Table 2) that were associated with severe clinical disease. First, concurrent with an outbreak of MenV that caused severe birth defects and stillbirths in swine at several affected piggeries in Australia during 1997, two piggery workers with extensive exposure to infected body fluids developed a severe influenza-like illness and rash, with no other identified cause (Chant et al., 1998; Philbey et al., 1998). While it remains possible that this novel bat paramyxovirus (Barr et al., 2012) was not the etiological agent responsible for the reported human disease, these were the only two piggery workers who were also seropositive for MenV, making it the most likely cause (Chant et al., 1998). Interestingly, this outbreak somewhat parallels the initial NiV outbreak, which was also transmitted to humans from the bat reservoir via infected domesticated swine, with no evidence of onward human-to-human transmission, in contrast to subsequent outbreaks where direct transmission from bats to humans and secondary transmission are well documented (reviewed in Eaton et al., 2006). The second documented case of likely human disease resulting from zoonotic transmission of a bat rubula-like virus occurred in 2012 when a wildlife biologist suffered severe acute febrile disease following collection and dissection of bat and rodent specimens in South Sudan and Uganda (Albariño et al., 2014). Deep sequencing of patient samples identified the presence of a novel paramyxovirus termed Sosuga virus (SosV), and further investigation confirmed seroconversion in the patient, as well as the presence of SosV in samples collected in the weeks immediately prior to the onset of symptoms in the patient, and more widely in bat samples collected by the researcher at multiple locations across Uganda (Albariño et al., 2014; Amman et al., 2015).

3.3 Zoonotic Transmission of Morbilliviruses

While the above are currently isolated events, they indicate that emergence of a novel rubula-like virus of global health concern is at least plausible. It is then relevant to also consider the repeated emergence of the relatively highly pathogenic morbillivirus, CDV, in nonhuman primates (Qiu et al., 2011; Sakai et al., 2013a; Sun et al., 2010; Yoshikawa et al., 1989). As recently reviewed (Nambulli et al., 2016), while CDV was originally thought to be restricted to canine host species, this paramyxovirus actually has a diverse range of potential hosts, and this recent emergence into primate species is perhaps cause for concern. MeV and CDV share significant antigenic similarity, and it has been suggested (discussed later) that CDV has not emerged into human populations already only because preexisting MeV immunity prevents this jump (Nambulli et al., 2016). However, the identification of hundreds of a paramyxoviruses currently grouped as unclassified morbilli-related viruses in wildlife with genetic diversity that vastly eclipses that of the classified morbilliviruses (Drexler et al., 2012; Mélade et al., 2016; Wilkinson et al., 2014) suggests there is reason to believe there could well be morbilli- or morbilli-related viruses circulating in wildlife with the potential to cause human epidemics unhampered by preexisting adaptive immune responses.

With these concerns in mind, in the following sections we examine the knowns and unknowns of the determinants of zoonotic emergence of pathogenic paramyxoviruses, considering both ecological and molecular factors.

4. ECOLOGICAL FACTORS DRIVING ZOONOTIC PARAMYXOVIRUS EMERGENCE

Following initial zoonotic transmission of a pathogenic virus to a human, whether this becomes an isolated spillover event, sparks an outbreak, or ignites an epidemic, is determined by the capacity for human-to-human transmission (Lloyd-Smith et al., 2009; Wolfe et al., 2007). This can be defined by the basic reproductive number (R_0) of a virus in the human population, where R_0 is the average number of new infections that will occur from a single infected individual, in the absence of preexisting immunity in the population. Of the two major emergent paramyxoviruses, HeV R_0 in human populations is zero, since there is no onward human-to-human transmission, whereas NiV can initiate short chains of secondary human transmission ($0 < R_0 < 1$). The R_0 for NiV in human populations in Bangladesh across 23 outbreaks between 2001 and 2007 was calculated to be 0.48, and so the authors conclude that the recurrent emergence of NiV seems unlikely to be capable of igniting an epidemic (Luby et al., 2009), which would require sustained human-to-human transmission, and therefore an R_0 at least equal to 1. As noted by Woolhouse et al. (2016), the R_0 of any pathogen is dependent on the unique factors of the specific host population in which it is circulating, and as such is far from a constant. Thus, emerging pathogens for which human-to-human transmission is currently self-limiting, but which have an R_0 approaching 1, are of particular concern, since reemergence in a population with even subtle differences in demographics or local ecological factors could be sufficient to provoke epidemic spread (Woolhouse et al., 2016).

From an evolutionary perspective, an important aspect of the emergence of pathogens capable of sustained transmission in human populations ($R_0 \geq 1$), is whether this is driven more by adaptive viral evolution within the new (human) host, or if it instead results primarily from multiple spillovers of diverse viruses, some of which may be preadapted for human-to-human transmission (Woolhouse et al., 2016). Woolhouse et al. propose that since virological factors such as tissue tropism and route of transmission, which are likely to determine human-to-human transmission rates, are generally phylogenetically conserved, then relatively dramatic adaptive evolution in a short time frame in the new host would be required to induce critical shifts in the R_0. Therefore, in most cases, preadaptation seems like the more probable evolutionary mechanism (Woolhouse et al., 2016). In this context, each individual transmission event from an animal reservoir to a human introduces additional viral diversity to the human population, and therefore contributes to the cumulative probability of transmission of a virus capable of initiating an epidemic.

The extent to which human populations are exposed to a potentially zoonotic pathogen is clearly a critical component of the likelihood of spillover infection. However, simply sharing a geographical area with infected animals alone is clearly not sufficient, given that transmission which initiates an outbreak is actually relatively rare, despite many people living at wildlife interfaces and the vast viral diversity hosted by wildlife species. Beyond basic proximity, the main ecological factors that govern the rates of such primary animal-to-human transmissions can be broadly categorized as either those that affect the prevalence rates and viral diversity in the reservoir host; or those that affect the frequency and nature of reservoir–human contacts (Lloyd-Smith et al., 2009). How these factors may relate to paramyxoviruses with zoonotic potential will be discussed later.

4.1 Viral Prevalence and Diversity in Reservoir Hosts

Bat and rodent species have been identified as key wildlife reservoir hosts, collectively harboring a vast diversity of paramyxoviruses with currently unknown zoonotic potential (e.g., Drexler et al., 2012; Mélade et al., 2016; Wilkinson et al., 2014). There are various traits associated with species of these two taxonomic orders (*Chiroptera* and *Rodentia*) that have been proposed to drive the observed high rates of viral infection and high viral diversity. For example, both rodents and bats have high species diversity (together comprising more than half of all mammalian species); frequently exhibit gregarious behaviors in large colony groups; and often share habitats with numerous other bat and rodent species. All of these are traits thought to contribute to frequent cross-species transmission of viruses (reviewed in Brook and Dobson, 2015; Han et al., 2015; Wang et al., 2008). Macroevolution of viral diversity is thought to be driven predominantly by such host-switching events between relatively related species, where the viral replication fitness landscape is sufficiently different in the donor and recipient hosts as to drive adaptive evolution, but not so extreme as to provide a serious impediment to transmission (Kitchen et al., 2011; Kreuder Johnson et al., 2015; Mélade et al., 2016; Parrish et al., 2008). Thus, the orders *Chiroptera* and *Rodentia* have ideal characteristics for amplification of the viral diversity important for virus spillover through optimized intra- and interspecies transmission of viruses.

