# Hendra and Nipah viruses: different and dangerous

*Bryan T. Eaton\*, Christopher C. Broder‡, Deborah Middleton\* and Lin-Fa Wang\**

Abstract | Hendra virus and Nipah virus are highly pathogenic paramyxoviruses that have recently emerged from flying foxes to cause serious disease outbreaks in humans and livestock in Australia, Malaysia, Singapore and Bangladesh. Their unique genetic constitution, high virulence and wide host range set them apart from other paramyxoviruses. These features led to their classification into the new genus Henipavirus within the family Paramyxoviridae and to their designation as Biosafety Level 4 pathogens. This review provides an overview of henipaviruses and the types of infection they cause, and describes how studies on the structure and function of henipavirus proteins expressed from cloned genes have provided insights into the unique biological properties of these emerging human pathogens.

 $\mathcal{L} \rightarrow \mathcal{L}$  (iii)  $\mathcal{L} \rightarrow \mathcal{L}$  and  $\mathcal{L} \rightarrow \mathcal{L}$ and growing list of viruses for  $\mu$  and  $\mu$  $i \in \{i\}$  as the natural host that started with started with started with started with started with  $i$ 1934 (REF. 1)  $\tau$ tions to which were severe acute respiratory syndromes acute respiratory syndromes  $\mathbf{q}$ 2005 (REFS 2,3).  $c_f$ classified in the order  $\mathbf{e}_i$  order  $\mathbf{e}_i$  (from the Greek (from the Greek  $f$  $c \in \mathbb{C}$ , is given it is and it is within the individual individual individual in the interval individual individual in  $\mathbb{R}$ *i* Pteropus We can be find that we find the natural hosts of  $\mathbb{R}$  and  $\mathbb{R}$  $\alpha$  and  $\alpha$  -commonly referred to assume to assume that are commonly referred to assume to assume to assume to assume that  $\alpha$ 

**now**,  $^{4}$  (FIG. 1).

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 $\mathcal{L} = \mathcal{L} = \mathcal{L} = \mathbb{R}$  and  $\mathbb{R} = \mathbb{R}$  and  $\mathcal{L} = \mathbb{R}$ likely to the function of the batter virus, which is  $\mathcal{A} = \{ \mathbf{A} \mathbf{A}, \mathbf{B} \}$  $c_4$ caused a reproductive disease in an Australian pig-Pteropus its natural form in the  $\mathbb{E}[\mathbf{A}^T \mathbf{A}^T]$  and  $\mathbf{A}^T$  and  $\mathbf{A}^T$  and  $\mathbf{A}^T$  and  $\mathbf{A}^T$ **u**wPteropus hypomela $nus^7$ . . Bat  $\mathcal{N}$  is  $\mathbb{R}$  virus  $P$  is  $\mathcal{N}$ from a member of the *Rousettus* genus within the family Pteropolis  $\mathcal{L}^{-8}$  $\mathbf{A}$  (as  $\mathbf{A}$  is  $\mathbf{A}$  is obtained in the virtual intervals was isolated in the virtual intervals was intervals Sturnira **j** a second in the family in t Phyllosophyllostomidae ( $\sim$  10  $\sim$   $(1-\mu)^9$  $(1)$ <sup>9</sup>. genetic constitution of  $\mathcal{L}^{\mathcal{A}}$  and  $\mathcal{L}^{\mathcal{A}}$  and  $\mathcal{L}^{\mathcal{A}}$  and  $\mathcal{L}^{\mathcal{A}}$  $p$  and  $p$  is the set them wide host range set them with  $p$  $\mathbb{Z}$ apart from other parameters. This review parameters  $\mathbb{Z}$ video an overview of the heavily consider  $\mathbb{R}^n$ recent molecular analyses of the structure analyses of the structure and function  $\mathbf{r}_i$  $\mathbf{u} = \mathbf{u}_0 \mathbf{v}_0 \mathbf{v}_0$  and  $\mathbf{u}_1 \mathbf{v}_1 \mathbf{v}_2 \mathbf{v}_3 \mathbf{v}_4 \mathbf{v}_5 \mathbf{v}_6$  to the contribution of the set  $\mathbf{u}_0$  is unique pathogens. These unique pathogens  $p_0$  is unique pathogens.