Paramyxoviruses which spillover into to human and domestic mammal populations in modern times display an obvious association with bat reservoirs (Table 2; HeV, NiV, SosV, MenV, compare reservoir hosts to spillover hosts). Indeed, there are no confirmed instances of recent pathogenic paramyxovirus spillover or emergence from a nonchiropteran reservoir species. The possible exception to this may be Mòjiāng virus (MojV), which was circumstantially associated with three human cases of respiratory illness in mine workers following isolation of MojV from rodents in the same mine (Wu et al., 2014). However, rodents have been identified as contributing to the spread of enzootic paramyxoviruses for which they are not the reservoir host (Wilkinson et al., 2014), so in the case of MojV, it remains to be determined which species constitute the reservoir host(s), as well as whether it was the causative agent of the observed human disease. Efforts in virus isolation, serology, and (RT)-PCR have detected unknown paramyxoviruses in bats from South America, Europe, Africa, Asia, and Australia (see Baker et al., 2013; Barr et al., 2015; Breed et al., 2010; Epstein et al., 2008; Henderson et al., 1995; Iehlé et al., 2007; Kurth et al., 2012; Li et al., 2008; Pavri et al., 1971; Weiss et al., 2012 for some examples of these diverse surveys). There are paramyxoviruses whose origins are unknown, like SalV, suggesting that researchers have yet to look in all the right hosts to find paramyxovirus reservoirs, but several (RT)-PCR surveys for paramyxoviruses in both bat and rodent wildlife indicate a particular association between paramyxoviruses and bat hosts (Drexler et al., 2012; Muleya et al., 2014; Sasaki et al., 2014; Wilkinson et al., 2014). Drexler et al. (2012) conclude that paramyxovirus host switches occur most frequently from bats to other mammalian species, suggesting that emergence of novel paramyxoviruses will likely continue to occur predominantly from spillover from bat reservoirs. In addition, in a survey of paramyxoviruses in small mammals covering four taxonomic orders (*Rodentia*, *Afrosoricida*, *Soricomorpha*, and *Chirpotera*) in the biodiversity hotspot of the South West Indian Ocean Islands, bat species showed slightly elevated rates of paramyxovirus infection, and importantly, hosted a greater collective paramyxovirus sequence diversity than that observed across any other mammalian order (Wilkinson et al., 2014). Although beyond the scope of this review, bats have received considerable recent attention as possible "special" reservoirs of viruses with zoonotic potential and high risk of virulence, and the possible immunological and ecological factors that may make bats unique in this regard have been recently reviewed by others (Brook and Dobson, 2015; Han et al., 2015; Wang et al., 2008).

4.2 Frequency and Nature of Human–Animal Contacts

With increasing human population size, and increasing resources demanded by each person, humans are continuously encroaching on previously unsettled land, therefore inevitably perturbing the balance in delicate ecosystems (Patz et al., 2004). For example, ecological change such as deforestation is considered a major driver of virus emergence due to increased mixing of wildlife, particularly bats and rodents, with domestic animals and humans (Jones et al., 2008; Loh et al., 2013). Similarly, urbanization and intensification of farming practices gather large populations of humans and domesticated animals in novel geographical areas, creating vulnerable host populations with sometimes extensive interfaces with wildlife species (Fournié et al., 2015; Luby and Gurley, 2015). In addition to these more localized human impacts on the environment, it has been proposed that global climate change will also likely drive changes in human–wildlife contacts, due to expansion or contraction of the ecological niches of reservoir hosts (Daszak et al., 2013). However, while climate change and anthropogenic land use changes have frequently been theorized or modeled as credible major ecological drivers of the documented increase in emergence of zoonotic diseases over the course of the last century (Daszak et al., 2013; Jones et al., 2008; Murray and Daszak, 2011; Smith et al., 2014; Wolfe et al., 2005), there largely remains a paucity of evidence in specific cases.

A recent serology study in Cameroon highlighted the importance of the collection of detailed metadata in efforts to identify risk factors for paramyxovirus spillover infections, and provided evidence of likely drivers. Analysis of serum samples from Cameroon found a high prevalence of henipavirus-seropositive bats across all regions tested, as well as a low rate (<2%), but substantial number (7–10 individuals), of human samples to be positive for NiV and HeV crossneutralizing antibodies, indicating likely spillover infections with related bat henipaviruses (Pernet et al., 2014b). While neither reported exposure to nor hunting of bats were alone associated with the probability of seropositivity in humans, those who specifically reported butchering bat bushmeat were 29 times more likely to be seropositive than those reporting no contact. Moreover, this study also provided evidence of the role of human land use changes, as individuals living in areas undergoing deforestation were also significantly more likely to be seropositive (Pernet et al., 2014b). While factors are likely to differ between regions, this study points to potential predictive ecological factors for bat henipavirus spillover risk, and suggests that targeted surveillance among those who prepare bushmeat in areas undergoing dramatic ecological change such as deforestation could be valuable in early identification of zoonotic emergence, by identifying potentially frequent spillover events that currently go detected unless a noticeable outbreak results.

An improved understanding of the ecological factors that govern the likelihood of zoonotic transmission could reduce the risk of serious epidemics by allowing targeted surveillance efforts, as well as appropriate social and environmental interventions. In order to consider more specific risk factors for emerging paramyxoviruses, we must look to emerging paramyxoviruses that have caused substantial enough numbers of outbreaks to be able to start to draw such conclusions, so in the following sections we will discuss the known risk factors for HeV and NiV outbreaks, as well as the evident gaps in existing knowledge.

4.3 Known Risk Factors: Hendra Virus and Nipah Virus

In cases of HeV infection, the clear risk factor for humans is close contact with infected horses, and so far can account for all human cases (Field, 2016). Similarly, there is an obvious required enabling factor for the primary outbreak from the bat reservoir to horses, which is the presence of infected bats roosting in fruit trees sufficiently near to horse paddocks (Plowright et al., 2015). However, there are many locations in which these basic enabling conditions are met without spillover, and thus additional, though currently unknown, factors must contribute to the observed clustering and seasonality of outbreaks, as discussed in more detail later. In recent years, development and introduction of an effective equine vaccine means that the vaccination status of horses is now also a key outbreak risk factor. Although vaccine coverage is not complete, and outbreaks still occur, there have so far been no HeV cases reported in vaccinated horses, suggesting that this should be an effective outbreak risk mitigation strategy (Broder et al., 2013; Middleton et al., 2014; Peel et al., 2016). This approach also exemplifies the "One Health" approach to protect humans from emerging zoonotic disease by vaccination of intermediate hosts (Middleton et al., 2014).

The ecological factors that drove the first NiV outbreak have been extensively investigated, and based on the levels of seroprevalence and active infection at the index farm, Pulliam et al. (2012) conclude that NiV circulation among pigs occurred at this farm for several years prior to the recorded start of the human outbreak. Moreover, the true human index case was retrospectively identified to have been a worker from the index farm in January 1997, with at least five additional human cases confirmed to have occurred prior to May 1998, months before the outbreak was detected in September of that year. Pulliam et al. (2012) identified intensification of farming practices at the index farm as key factors that facilitated NiV emergence. First, the planting of mango trees (to increase agricultural output by also selling fruit) within contact range of pigsties a few years before the outbreak attracted bats, and dramatically increased the chances of pigs coming into contact with saliva and other body fluids from bats on dropped fruits. There are now restrictions on planting of fruit trees near piggeries throughout Malaysia, and though one cannot conclude from the absence of further outbreaks, it is possible this has helped to prevent a second NiV outbreak in Malaysia. Second, to maximize efficiency, pigs were kept in separate pens for breeding, early growth, and finishing, and this turnover and segregation of young naïve piglets therefore maintained a highly susceptible population, whereas adult breeding pigs were more likely to acquire protective immunity (Pulliam et al., 2012). Once the outbreak among pigs at the index farm was established, transportation of infected pigs for sale or slaughter dramatically spread the NiV to relatively distant regions of Malaysia, as well as to Singapore, and the outbreak was only contained after almost one million pigs were culled (Mohd Nor et al., 2000).

As noted earlier, following the initial NiV outbreak in which pigs were an intermediate host, reemergence has generally occurred directly from the bat reservoir to humans, with the majority of these outbreaks occurring in Bangladesh and India. At the individual level, as for HeV infection, the main risk factors for NiV infection in such outbreaks are very clear. The main risk for initial transmission to humans is consumption of raw date palm sap contaminated with urine or saliva from infected bats (Islam et al., 2016; Luby et al., 2006; Openshaw et al., 2016; Rahman et al., 2012), while close contact with an infected person then enables secondary human-to-human transmission (Hegde et al., 2016; Homaira et al., 2010; Sazzad et al., 2013). However, consumption of date palm sap, as well as hunting bats for bushmeat, are relatively common practices throughout Bangladesh (Openshaw et al., 2016), and yet the majority of outbreaks have occurred in central and northwest Bangladesh, to the extent that these regions are colloquially referred to as the "Nipah belt." This has provoked attempts to correlate ecological factors in these regions with the high outbreak prevalence (Hahn et al., 2014a,b). One analysis found that Nipah belt villages have significantly higher population densities, and occur in regions where forest land is more fragmented, suggesting these factors could promote NiV outbreaks (Hahn et al., 2014b). A similar analysis sought to identify risk factors by better understanding the features of preferred habitats of *Pteropus giganteus*, a key NiV reservoir bat species—an approach validated by their finding that outbreak villages were 2.6 times more likely to map to a location their model predicts as a likely preferred habitat (Hahn et al., 2014a). The major contributing factors determining habitat preference included tree species, forest fragmentation, rainfall, temperature gradients, and human disturbance levels. Interestingly, this model also identifies a number of villages outside the Nipah belt where outbreaks seem likely, which raises the possibility that outbreaks may go undetected in some regions, due to a lack of local awareness or surveillance bias (Hahn et al., 2014a).

4.4 Observed Trends With Unknown Driving Factors

For both NiV and HeV outbreaks, there is a strong seasonality in documented cases, clearly implicating seasonal ecological factors. Excluding the initial NiV outbreak, which began in Malaysia in September 1998 and continued until April 1999, every documented human case of NiV infection has occurred between the months of December and May (Islam et al., 2016; Luby et al., 2009; Wacharapluesadee et al., 2010). HeV spillover events also exhibit strong seasonality (though the timing is shifted relative to NiV outbreaks), occurring almost exclusively between May and October (McFarlane et al., 2011; Plowright et al., 2011). While it is unclear what drives these observed seasonal trends, and whether drivers differ for NiV compared to HeV, current hypotheses regarding the contribution of various factors will be discussed.

Human HeV infection has always been documented to occur via contact with an infected horse, so it is critical to consider what drives the primary host switch from the bat reservoir to initiate an outbreak in horses. It is thought that the main route of transmission from bat to horse is a result of horses eating fruit contaminated with saliva and other body fluids from infected bats. One factor proposed to contribute to the seasonality of HeV outbreaks in horses is the relative stability of the virus in the environment, with increased persistence of infectious virions on contaminated fruit during the cooler, dryer season in the Australian provinces of Queensland and New South Wales when outbreaks occur (Fogarty et al., 2008; McFarlane et al., 2011).

An alternative, but not incompatible, hypothesis posits that there are seasonal changes in the likelihood of bats being infected, or of actively shedding virus, and indeed there is evidence of seasonal increases in levels of HeV seropositivity in bat populations that correlate with the timings of spillover events (Plowright et al., 2008). It has been variously suggested that there could be pulses of infection due to migration; waning population immunity because of seasonal birth pulses and infection of juveniles; or population-level stresses such as the metabolic stress of pregnancy and seasonal food shortages (McFarlane et al., 2011; Plowright et al., 2008, 2011, 2015). It has been noted that in recent decades, many Australian colonies of *Pteropus* species bats have dramatically reduced their tendency to migrate during the winter months, perhaps due to increased availability of year-round food sources in urban and peri-urban settings. Plowright et al. (2011) have proposed that this change in migratory behavior might result in increased shedding of HeV during winter months, as a result of nutritional stress due to lower quality food sources in urbanizing areas, as compared to forest environments. Furthermore, they suggest that increasing geographical isolation of colonies could facilitate localized pockets of bats with waning population immunity, and therefore result in more dramatic pulses of infection upon viral reintroduction than when seasonal migration was more prevalent, which could increase risk of viral shedding (Plowright et al., 2011).

The seasonality of outbreaks of NiV in Bangladesh and India has also been correlated with seasonal increases in both the percentages of bats that test positive for NiV antibodies, and in levels of shed NiV detected in bat urine (Wacharapluesadee et al., 2010). A longitudinal study of a bat colony in Ghana comprised of wild-caught bats that were then kept in captivity found a corresponding seasonal pattern in henipavirus seroconversion, and therefore in inferred henipavirus infection. The pattern was specific to adult female bats and coincided with late pregnancy and lactation (Baker et al., 2014). Similar results were obtained in a bat serum survey in Malaysia, in which bats most likely to be positive for henipavirus antibodies were adult females that were either pregnant, lactating, or had a dependent pup (Rahman et al., 2013). These studies collectively suggest that seasonal reproductive stress is a contributory factor causing seasonal increases in NiV infection and shedding, and therefore increased probability of human exposure to contaminated fruit or date palm sap. Seasonal pulses of virus replication and documented human spillover associated with bat reproduction have also been identified for the zoonotic filovirus Marburg virus in *Rousettus aegypticus* bats (Amman et al., 2012), which can also host paramyxoviruses (Amman et al., 2015; Drexler et al., 2012). However, longitudinal analysis of morbili-related viruses in urine collected from a German maternal *Myotis myotis* colony over several years saw no temporal changes in shedding, and no evidence that reproduction, parturition, or age affected shedding (Drexler et al., 2012). Thus, these trends remain incompletely understood, could vary by geography, climate, bat host, or virus, and therefore may not be broadly applicable.