#### The genus Henipavirus

 $\Gamma$ aramies are comparamyzovirus are comparamyzovirus are comparamyzovirus are comparameters. *Paramyxovirinae (Pneumovirinae* (BOX 1).  $A$  $f \rightarrow f f$ *Paramyxovirinae* (FIG. 2a,b),  $\mathbf{t} = \mathbf{t}_1 - \mathbf{t}_2 + \mathbf{t}_3$  that found is the Respirovirus in the Respiration in the Respiration in the Respiration of  $\mathbf{t}_1$ and Morbins and Morbins generation  $\Lambda$  in the fIG. 2c).  $\mathbb{R}^n$  features distinguish hencipavirus from other  $\mathbb{R}^n$ paramyxoviruses. Genetic attributes include the unique,  $\mathbf{s}\mapsto\mathbf{a}^*\mathbf{a}\cup\mathbf{3}'$  if and  $\mathbf{s}'$  trailer sequences, which seems that for as proportion as proportion and replication and  $f(x)$ **u** general  $\mathbf{A} = \frac{11,12}{11}$ sepuence  $\mathcal{L}$  in a highly conserved catalytic site in a highly conserved catalytic site in the transcriptase protein, instead of the GDNQ sequence  $\mathbf{p}_i$  $t\in\{1,2,\ldots,n\}$  is all other non-segmented negative-segments all other non-segments  $\{t\in\mathbb{R}^n\}$  $s_{\text{max}}$  and  $r_{\text{max}}$  is the most of the most term of the most prominent features that differentiates from the differentiates from  $\mathbf{f}_i$  $\blacksquare$ other parameters is the length of the viral generator  $\blacksquare$  $\mu$  18,234 **n** (*i*) **n**  $\mu$  18,246  $2,700$  .  $(15%)$ the family  $f: A \rightarrow B$  as far as far as far as  $f: A \rightarrow B$  as far as  $g: A \rightarrow B$  as  $g: A \rightarrow B$ the height hence are not alone, and the genomes of the g as-yet-unclassified parameters  $\mathcal{A}$  and  $\mathcal{A}$  and  $\mathcal{A}$  and  $\mathcal{A}$  and  $\mathcal{A}$  $\blacksquare$  J<sup>15</sup> are 300 nt longer and  $\blacksquare$  300 nt longer, respectively, respectively, respectively, respectively, respectively,  $\blacksquare$  $t_{\rm eff}$ than those of henipa $t_{\rm eff}$ nipavirus est. However, henipavirus $t_{\rm eff}$  $r_1$  remain unique in the train  $\mathbf{w}_1^2$  or  $\mathbf{w}_2$  and  $\mathbf{w}_3$  and  $\mathbf{w}_4$ in the form of long units of the form of the form of the theorem of the theorem  $\mu$  $3'$  end in the six transfer transcription units, the exception units, the exception  $\mathcal{X}$  $^{10}$   $^{12}$  (FIG. 2c).



Figure 1 | **F**, **i q f**<sub>**l**</sub> **e** , **heidi ib j a d he locations of disease outbreaks caused by Hendra virus a d Ni ah i** . **a** | Pteropus poliocephalus is an Australian flying fox and member of the family Pteropodidae, one of 18 bat families in the order Chiroptera*.* There are four Pteropus species in Australia<sup>4</sup>. **b** Sixty-five Pteropus species are distributed from Madagascar through the Indian subcontinent to south-eastern Asia and Australia and as far east as the Cook Islands<sup>4</sup>. Some Pteropus species are among the largest of all bats, weighing as much as 1.2 kg and displaying a wing span of up to 1.7 m. Pteropus species are unique because they lack the complex neural and behavioural mechanisms required for echolocation that characterize the vast majority of bat species. Instead, they have large eyes and they navigate visually, feeding mainly on fruit and flowers, which they locate by smell. The sites of disease outbreaks caused by henipaviruses are indicated. Map modified with permission from REF. 4© (2002) University of New South Wales Press.

 $\mathbf{u}_n = -\mathbf{u}_n$ ins  $\mathbf{u}_n = \mathbf{u}_n$  by all proteins except one, the  $\mathbf{u}_n$ phosphoropho protein  $\rho$  and  $\rho$  in a same size in a same size in a same size in a same size in  $\mathcal{A}$ the Respirovirus and  $\mathcal{L} = \mathbb{R}$  and  $\mathcal{L} = \mathbb{R}$  $\epsilon$  is a proton is a proton is approximately  $\rho = 100$  to  $200 \text{ A}$  and  $c \times \text{C}$  and compute respirovirus and compute respirations are provided as  $\mu$  $\lambda$   $\lambda$  /  $\lambda$   $\lambda$   $\lambda$  = 10.  $\lambda$   $^{13,16}$ 

 $\mathcal{L}$  Henipavirus estimatures. The matrix  $\mathcal{L}$  is a feature biological feature biological features. zoonotic  $\mathcal{A}$ highly pathogenic. Although the no data on the no  $\mathbf{A}$  $\mathbf{H}_{\mathcal{L}}^{\mathcal{L}}[\mathbf{1}] = \mathbf{H}_{\mathcal{M}}^{\mathcal{L}} \mathbf{H}_{\mathcal{M}}^{\mathcal{L}} \mathbf{N}_{\mathcal{M}}$  during an out-during an out-during an out- $\beta$  in  $\beta$  in 2004, 75% of patients that we have the state of the 2004, 75% of patients that we have the state of the 2004, 75% of patients that we have the state of the 2004, 75% of patients that we have the state of t identified as having  $\mathcal{L}$  as having  $\mathcal{L}$  as the basis of  $p$ ositive serology or on epidemiology or  $\mathbb{P}_p$ The range of species that are susceptible to the susceptible to the susceptible to  $\mathcal{A}$  $\mathbb{I}$  also  $\mathbb{I}$  and  $\mathbb{I}$  and opid species, NiV infects five terrestrial species in four mammalian orders18–23. Experimental henipavirus infec- $\mathbf{u} \times \mathbf{w}$  tions extend the number of susceptible terrestrial orders or  $\mathbf{u}$ 

to find the Rodentia  $\mathbb{R}^{\mathbb{N}}$  including the Rodentia  $\mathbb{R}^{\mathbb{N}}$  including the Rodentia theorem  $\mathbf{W}_{\mathcal{A}} = \mathbf{U}_{\mathcal{A}} \left( \mathbf{U}_{\mathcal{A}} \right) = \mathbf{U}_{\mathcal{A}} \left( \mathbf{U}_{\mathcal{A}} \right) = \mathbf{V}_{\mathcal{A}} \left( \mathbf{U}_{\mathcal{A}} \right) = \mathbf{V}_{\mathcal{A}} \left( \mathbf{U}_{\mathcal{A}} \right)$ virus that  $\{A_i\}_{i=1}^N$  is the order order that  $\mathbf{u}_i$  $\mathbf{C}_i \in \mathbf{R}_i$  , such as dogs, ratios and lines, ratios and lines, ratios and lines,  $\mathbf{C}_i$ can also experimentally infect hamsters and pigs  $\mathcal{A}$  and  $\mathcal{A}$  and  $\mathcal{A}$  $\mathbb{R}^2$  and  $\mathbb{R}$  and  $\mathbb{R}$  and  $\mathbb{R}^2$ .  $\mathbb{R}^2$ . The susceptibility of humans, the high virulence of  $\mathbf{A}$ the viruses and the absence of the  $\mathcal{A}$  $\gamma$  and  $\gamma$  as  $\gamma$  and  $\gamma$  and  $\gamma$  as  $\gamma$ Biosafety Level  $4(4)$ ited number of laboratories have appropriate facilities  $\mathbf{f} = \mathbf{f} \mathbf{f} = \mathbf{f} \mathbf{f} = \mathbf{f} \mathbf{f} = \mathbf{f} \mathbf{f} = \mathbf{f} \mathbf{f}$ 

 $\mathbf{R} \times \mathbf{A} = \mathbf{A}$  pathogens. Among these,  $\mathbf{R} \times \mathbf{A}$  $e^{i\theta}$  in  $\lambda$  $\frac{1}{2}$  for  $i$  and infected with HeV or  $i$ which workers can be protected in plastic sub-protected in plastic suits, sub-protected in plastic suits, supplied with breathing air. This has limited the number of  $\mathbf{h}_i$ investigations into the interaction of  $\mu$  and  $\mu$  into the interaction of  $\mu$ their natural hosts, susceptible livestock and laboratory  $\mathcal{L}^{\text{in}}$  $a_1 + a_2 + \cdots + a_n = a_n$  , is a function of personal safety and biocontains a region are minimized with  $\mathbb{R}^n$  and with cloned with  $\mathbb{R}^n$ hence in each  $\mathbf{y}^{\prime}_{1}$  . Then the  $\mathbf{y}^{\prime}_{2}$  and  $\mathbf{y}^{\prime}_{3}$  and  $\mathbf{y}^{\prime}_{4}$ it is from such studies that  $\mu_1$  with  $\mu_2$  our current knowledge  $\mu_2$ on the structure and function of  $\mathcal{L}^2$  and  $\mathcal{L}^2$  and  $\mathcal{L}^2$  and  $\mathcal{L}^2$ been obtained. Before discussing the molecular observation of  $\mathbb{R}^n$ tions that she shed light on the unusual biological properties  $\mu$  $1 \longrightarrow \mathbb{R}^2 \setminus \{1, \ldots, n\}$  , let us first summarize the  $1 \notin \mathbb{R}$ .  $\left\{\cdot, \cdot\right\}$  (TIMELINE)  $\left\{\cdot\right\}$  $\mathcal{L} \mathcal{L} = \mathcal{A} \mathbf{A}$  and  $\mathcal{L} \mathcal{L} = \mathcal{L} \mathbf{A}$ virus infection.