A better understanding of what determines spillover risk is clearly critical for mitigating the risks of recurrent NiV and HeV spillover, and for predicting and managing risk associated with the emergence of other pathogenic paramyxoviruses. In particular, if birthing pulses or population level stresses increase the likelihood of spillover events, then attempting to curb risk by reducing urban and peri-urban bat colony population size, as has been proposed in Australia, could have the opposite effect to that intended, as recently discussed elsewhere (Plowright et al., 2015, 2016). In this instance, as suggested by Hahn et al., land management strategies such as forest conservation of known ideal roosting sites for bat reservoir species in areas away from villages could be a useful means of risk management (Hahn et al., 2014a). Similarly, by identifying at-risk communities based on more detailed understanding of ecological drivers of spillover risk, targeted surveillance can be employed to allow early identification of outbreaks. Combined with education of the most at-risk human populations to minimize the social and cultural practices that are known to determine infection risk at the individual level (Kamins et al., 2015; Nahar et al., 2010), such measures may improve containment of future outbreaks.

5. VIRUS–HOST MOLECULAR INTERACTIONS AFFECTING PARAMYXOVIRUS EMERGENCE

As discussed earlier, paramyxoviruses have been observed to switch hosts at a high rate (Kitchen et al., 2011), which has also been associated with higher viral diversity (Brierley et al., 2016; Kreuder Johnson et al., 2015;

Mélade et al., 2016) and thus with a potentially increased capacity to overcome the molecular viral and host barriers to spillover into susceptible human and domestic animal populations (Woolhouse et al., 2016). Such barriers in a new host include the need for efficient receptor usage and tissue targeting, interactions with required host factors, and evasion of innate immune signaling; as well as potential preexisting immunity to antigenically similar viruses. P (phosphoprotein) and its accessory gene products (Table 1), as well as the viral attachment proteins (G/H/HN), have the most frequent and direct molecular interface with these host processes. P is an essential component of the polymerase, but has immunomodulatory functions for some paramyxoviruses, and P-derived alternative reading frame proteins (discussed later) are important for controlling the innate immune response in infected cells. Evidence for the evolutionary pressure exerted by the need to interact with different hosts through these proteins can be seen in Fig. 3A; note that both P and H/HN/G proteins demonstrate a marked increase in diversity above the other viral proteins in each paramyxovirus genus (see also Fig. 2, "P" top left and

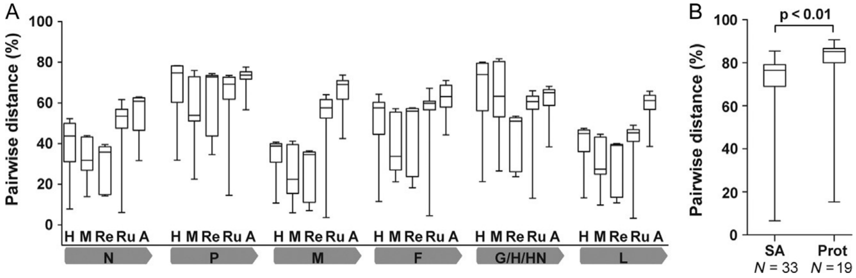

Fig. 3 Paramyxoviruses demonstrate greater diversity within each genus at virus proteins with significant host interactions. (A) Pairwise distances per gene and per genus across *Paramyxoviridae*. Genera are labeled within the graph; H = *Henipavirus*, *n* = 5 (HeV, NiV, CedV, GH-M74a, and MojV); M = *Morbillivirus*, *n* = 7 (FeMV, PDV, CDV, MeV, PPRV, and CeMV); Re = *Respirovirus*, *n* = 6 (SeV, HPIV-1, PPIV-1, CPIV-3, HPIV-3, and BPIV-3); Ru = *Rubulavirus*, *n* = 9 (MuV, BMV, PIV-5, HPIV-2, SV-41, PorV, MapV, HPIV-4a, and HPIV-4b); and A = *Avulavirus*, *n* = 6 (APMV-2, APMV-5, APMV-11, APMV-3, APMV-9, and NDV). *Gray bars* indicate the virus gene being evaluated. *Whiskers* show minimal and maximal variation within the genus, *boxes* denote the 25% (low) and 75% (high) percentiles, and *horizontal lines* indicate medians. (B) Pairwise distances of sialic acid (SA)-using paramyxoviruses vs protein (Prot)-receptor-using viruses, indicating the number of virus species attachment proteins. Genera included in SA: *Rubulavirus*, *Respirovirus*, *Ferlavirus*, *Avulavirus*, *Aquaparamyxovirus*, and Unclassified (including rubula-like viruses). Genera included in Prot: *Morbillivirus*, *Henipavirus*, and Unclassified (including Jeilongvirus and morbilli-like viruses). Pairwise distance was calculated in MEGA 6.0, and *T*-test was done using SPSS software (IBM).

"HN/H/G" right). What is known, and what is not, about paramyxoviral tools and strategies to overcome these barriers is described below.