#### Henipavirus infections

 $H^{\text{ch}}$  in the characterized by  $\mathcal{L}$  $n$  in the contribution in multiple organism in multiple organism in  $n$  $\mathbf{t}_1$  tems. The outcome of infection differs significantly infection differs significantly in terms.  $r \sim \sqrt{1 - \frac{1}{2} \sum_{i=1}^{n} \sum_{j=1}^{n} \sum_{j=$  $\mathbf{B} = \mathbf{A}$  and  $\mathbf{A} = \mathbf{A}$  and  $\mathbf{A} = \mathbf{A}$  and  $\mathbf{A} = \mathbf{A}$  and  $\mathbf{A} = \mathbf{A}$ neurological transportation that is interested on the host. In the host of  $\mathbf{u}_i$ can be associated with high more fatality and cases  $\mathbb{R}^n$  and cases fatality and cases  $\mathbb{R}^n$  $\mathcal{L}$  as  $\mathcal{L}$  in the such as in HeV and NiV and  $\mathcal{L}$  and  $\mathcal{L}$  and NiV  $H = \{1, 2, \ldots, N\}$  in  $\{1, 3, \ldots, N\}$  in  $\{1, 3, \ldots, N\}$  in  $\{1, 3, \ldots, N\}$ ity rates, by  $\mathbf{A} = \mathbf{A} \cdot \mathbf{A}$  in  $\mathbf{A} = \mathbf{A} \cdot \mathbf{A}$  in  $\mathbf{A} = \mathbf{A} \cdot \mathbf{A} \cdot \mathbf{A}$ .  $\mathbb{H}_\mathbb{R}$ -infected horses develop acute, febri  $\alpha$  for some that is sometimes accompanied by facial sweets accompanied by facial sweets  $\alpha_1\in\mathbb{Z}^d$  and, the set of  $\mathbb{Z}^d$  and, the set of  $\mathbb{Z}^3$ . Respiratory signals also predominate in  $\mathcal{L}^{\mathcal{A}}$  in  $\mathcal{L}^{\mathcal{A}}$  in  $\mathcal{L}^{\mathcal{A}}$  in  $\mathcal{L}^{\mathcal{A}}$  in  $\mathcal{L}^{\mathcal{A}}$  $p_1$  and  $p_2$  in the special fever, nasalign and develop feature  $p_1$  $d = \frac{1}{2} \int_{\mathbb{R}^d} \left( \int_{\mathbb{R}^d} \mathbf{u}_i \right)^2 \, d\mathbf{u}_i \, d$  $\mathcal{L} \times \mathcal{L} = \mathbb{R}$  in  $\mathbb{R}$  and  $\mathbb{R}$  rise to the name rise of  $\mathbb{R}$  $\hat{p}$  is  $\hat{p}$  and  $\hat{p}$   $\hat{p}$  $\mathbb{R}^n$  cause as solutions as solved in horses and  $\mathbb{R}^n$  respiratory syndrome in horses and  $\mathbb{R}^n$ pigs, respectively. A proportion of convex  $p$  is a proportion of convex  $p$  $f = \pi \Phi$  is a sign signs, and clinical si  $s$ igns consistent with multiplo $\mathcal{L}^{\mathcal{A}}$  and  $\mathcal{L}^{\mathcal{A}}$ also been observed in growing pigs, to gether with subset  $p$  $\ell=1$  is and in the  $\ell^{22}$ .

 $\mathcal{H}$  in humans, symptomatic  $\mathcal{H}$  infection has matrix  $\mathcal{H}$  infection has matrix  $\mathcal{H}$  $\tau(t)$  is contributed to form of severe acute encephalities. Many  $\tau$ infected patients have reduced levels of consciousness at  $\rho$  $p$  and signs construction and signs consistent with brain-stem involves  $\{p, \infty\}$  and  $\mathbf{R}$  in 1  $\frac{32}{\sqrt{10}}$  H  $\frac{30,33}{\sqrt{10}}$   $\frac{1}{\sqrt{10}}$   $\frac{25\% \text{ N}}{\sqrt{10}}$   $\frac{1}{\sqrt{10}}$   $\frac{1}{\sqrt{10}}$  $\mathcal{L}$  and  $\mathcal{L}$   $\mathcal{L}$   $\mathcal{L}$  and  $\mathcal{L}$  infection with  $\mathcal{L}$   $\mathcal{L}$ 

#### Zoonotic

A zoonotic infection is an infection of animals that can be transmitted to humans.

#### Biosafety Level 4

(BSL4). BSL4 is the highest safety rating for laboratories, used for handling agents that pose a high risk of lifethreatening disease and for which there is no vaccine or therapy. Other BSL4 agents include Ebola virus and Marburg virus.

chronic course, with serious  $\mu$  and  $\mu$  and  $\mu$  and  $\mu$ ring late (in encephalities) for  $\mathbf{q}$  and  $\mathbf{q}$  and  $\mathbf{q}$  and  $\mathbf{q}$ Using asymptomatic infections  $\mathbf{A}$  as a recorded of  $\mathbf{A}$  $\mathbf{U} = \left\{ \begin{array}{l} 1 \leq i \leq p, \mathbf{U} = p \leq p, \mathbf{U} = \mathbf{U} = \mathbf{U} = \mathbf{U} \end{array} \right.$  $\mathbb{R}^n$  in the from access recovered from acute encephalities  $\mathbb{R}^n$  recovered from acute encodered from acut  $(-\rho\mathbf{r}^{\mathbf{a}}+\mathbf{r}^{\mathbf{a}}+\mathbf{r}^{\mathbf{a}})^{34}\mathbf{p}\rho^{\mathbf{a}}\cdot\mathbf{r}^{\mathbf{a}}$  . Cases of relations of  $\mathbf{r}$ litis presented from several months to nearly 2 years after the initial infection and, in the interestingly, the interestingly, the interestingly, two functions  $\mathbf{f}_i$ cases of relations were observed in the contract of  $\mathbf{r}_i$ **a.** a<sub>1</sub> a 2003, some 4 years after in the <sup>35</sup>. There is no array and  $\frac{10\%}{\epsilon}$  increases rate of  $\epsilon$  of  $\ell = \ell$  and  $\ell = \ell$  encephalities of  $\ell$  and  $\ell = \ell$ of  $18\%$ . So, with and  $\alpha$  and  $\alpha$  and  $\alpha$  and  $\alpha$ of infection is possible before the manifestation of serious  $p$ neurological disease. Viral antigen was found in  $\mathcal{L}$ in patients who died of lateralities who died of  $\mathbb{R}^3$  for lateral times  $\mathbb{R}^3$  $\mathbf{p}$ ians about the underlying mechanisms that allowing  $\mathbf{u}$  mechanisms that allowing  $\mathbf{u}$ these viruses to escape immunological clearance for such as  $\mathcal{C}$  $\overline{a}$   $\overline{b}$   $\overline{c}$   $\overline{d}$   $\overline{$ 

 $M$  is a case of human HeV infection have been here been here been here been have been have been have been have been here. recorded, and the associated disease syndrome is corrected associated associat respondingly less well defined. Affected patients have  $\mathcal{L}$  in  $\mathbb{R}$  in and fatal HeV encephalism symptoms, and fatal HeV encephalism symptoms, and fatal HeV encephalitis has been described in one patient more than  $\mathbf{A} = \mathbf{A} + \mathbf{A} + \mathbf{A} + \mathbf{A}$ after a self-limiting  $\mathbb{R}^n$  . The mention of meningitis that was, in the  $\mathbb{R}^n$ retrospectrospectrum attributed to  $\mathbb{R}^n$  in  $\mathbb$ 

#### Molecular insights into henipavirus biology

 $T$  **T**  $\rightarrow$   $T$   $\rightarrow$   $T$   $\rightarrow$   $T$   $\rightarrow$   $T$   $\rightarrow$   $T$  $r$ ange and cell tropism is determined to a significant  $r$  $d_{\mathcal{C}}$  and  $d_{\mathcal{C}}$  and  $d_{\mathcal{C}}$  and  $f$  $t_1$  is a determined and cell transmitted by  $t_1$ 

virtue of their roles in binding to cell  $\mathcal{U}_\mathbf{r}$  and fusing and fusing and fusing and fusing and fusing and functions and function  $t\in \mathcal{M}$  and  $\mathcal{M}$  and  $\mathcal{M}$  and  $\mathcal{M}$  and  $\mathcal{M}$ **u**, which  $\begin{bmatrix} 1 & 1 & 2 \end{bmatrix}$  above by abrogating  $\mathcal{L} = \begin{bmatrix} 1 & 1 \end{bmatrix}$ the cellular interferon interferon interferon interferon  $\mathbf{R}$  (IFN) respectively. Recent studies on the theorem  $s$  structure and function of  $\mathbb{R}^n$  virus proteins expressed virus from cloned genes have shown that the hence  $\mathcal{A}$ and F glycoproteins and the P proteins and the P protein also influence host influence  $r$ ange, cell tropism and virulence, but do so in ways that  $\alpha$  $\alpha$  are both surprising and unique.

*The henipavirus G protein.*  $\overline{I}$  i **n** 1 Paramyxoviridae, which have a limited host range hence  $f: \mathcal{L} \times \mathcal{L} \times \mathcal{L} \times \mathcal{L}$  is the set of  $\mathbb{R}$ .  $\alpha_{\ell}$ cats, dogs and humans, and  $\alpha_{\ell}$  investigations, and  $\alpha_{\ell}$  $f \in W$  extended to include the include guinea pigs  $f \in W$ and hamsters. The susceptibility of several culture  $\mathcal{A}$  $t_{\rm eff}$  to isolate during the initial attention the isolated during the isolated during to isolated the isolated during the isolated during the isolated during the isolated during  $\alpha$  $H = \mathbb{P} \left[ \begin{array}{ccc} \mathbf{0} & \mathbf{0}$ in vitro **funcional**  $\alpha$  in the construction of the construction of and  $\alpha$  proteins that were  $\alpha$  $\mathbf{W}_k$ expressed on the surface of effective cells by vacciniating  $\mathbf{V}_k$ virus facilitated function with adjacent target cells from a  $\mathbb{F}_4$  $r_A$  including rabbit, including radius  $r_A$  and  $r_B$  and mouse  $r_A$ .  $T_{\rm eff}$  factories and  $T_{\rm eff}$  pattern of target-cell susception of target-cell susception tibility was observed in function assays using  $\mathcal{L}^{\mathcal{A}}$  $N_{\rm H}$  glycoproteins indicated that both viruses used that both viruses used that both viruses used the  $\mu$ same cell receptor  $\mathcal{A}^{(38)}$ . These observations indicate that hencipavirus receptors are uping  $\mathbf{u}_i$  . We use  $\mathbf{u}_i$  $P_A$  Message and two broad categories, depending on the whole their order or not the  $\mu$  $\mathbf{p}^{\mathbf{q}} = p \cdot \mathbf{q}$  domains that bind  $\mathbf{q}$ release the least  $\mathcal{N}_{\mathcal{A}}$  access from  $A$  acid residues from  $\mathcal{A}$ 



#### Timeline | **Emergence of henipaviruses**

The emergence of Hendra virus and Nipah virus is detailed in boxes outlined in turquoise and purple, respectively.