5.1 Successful Emergence Requires Host-Specific Interactions

5.1.1 Effects of Receptor Specificity on Species and Tissue Tropism

Virus attachment and entry is the first direct interaction between an emergent virus and its new host, and would appear to be one of the clearest barriers that prevent interspecies paramyxovirus transmission. Paramyxovirus entry requires the coordinated action of both the fusion (F) and attachment glycoproteins, the latter variously termed HN, H, or G depending on the nature of the receptor used (Fig. 1). While paramyxoviruses are primarily classified based on sequence analysis of L proteins (Fig. 2, "L" bottom left), the attachment glycoproteins are much more divergent (Fig. 2, compare "L" bottom left to "HN/H/G" right; Fig. 3A) and have functional characteristics that provide useful delineations within the virus family as well. HN glycoproteins have sialic acid (SA)-dependent hemagglutinin and neuraminidase (HN) activities, H glycoproteins have hemagglutinin activity (unrelated to SA binding), and G glycoproteins have neither. H and G designate the attachment glycoproteins of the morbilliviruses and henipaviruses, respectively. The glycoproteins from many of the unclassified paramyxoviruses that have none of the essential SA-binding site residues found in HN proteins are presumed to also use protein-based receptors and are thus designated as G (Figs. 1 and 2, "HN/H/G" right). Morbillivirus H glycoproteins use protein-based receptors, too (see later); the hemagglutination activity in absence of neuraminidase activity that was attributed initially to MeV-H is not SA dependent, but is rather due to the expression of CD46, an alternative cell culture receptor for the vaccine strain of MeV, on the RBCs from certain nonhuman primates (Krah, 1991; Lee and Ataman, 2011). Although HN-bearing, SA-using viruses comprise a majority of paramyxovirus genera and infect a larger of number host species/orders than protein receptor-using (H or G) paramyxoviruses, the attachment proteins from the latter have significantly greater diversity than the former (Fig. 3B). This likely represents the diversity of receptor molecules used by these attachment proteins, since SA-based receptors are relatively structurally constrained compared to the universe of potential protein receptors (discussed later). Despite the divergent nature of the receptors used, paramyxovirus attachment glycoproteins all bear common features such as a receptor-binding globular head domain that adopts a six-bladed beta-propeller fold, which is connected to a flexible stalk region. The stalk region triggers the metastable F protein upon receptor binding, which is what initiates the conformational cascade that eventually results in membrane fusion (reviewed in Bose et al., 2015). Later, we will explore whether receptor specificity can be an important contributor to species and tissue tropism at the level of viral entry, and propose that viral use of a highly conserved receptor molecule may remove at least one barrier to interspecies transmissibility.

5.1.2 Use of SA as a Paramyxovirus Receptor

Five of the seven recognized genera of paramyxoviruses (Fig. 2) use SAs on cell surface glycoproteins or gangliosides as receptors. These HN-bearing paramyxoviruses infect a wide variety of vertebrate hosts (mammals, birds, reptiles, and fish), but *Avulavirus*, *Ferlavirus*, and *Aquaparamyxovirus* species have not demonstrated consistent infection of mammals, and thus are unlikely source genera for zoonotic transmission of emerging paramyxoviruses into humans, so we focus here on respiroviruses and rubulaviruses. Paramyxovirus HN proteins have two important activities: the first is the hemagglutination, or SA-binding activity, that is important for attachment and triggering of fusion during entry, while the second is the neuraminidase, or SA-cleavage activity, that is important to release the virion from the parent cell during budding, and prevent reinfection of the same cell. HN proteins have differences in their binding and cleavage activity for various terminal sialyl linkages. For example, while the HN proteins from most human parainfluenza viruses (HPIVs) preferentially bind and cleave α2,3 linked SAs, HPIV-3 HN can also recognize α2,6 linked SAs (Amonsen et al., 2007; Fukushima et al., 2014, 2015). For MuV, a single amino acid change can switch the viral HN preference from α2,3 to α2,6 SA linkages (Reyes-Leyva et al., 2007). Importantly, this E335K mutation in the HN protein also results in heightened neurotropism and neurovirulence associated with the differential distribution of these SA linkages on nervous tissues (Santos-López et al., 2009), indicating that receptor usage and tissue distribution can affect viral pathogenesis, as well.

Along with preference for specific linkages, HN proteins additionally demonstrate preference for the context of terminal SAs: MuV-HN binding to α2,3 sialylated oligosaccharides is significantly weaker when the terminal SAs are present on branched tri- and tetraantennary complex glycans than on their simple or biantennary counterparts. Such preferences could potentially modulate the tissue tropism and transmissibility for HN-bearing paramyxoviruses (Fukushima et al., 2014; Reyes-Leyva et al., 2007; Villar and

Barroso, 2006) since sialylated glycans with diverse structures and compositions are differentially expressed in different tissues. Although much remains to be determined about the systemic distribution of glycan structures, the classical notion established by lectin immunohistochemistry that α2,6 and α2,3 receptors are concentrated in the human upper (LRT) and lower respiratory tract (LRT), respectively (Wright et al., 2013), are being revised. Glycomic analysis based on lectin binding (Kogure et al., 2006; Nicholls et al., 2007) and mass spectrometry methods (Walther et al., 2013) have revealed that both upper and lower human respiratory tract tissues have a spectrum of α2,6 and α2,3 terminated glycans in varying portions, and at least for influenza viruses, binding to sialyated α2,6 or α2,3 glycans is not necessarily predictive of productive replication in ex vivo human bronchial or lung tissues (Walther et al., 2013). Thus, the paradigm that the preferential α2,3 binding of avian influenza viruses is a determinant of its lack of transmissibility among humans may need to be refined, and we must also consider this improved understanding of SA linkage distribution when exploring receptors for HN-bearing paramyxoviruses. Overall, detailed study of the systemic distribution of glycan structures—both respiratory, and elsewhere in the body—in different hosts may shed light on the tropism and pathogenesis of HN-bearing paramyxoviruses that disseminate systemically to cause disease, such as MuV and the recently discovered Menangle and Sosuga viruses (Table 2).

In addition to direct interaction with SAs on the target cell, respiratory viruses must navigate a respiratory tract that is known to be densely packed with secreted SA-bearing mucins and free sialylated oligosaccharides (Zanin et al., 2016) that could act as decoys for viral HN (Wasik et al., 2016). The ability to evade such decoys would depend, in part, on the neuraminidase (SA cleavage) activity of the HN, by allowing the virus to penetrate the mucus barrier and reach the susceptible respiratory epithelial cells. Human respiratory secretions differentially restrict avian, porcine, and human-tropic influenza virus entry into the same cells in vitro (Zanin et al., 2016), providing indirect evidence that the lung surfactant environment varies between species, but this has not yet been studied for paramyxoviruses. It is therefore not clear whether evasion of these "decoy" SAs is a determinant of HN-bearing paramyxovirus species specificity. Overall, given the heterogeneous expression of α2,6 and α2,3 SAs in the human respiratory tract, it is likely receptor specificity alone for HN-bearing respiroviruses and rubulaviruses does not dictate their potential for cross-species transmission. Furthermore, since single amino acid changes in the HN protein of HPIV-3 (*Respirovirus*) or MuV (*Rubulavirus*) can markedly affect α2,3 vs α2,6 receptor binding (Fukushima et al., 2015; Mishin et al., 2010; Reyes-Leyva et al., 2007), it is unlikely that SA linkage receptor specificity is a strong barrier to spillover of HN-bearing paramyxoviruses.

5.1.3 Paramyxoviruses That Use Protein-Based Receptors

Two of the currently recognized genera of paramyxoviruses, morbilliviruses and henipaviruses, use protein-based receptors. Structural phylogeny analysis indicates that morbillivirus H and henipavirus G proteins independently evolved from what is thought to be the ancestral HN attachment protein (Bowden et al., 2008; Lee and Ataman, 2011). Interestingly, extant henipavirus G proteins are structurally more related to extant HN proteins than MeV-H (Zeltina et al., 2016; see also Fig. 2, "HN/H/G" right), suggesting that morbillivirus H evolved the use of protein-based receptors before henipaviruses (Bowden et al., 2008, 2010; Lee et al., 2008), assuming that its structural diversity and divergence from other paramyxoviruses is a function of time and not due to other evolutionary constraints. We speculate that morbilliviruses may thus have speciated in their respective hosts for a longer period of time, which may explain in part the species specificity of each morbillivirus in comparison to the species promiscuity of a given henipavirus. These factors may also be responsible for the greater divergence among protein receptor-using viruses demonstrated in Fig. 3B. Here, we discuss how for both morbilliviruses and henipaviruses, the use of specific protein receptors is correlated with aspects of transmission, species and tissue tropism, and pathogenesis.