#### Box 1 | Classification of henipaviruses

Viruses in the family *Paramyxoviridae* are classified in two subfamilies, *Paramyxovirinae* and *Pneumovirinae*. The latter subfamily contains two genera, Pneumovirus and Metapneumovirus. The number of genera in the *Paramyxovirinae* was increased in 2002 from three (Respirovirus, Morbillivirus and Rubulavirus) to five by the addition of two new genera, Avulavirus and Henipavirus<sup>133</sup>. The Avulavirus genus contains avian paramyxoviruses that were previously classified in the Rubulavirus genus, and the Henipavirus genus was created to accommodate Hendra virus and Nipah virus.

The phylogenetic tree shown here is based on an alignment of the deduced amino-acid sequence of the N gene of selected *Paramyxovirinae* subfamily members using the Neighbour-Joining method (see the genome organization of henipaviruses in FIG. 2). Viruses are grouped according to genus and abbreviated as follows. Morbillivirus genus: MeV (measles virus), CDV (canine distemper virus); Henipavirus genus: HeV (Hendra virus), NiV (Nipah virus); Respirovirus genus: SeV (Sendai virus), hPIV3 (human parainfluenza virus 3); Avulavirus genus: NDV (Newcastle disease virus); Rubulavirus genus: hPIV2 (human parainfluenza virus 2), MaV (Mapuera virus), MuV (mumps virus), PIV4a (parainfluenza virus 4a), PoRV (porcine rubulavirus), SV5 (simian parainfluenza virus 5), SV41 (simian parainfluenza virus 41); and unclassified viruses SalV (Salem virus) and TPMV (Tupaia paramyxovirus).



 $c_1$ drate moieties. The presence of such has  $c_1$   $c_2$  in  $c_3$ tination and neural distribution and  $\mathcal{A}$  avulavirus and  $\mathcal{A}$ **r**  $\mathbf{r}_1 \cdot \mathbf{r}_2 \cdot \mathbf{w}_3 = \mathbf{r}_1 \cdot \mathbf{r}_2 \cdot \mathbf{w}_4$ neuraminic acid in cell-surface glycoprotein and gl receptors  $\mathbf{R}^{\text{max}}$ , and although  $\mathbf{R}^{\text{max}}$  is although measure  $\mathbf{R}^{\text{max}}$  $\mathbb{R}$  more displays has plays have  $\mathbb{R}$  for a split type  $\mathbb{R}$  for a split type  $\mathbb{R}$ to cells a signification of  $\mathcal{A} = \{ \mathcal{A} \in \mathcal{A} \mid \mathcal{A} \in \mathcal{A} \}$  and the contribution of  $\mathcal{A} = \{ \mathcal{A} \mid \mathcal{A} \in \mathcal{A} \}$ cell-surface-expressed protons  $46$ <sub>4</sub> and S<sub>2</sub>,  $150$ )  $h(x) = h(x)h(x) + h(x)h(x) + h(x)h(x) + h(x)h(x)$ now regard as a universal mortgage as a universal mortgage  $\mathcal{A}$  $B = \begin{bmatrix} 1 & 1 \\ 1 & 1 \end{bmatrix}$  and  $\begin{bmatrix} 1 & 1 \\ 1 & 1 \end{bmatrix}$  of the members of the theory of the t **Pneumovirinae in possessing a third class of attachment** control attachment control at the control of attachment  $p$ rether displays neither has neither has  $p$  and  $p$  aggregating neither has  $p$ neural minidase activities. However, the G protein of HeV protein of HeV protein of HeV protein of HeV protein and Niv is structurally uncertainty unrelated to the cognation  $\mathbf{u}_i$ virus protein  $\mathcal{P}_1$  . These early observations indicated that  $\mathcal{P}_2$ henipa viruses,  $\mathbf{j} \in \mathbb{R}$ iruses, might use cell-surface cell-surface cell-surface cell-surface cell-surface ce proteins as receptors in a process that does not require  $p$ *N*- $\alpha$  **i**  $\Lambda$  is  $\alpha$  in  $\alpha$ <sup>11,28,45,46. Indeed, the subset of  $\Lambda$ </sup>  $\mathbf{u}_0$  target cells to  $\mathbf{H} = \frac{1}{2} - \frac{1}{2}$  mediated functions of  $\mathbf{u}_0$ could be destroyed by protein  $\mathbb{R}^4$  proteins  $\mathbb{R}^3$ .

 $f\cdot f$  and  $\mathbf{I}$ type II membrane glycoproteins  $\mathbf{u}$  ...  $\mathbf{u}$  a cytoplasmic  $\mathbf{v}$ tail, a transmetric region, which and  $\mathcal{L}$ to the viral envelope, a globular head, which is a globular head,  $c\in\mathbb{R}$  and the six protein sheets of six protein sheets or  $c\in\mathbb{R}$  and  $c\in\mathbb{R}$ showed structure  $47,48$ . Although the HeV G attachment that the HeV G attachment the HeV G attachment the HeV G att  $p$ rotein has low amino-acid-sequence homology with  $p$  and  $p$  and  $p$  $\alpha\in\mathbb{R}^n$ attachment proteins from  $\mathbb{R}^n$  paramyxovirus  $\mathbb{R}^n$  $g(\mathbf{u},\mathbf{y}) = \mathbf{y} - \mathbf{y}$  for a propeller shape propeller shape predicted for  $\mathbf{y}$  $\Box$ members of the family, and the state  $\mathbb{R}$  $e_{\mathbf{r}}$ epitopes resembles that  $e_{\mathbf{r}}$  and  $e_{\mathbf{$ Paramyxovirinae<sup>45,49</sup>.  $\mathbf{G} = \mathbf{G} \cdot \mathbf{G$ tail and the domain domains with an immuno**g** in  $K \neq \emptyset$  biological activity  $f(x) = \frac{50,51}{2}$ . The  $\mathcal{L}^{\text{eff}}$  and  $\mathcal{L}^{\text{eff}}$  and bind to cells  $t\in\{1,\ldots,n\}$  are susceptible to the susceptible to  $f$ attach to infection-resistant cells, and as immunosites  $\alpha$ the construction of  $\mathbf{u}_i$  and  $\mathbf{u}_i$  and  $\mathbf{u}_i$  and  $\mathbf{u}_i$ response a gainst infectious HeV and  $\mathcal{L}=\mathcal{L}=\mathcal{L}^{-50}$ .

Preincubation of cells with HeV sG resulted in  $\mathbf{u} = \mathbf{u}$ dose-dependent inhibition of both HeV and  $\mathbf{v} = \mathbf{v}$ infection, probability by blocking viral receptor  $\chi$  is a set of  $\chi$  $\vert \cdot \vert \cdot \vert^{50}$ , and surprisingly, surprisingly, see roles in the surprisingly, see roles in the surprisingly see roles in the surprising  $\mathbf{u}$ in determining and confirming the recent identification  $\mathcal{E}$  $\mathbf{0}$  the henipality cell receptor. Niv sG fused to the function  $\mathbf{0}$  sG fused to the theorem Fc region  $\mathbf{u}$   $\mathbf{u}$  /  $\mathbf{u}$  1  $t_{\text{ref}}$  receptor from the plasma members of cells that we recept the plasma members of cells that we recept that we recept that we recept the cells that we recept that we recept the cells that we recept that we recept t  $\mathbf{p}=\mathbf{$ The receptor was identified as  $2\pm \mu m$  as  $\Phi$  $\mathbf{t} = \mathbf{t}^{\mathrm{SL}}$  and  $\mathbf{t} = \mathbf{A}$  and  $\mathbf{t} = \mathbf{A}$  and  $\mathbf{t} = \mathbf{t}^{\mathrm{SL}}$  $u_1, u_2, \ldots$  is equences to identify matrix  $\mu$ heniparite cells but not in cells  $\mathbf{h}$  and  $\mathbf{v}$  are free to increase  $\mathbf{r}_i$ to heniparite infection  $\mathbf{F}^{12}$ . From a list of  $\mathbf{F}^{12}$ ing predicted members for  $\mathbb{R}^n$  in the proteins found only  $\mathbb{R}^n$  in the proteins found only  $\mathbb{R}^n$ in susceptible cells, one and  $\alpha=2$  — encoding experimental encoding  $\alpha=2$   $c\mathbf{u} = \mathbf{v} = \mathbf{v}$ could susceptible to fusion as well as infection not only by  $\mathcal{L}^{\mathcal{A}}$  but also by Henipavirus by Henipavirus by Henipavirus by Henipavirus by Henipavirus by  $\mathcal{L}^{\mathcal{A}}$ infection of expression of expression  $\mathcal{L}_2$  in  $\mathcal{L}_2$ **b**inant recombinant recombinant recombinant ephrin B2 (REF. 52),  $\alpha$ the ability of extending  $\mu$  as a receptor for virus was a receptor for virus was a receptor for virus was a receptor  $\mu$ confirmed by showing that the sG protein of  $\mathcal{A}$ 2 *in vitro*  $\mathbf{A}^{\mathbf{A}} = 2 \times (1 \ 1 \ \mathbf{A} \mathbf{A} + \mathbf{A} \times \mathbf{A} \mathbf{A})$ glycoprotein ligands that bind to exhibit  $\mathcal{E}(\mathbf{E})$ and a large family of  $f$  receptor tyrosine  $f$  receptor tyrosine  $f$ initially identified in vertebrates as  $\rho$  as  $\rho$  as  $\rho$  axonomic axonomic axonomic axonomic axonomic axonomic  $p$ and and neuronal cell migration,  $\mathbb{R}^n$  and  $\mathbb{R}^n$  receptors in Eq. ( and external found in a regular found in a regular formulation  $\mathbf{r}_i$ and even spongester  $\mathcal{E} = \{x_i\}$  and  $\mathcal{E} = \{x_i\}$  $f(\mathbf{r}, \mathbf{r})$  is the set of molecules, and they are now known to mediately are now known to mediately set of mediately set of  $\mathbf{r}$ cell-to-cell communication and regulate cell at the cell attachment and  $r$ and republicity. Equivalently, and equipment  $\mathcal{E} = \{ \mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_n \}$  $\mathbf{d}$  during development, especially in the nervous and variable nervous and variable  $\mathbf{d}$  $c_1$  systems  $\mathbb{R}^5$ ,  $\mathbb{R}^4$ ,  $\mathbb{R}^5$ , smoothed in  $\mathbb{R}^5$ , smoothed in  $\mathbb{R}^5$ , smoothed in  $\mathbb{R}^5$ , are respectively. The contract and capital cells  $\mathcal{M} \sim \frac{55,57-59}{\sqrt{2}}$ . The structure of the Ephrin B2 receptor, ephrin B2  $r = 2$  and the Ephrin B2 and the B2 and the Ephrin B2 and the