All extant henipaviruses whose receptors have been functionally defined use ephrin-B2, a receptor tyrosine kinase, as an entry receptor (Bonaparte et al., 2005; Lawrence et al., 2014; Lee et al., 2015; Marsh et al., 2012; Negrete et al., 2005; Weis et al., 2014). The presumed mode of transmission and systemic dissemination is consistent with the expression of ephrin-B2 on microvascular endothelial cells, neurons, and some cells in the respiratory epithelium (Bennett et al., 2013; Gale et al., 2001; Pernet et al., 2012); like most other paramyxoviruses, henipaviruses are likely spread via the oropharyngeal route, and often result in fatal neurological and respiratory disease in nonreservoir susceptible hosts (de Wit and Munster, 2015; Middleton and Weingartl, 2012; Wong and Tan, 2012). Ephrin-B2 is highly conserved across mammalian species from bats to humans (Bossart et al., 2008; Pernet et al., 2012), which explains in part the ability of HeV and NiV to infect a wide range of mammals under natural (bats, horses, pigs, cats, dogs, and humans) and laboratory (hamsters, guinea pigs, and rodents) conditions (Ching et al., 2015; Mills et al., 2009; Vigant and Lee, 2011). Correlation of ephrin-B2 conservation and susceptibility to henipaviruses like NiV across so many mammalian species supports the proposition that paramyxoviruses using highly conserved receptors are better equipped to achieve transmission to new host species.

Morbilliviruses, in contrast, utilize CD150 (SLAM/F1—signaling lymphocyte activation molecule family member 1) as the major morbillivirus host receptor protein and first point of contact with the new host (Delpeut et al., 2014; Tatsuo et al., 2001). Morbilliviruses are also primarily contracted through respiratory exposure, but spread via initial infection of SLAM/F1-bearing alveolar macrophages, which then disseminate the virus to local lymph nodes where the virus replicates in subsets of B- and T-cells (Delpeut et al., 2014). Incidentally, infection of SLAM/F1 expressing B- and T-cells is likely responsible for both the short- and long-term immune dysfunction that follows infection with MeV (de Vries et al., 2012; Mina et al., 2015). In the respiratory epithelium, morbilliviruses complete their infection cycle by entry at the basolateral surface using nectin-4 (PVRL4), the other major morbillivirus attachment receptor (reviewed in Delpeut et al., 2014), and are then secreted into the respiratory tract lumen for transmission.

Nectin-4 is highly conserved and does not appear to enforce species-specific limitations in morbilliviruses, since CDV can utilize human nectin-4 with no adaptation (Bieringer et al., 2013; Sakai et al., 2013b). However, nectin-4 is only required for morbillivirus exit from the host; indeed, recombinant MeV that is selectively blind for nectin-4 can infect and cause primary disease in nonhuman primates, but is unable to transmit or be shed (Frenzke et al., 2013). Although evidence exists for additional natural MeV attachment receptors (Griffin, 2013; Sato et al., 2012), SLAM/F1-specificity is best characterized and appears to be the main barrier to morbillivirus entry in hosts of different species. SLAM/F1 from various mammalian species, while functionally conserved, is much more divergent than the henipavirus receptor, ephrin-B2 (Ohishi et al., 2010; Zeltina et al., 2016), and it has been shown experimentally that species-specific use of SLAM/F1 is an important determinant of host species restriction of viruses like MeV, CDV, and the recently eradicated rinderpest virus (RPV) (reviewed in Adombi et al., 2011; Baron, 2005; Nambulli et al., 2016; Tatsuo et al., 2001; Yanagi et al., 2000). This provides further support for the concept of receptor conservation contributing to interspecies transmission and restriction. However, this has been overcome in both experimental (Bieringer et al., 2013) and natural settings (Sakai et al., 2013b) with CDV, so other barriers discussed later likely function in concert with receptor specificity to maintain the observed morbillivirus and other paramyxovirus host restriction.

5.1.4 Contribution of Host Conservation of Paramyxovirus Receptors to Spillover Risk

Both henipaviruses and HN-bearing paramyxoviruses like rubulaviruses have demonstrated the ability to attach and enter cells from a broad range of species, eliminating one of the restrictions on interspecies transmission. This receptor promiscuity is likely important for the diversity of these and related viruses in both bat and rodent reservoirs (for example, Baker et al., 2012; Drexler et al., 2012; Wilkinson et al., 2012, 2014), and for the large number of spillovers and infected species associated with these viruses. Thus, paramyxoviruses with the ability to use a receptor molecule that is highly conserved across animal species—whether carbohydrate or protein—appear better equipped to overcome the initial molecular restrictions of attachment and entry to new host species, and may therefore have a greater likelihood of spilling over into human and domestic animal populations.

5.1.5 Postentry Essential Host Factors That Are Species-Specific Are Not Yet Known

While both human and bovine parainfluenza virus 3 (BPIV-3) are extremely similar at both an antigenic and genetic level (see Fig. 2 and Table 1), BPIV-3 is known to be attenuated for human infection (Karron et al., 1995), while HPIV-3 is decidedly not (Pecchini et al., 2015). Interestingly, simply replacing the N (nucleocapsid) protein of HPIV-3 with that of BPIV-3 attenuates the human virus in macaques (Bailly et al., 2000), as does swapping other BPIV-3/HPIV-3 ORFs (Skiadopoulos et al., 2003), although the converse experiment in cattle has not been performed. Infection of macaques and humans with BPIV-3 results in 1- to 3-log lower viral titers recovered, but viral replication does occur and antibody responses are induced (Bailly et al., 2000; Schmidt et al., 2000; Skiadopoulos et al., 2003), which indicates that the species restriction for BPIV-3/HPIV-3 is not absolute. Since we know that BPIV-3 is competent to enter primate cells (Schmidt et al., 2000; Skiadopoulos et al., 2003) and is able to successfully antagonize the human innate immune response by blocking interferon induction with both

C and V accessory proteins (Komatsu et al., 2007; Yamaguchi et al., 2014), the species-specific attenuation of BPIV-3 in humans may instead be explained by an incompatibility with a required host factor during RNA replication or virion production. Although examples of species-specific virus–host interactions outside of entry and immune evasion are limited and not well characterized in paramyxoviruses (Tao and Ryan, 1996), a biologically related example of such can be found in H5N1 avian influenza. A mutation in the PB2 polymerase subunit, E-to-K at amino acid 627, is associated with adaptation to replication, transmission, and pathogenicity in mammalian cells (Gabriel et al., 2013). This mutation has recently been determined to restore interaction of the avian influenza polymerase and the mammalian version of ANP32A, a required host factor with significant differences from the avian protein (Long et al., 2016). Paramyxoviruses are likely to have analogous interactions with host proteins that facilitate important stages of the virus life cycle, but since discovery and characterization of enzootic paramyxoviruses in both their current hosts and potential emergent host systems have received less attention and research energy than pandemic and avian influenza viruses, the significance of species-specific host factor restriction remains to be determined and is a ripe area for exploration. As this area of paramyxovirus biology is examined, we may also find that lack of a required host factor negatively synergizes with other barriers like suboptimal receptor interactions to ultimately prevent successful cross-species infection and/or sustained transmissibility in humans.

5.1.6 Antagonism of Innate Immune Responses Is Known to Be Key to Successful Infection

Species-specific mechanisms of immune modulation carried out by paramyxoviruses that infect humans and our domestic mammals are relevant to our understanding of paramyxovirus host biology and interactions. General paramyxovirus strategies to modulate the host's immune environment have been most recently reviewed by Audsley and Moseley (2013) and Parks and Alexander-Miller (2013). Broadly speaking, paramyxoviruses have transcriptional frameshift protein products of the phosphoprotein (Fig. 1; catalogued in Table 1) that manipulate interferon induction and signaling in the host cells to varying degrees, with the known exceptions of HPIV-1 (Power et al., 1992) and CedV (Marsh et al., 2012), although both HPIV-1 and CedV still produce alternate start C proteins from the phosphoprotein transcript (Table 1). The phosphoprotein itself (Ciancanelli et al., 2009; Devaux et al., 2013; Gainey et al., 2008), along with the small hydrophobic

(SH) protein found in rubulaviruses and jeilongviruses (Fig. 1, Table 1), have further been implicated in modulating the host innate response to the virus' benefit (Li et al., 2011; Wilson et al., 2006). As compared in Table 1 and illustrated for P in Figs. 2 and 3A, each of these proteins is highly divergent, even within the same genus, which may represent the fact that these proteins must frequently interact with some of the proteins that are so variable within and between host species, like those of the innate immune response (Du Pasquier, 2005; Kwiatkowski, 2005).

Overall, efforts to determine the species specificity of these virus–host interactions have been piecemeal, particularly in enzootic viruses that have not yet been detected to jump species. Generalizations or predictions about the effect of specific viral protein–host factor interactions on species tropism are difficult to make, since significant variability in viral innate immune evasion occurs even within a given viral genus. Both the P and accessory proteins of viruses from a given genus typically demonstrate less than 50% identity at the amino acid level (Table 1; see also Fig. 2, "P" upper left), and so prediction of host-specific interactions with innate immune signaling by analogy to other viruses within the genus is impractical. As a functional example, rubulavirus V proteins are known to antagonize STAT1-mediated interferon signaling through a common mechanism of facilitating ubiquitination and proteasomal degradation of STAT1 (Audsley and Moseley, 2013; Horvath, 2004). Although the mechanism is shared, the species restrictions of these viruses are not: human MuV is not known to infect any other animals in the wild and only infects certain nonhuman primates in a laboratory setting (Xu et al., 2013), while parainfluenza virus 5 (PIV-5) naturally infects a multitude of wild and domestic mammals—often asymptomatically (Chatziandreou et al., 2004). Despite its species promiscuity, PIV-5 only poorly infects mouse cells, and causes no disease in infected mice, because its V protein cannot disrupt murine STAT1-mediated interferon signaling (Young et al., 2001). The PIV-5 V protein can, however, disrupt human STAT1-mediated interferon signaling, and thus, its ability to infect a host is correlated with its ability to control interferon signaling. Conversely, although the capacity of human MuV to manipulate other mammalian interferon induction and signaling pathways has not been systematically characterized to determine the basis of its species restriction, the inability of MuV to productively infect ferret airway epithelial cultures even at high MOIs suggests a very early block involving incompatible host factors prior to innate immune signaling (Elderfield et al., 2015).

Not only do paramyxoviruses from various hosts have to contend with antagonizing innate immune signaling, they must also contend with innate immune effectors. Even such highly human-adapted viruses as MeV, MuV, or HPIV-2 do not completely abrogate innate antiviral signaling (Young et al., 2003) and are therefore under pressure from interferon-stimulated host effectors (Rabbani et al., 2016; Young et al., 2016). As an example, the IFIT family of proteins use a variety of means to recognize and inhibit translation of nonself-transcripts (Daugherty et al., 2016), therefore each requiring different mechanisms of viral evasion or antagonism (Diamond and Farzan, 2012). Daugherty et al. demonstrate that within the IFITs, principally encompassing IFIT1, 1B, 2, 3, and 5 and their homologs, there is a large diversity in coding and expression of these proteins across the order *Mammalia* (2016). For example, primates encode both IFIT1 and IFIT1B, although human IFIT1B does not appear to be functional; *Chiroptera* and *Artiodactyla* (goats, cows, and pigs) lack IFIT1B entirely and only encode IFIT1; and *Myomorpha* (a suborder of rodents that includes mice, rats, and voles) lack IFIT1 and encode only IFIT1B (Daugherty et al., 2016). Thus, viruses that are highly adapted to rodent infection may lack molecular tools to evade or inhibit IFIT1 effector functions and may therefore experience a higher restriction barrier in human and bat cells, while viruses that are adapted to bats may have IFIT1 evasion mechanisms that can function to some degree in humans (or pigs or cattle) and may therefore not be restricted by the human version of this effector. IFIT proteins are just one family among many, and protein families—effectors, signal transducers, and sensors—throughout the mammalian innate immune network demonstrate analogous diversity in various mammalian species (e.g., NOD-like receptors, or TLR4: Motta et al., 2014; Vaure and Liu, 2014), posing an intricate web of obstacles that viruses must navigate when expanding their host repertoire.

5.2 Unknown Connection Between Emergence and Pathogenicity

As evidenced by the serosurveillance study discussed earlier (Pernet et al., 2014b), and by other indications of human serological responses to enzootic paramyxoviruses (Table 2), zoonotic virus spillover does not always result in pathogenesis in the new host. However, factors that impact paramyxovirus interspecies transmission may also play a separate role in defining the pathogenicity of novel viruses. For HPIVs (respiroviruses—HPIV-1 and 3; and rubulaviruses—HPIV-2, 4, and PIV-5), transmissibility is associated with upper respiratory tract (URT) infection, while pathogenesis correlates with lower respiratory tract (LRT) infections (Burke et al., 2011). As such, efforts to understand and limit the transmission potential of PIVs and any novel zoonotic relatives should not focus solely on the severity of respiratory symptoms (which is a consequence of LRT infection), but on factors that facilitate virus replication and shedding in the URT, which could result in transmission from asymptomatic hosts (Henrickson, 2003). Lower temperature in the URT, differential innate immune responses and cytokine milieu, and the presence of antiviral (e.g., surfactant proteins in the lung) or proviral (e.g., secreted proteases required for F cleavage) factors may all contribute in a host-specific manner to increase the capacity for transmissibility and emergence of a potential pathogen.

In some instances, it is possible that manipulation of host immune signaling merely defines the virus' pathogenicity in a given species, rather than its ability to infect that species overall. For example, Tioman virus (TioV; Chua et al., 2002) is another rubulavirus which is found in flying foxes (Yadav et al., 2016). TioV does not antagonize IFN-β signaling in human cells, yet it also does not appear to interact with STAT2 from its fruit bat reservoir host (Caignard et al., 2013). Thus, TioV appears capable of infection irrespective of its ability to antagonize interferon signaling, but evidence for human infection, at least, suggests that it may be asymptomatic (Yaiw et al., 2007). This can also be observed with MeV, where specific abolition of its ability to counter STAT1 signaling severely attenuates virus pathogenesis in the *Rhesus macaque* model of infection (Devaux et al., 2011). However, a counterexample can be found in NiV and HeV evasion of both bat and human interferon induction (Glennon et al., 2015)—and yet these viruses do not appear to cause disease in the bat host (Middleton et al., 2007), but most definitely do in humans. This may relate to the potential differences in immune responses and homeostasis between bats and humans alluded to earlier (see also Brook and Dobson, 2015; Han et al., 2015; Mandl et al., 2015; O'Shea et al., 2014), but clearly, further work in exploring paramyxovirus mechanisms of innate immune modulation comparing enzootic, emergent, and nonpermissive hosts is needed to gain a better understanding of molecular factors that drive emergence of zoonotic paramyxoviruses.

5.3 Preexisting Immunity May Restrict Emergence

In addition to the virus' ability to antagonize the innate immune response in a new host, another important determinant of the capacity to both initiate productive infection and cause disease is the ability of the host immune system to recognize a novel pathogen. Parrish et al. (2008) have proposed that an emergent virus must spillover from just the right host—a species that is genetically similar to the at-risk species, but not so similar that the at-risk species has already encountered a similar virus and has preexisting immunity. Unlike many other virus families where single virus species can have multiple serotypes, paramyxoviruses can even share the same serotype with other members of the same genus, such as is the case between human, bovine, and caprine parainfluenza virus 3 (HPIV-3, BPIV-3, CPIV-3; Abinanti and Huebner, 1959; Barrett and Chalmers, 1975; Chowdhury et al., 2014; Ditchfield et al., 1965; Henrickson, 2003; Lehmkuhl and Cutlip, 1982; Lyon et al., 1997; Maidana et al., 2012). For instance, cross-protection via this antigenic similarity between different PIVs has been proposed to restrict infection of BPIV-3 to cattle, and HPIV-3 to humans, since exposure to HPIV-3 in childhood establishes a sufficient adaptive response to limit subsequent infection by BPIV-3 (Karron et al., 1995).

If amplification of human-adapted viruses like HPIV-1 and 3 can be affected by preexisting immunity (Bhattacharyya et al., 2015), despite the fact that natural immune responses to these viruses are known to be short lived and poorly protective (Cooney et al., 1975), then it is logical that cross-reactive immunity could be capable of preventing or limiting infection with a poorly adapted emergent virus. As mentioned earlier, such is believed to be the case with Morbilliviruses, where preexisting immunity to MeV in humans is sufficient to prevent successful transmission of CDV (a closely related morbillivirus), despite humanity's frequent encounters—and close relationships—with CDV-infected animals like the domestic dog (Nambulli et al., 2016). MeV in humans is believed to be the result of a successful zoonosis of a RPV-like virus from domesticated cattle (Furuse et al., 2010), at a time when humans presumably did not yet have preexisting immunity from yet another related virus to prevent such a transmission. Rubulaviruses may provide another example of this: recently, Drexler et al. found a mumps-like virus in African fruit bats (BMV; Drexler et al., 2012) that we and others have shown to be sensitive to human and murine antibodies generated against human MuV (Beaty et al., 2016; Katoh et al., 2016; Krüger et al., 2016). Coupled with phylogenetic analysis that suggests BMV could be another strain within the MuV species (see also Fig. 2), this suggests that human MuV may have first arisen in bats (Drexler et al., 2012), and that since it has not fully speciated from BMV, it may have emerged into humans more recently than MeV did. Since then, immunity to human MuV may have been cross-protecting humans from further spillover events of other bat–borne MuV-like viruses. Given these examples of possible cross-protection from zoonotic viruses mediated by exposure to endemic human viruses, it is further possible that the antigenic relatedness of at least some bat–borne henipaviruses (Chua et al., 2000; Drexler et al., 2012; Eaton et al., 2006; Marsh et al., 2012; Pernet et al., 2014a,b) may also influence future henipavirus emergence dynamics in certain human or animal populations that have been frequently exposed to zoonotic henipavirus spillover.

6. SUMMARY

Spillover of enzootic paramyxoviruses into susceptible human and domestic animal populations is defined by a broad collection of ecological and molecular factors that interact in ways we do not yet fully understand. Here, we have summarized the key known determinants of paramyxovirus spillover, while also highlighting some of the unexplored avenues defining paramyxovirus emergence. The continued expansion of human populations and consumption of resources ensure that we will continue to see spillovers and emergence of zoonotic viruses from reservoir hosts like bats into both humans and our domestic animals. It is clear that we need a better understanding of the paramyxoviruses that bats and other reservoirs harbor. We require a sense of paramyxovirus diversity and dynamics within their host populations, and mechanisms of immune evasion that can be compared across different species to evaluate risk; we also need a more comprehensive understanding of the species restrictions—or lack thereof—on these immune evasion mechanisms. To this end, systematic research is needed to characterize paramyxoviruses that have emerged with little detectable pathology. We can benefit from understanding paramyxoviruses like the rubulaviruses PIV-5 and Tioman virus, or henipaviruses like CedV and the unidentified Cameroonian henipavirus(es) detected by serosurveillance, to explore the differences between viruses that have not spilled over into humans, those that have but did not cause disease, and those that give us the greatest concern: highly pathogenic and lethal emerging paramyxoviruses. We also need to improve our understanding of spillover events, and our detection of "silent" spillovers, before we can establish predictive parameters or algorithms for future paramyxovirus emergence. Characterization of cross-protective immunity provided by less-pathogenic paramyxoviruses and how it may prevent emergence of high-pathogenicity paramyxoviruses will also be valuable, because it could inform preventative approaches in vulnerable populations. Over the last several decades, we have become aware of humanity's vulnerability to the threat of emerging pathogens, such that it has seeped into popular culture in the form of books, comics, and movies; but concomitant with this awareness we are developing the techniques and resources to begin to accurately assess the threat and hopefully, one day, predict and contain viral outbreaks before they can cause serious repercussions.

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