complex that they form has been determined by  $\mathcal{L}$ crystallography $\mathcal{L}$  is glycosylated but the side of side  $\mathcal{L}$ chain is short that is single mannose residue and  $\epsilon$ two  $N_{\rm T}$  glucosamine residues, and lacks single residues, and lacks single  $\alpha$ 

#### Type II membrane glycoproteins

Transmembrane glycoproteins with a cytoplasmic N terminus.

#### Fc region

The region of an antibody that is responsible for binding to antibody receptors (FcR) on cells and the C1q component of complement.



#### Clathrin

A structural protein that polymerizes into polyhedral lattices to form a membrane coat around vesicles involved in membrane transport in both the endocytic and biosynthetic pathways.

 $s$ use as MeV, cause systemic infections after initial initial initial initial initial initial initial initial initial in  $\mathbf{t}$ tion of the respiratory tract. By contrast, a small number of the respiratory tract. By contrast, a small number of the small  $\mathbf{t}$ of parameters  $\mathbf{A} = \mathbf{A} + \mathbf{A} + \mathbf{A} + \mathbf{A}$ by extracting the protection of  $\mathbb{R}^n$ single basic residue at the cleavage site. Cleavage *in vivo* is achieved by tryptases such as tryptases such as the protection of  $\mathcal{L}$ and miniplasminiplasminiplasminiplasminiplasminiplasmini $\mathcal{A}$ results in the Sendan virus  $\mathcal{L}^{\mathcal{L}}$  remain localized in localized in localized in localized in  $\mathcal{L}^{\mathcal{L}}$ the respiratory traction of the fact that  $\mathbf{f}^{\text{max}}$ virus estimic infections, it was surprising to surprising the surprising to  $\mathbf{u}$ find that the henipavirus F-protein cleavage site does not  $c\mathbf{t}$  of  $\mathbf{t}$  and  $\mathbf{t}$  residues. The cleavage site in the clea  $H = H \cdot \int_{\mathbb{R}^d} \mathcal{F}(\mathcal{F}) \mathcal{F}(\mathcal{F}) = \int_{\mathbb{R}^d} \mathcal{F}(\mathcal{F}) \mathcal{F}(\mathcal{F}) \mathcal{F}(\mathcal{F})$ 

the sequence  $\mathbb{I}$  of  $^{75}$ , the lysine is replaced by  $\mathbb{I}$  $\alpha$ rginine $11.$  A role for  $\alpha$  and  $\alpha$  and  $\alpha$  and  $\alpha$  and  $\alpha$  $i$ it was shown that Lovo cells, human colon-care coloncells that lack furing the replication of  $\mathcal{M}$  and  $\mathcal{M}$  and  $\mathcal{M}$  and  $\mathcal{M}$ permit cleavage of the  $\mathbf{A}$   $\mathbf{I}$   $^{75,76}$ . The involvement involvement involvement involvement involvement in  $\mathbf{I}$  $\mathbf{u}_f$  and  $\mathbf{g}_1$  and specificity for single basic residues was generated basic residues was generated was generated by  $\mathcal{A}$  and ruled out by the fact that activation of the HeV and  $\mathcal{A}$  $N$   $\mathbb{R}$   $\mathbb{R}$  in vitro<sup>11,38,75</sup>  $S$  studies using a range  $\mu$  range of proteins in conjunctions in conjunctions in conjunctions in conjunctions in conjunctions in  $\mu$  $\mathbf{u}_1$ tion with  $\mu$  and  $\mu$  the movement of  $\mathbf{u}_1$ teins through the secretory pathway indicated the secretory pathway indicated that the HeV  $\mathcal{A}$ For protein is cleaved in the secretory vesicles that budgets that budgets  $\mathbf{f}_i$ trans- $\mathbf{u}$  , more  $\mathbf{j}^{76}$ .  $\mathbf{u}$  ,  $\mathbf{j}$   $\mathbf{u}$  , since  $\mathbf{s}$  ies on the NiV  $\mathcal{L}^{\mathcal{A}}$  for the NiV  $\mathcal{L}^{\mathcal{A}}$  for  $\mathcal{L}^{\mathcal{A}}$  and  $\mathcal{L}^{\mathcal{A}}$  $\mathbb{R}^d$  at a vesicles during transport along the secretory  $\mathbb{R}^d$  $p(\lambda, \gamma, \lambda, \mathbf{t}, \gamma) = p(\lambda, \mathbf{t}, \mathbf{t}, \mathbf{t}, \mathbf{t}, \gamma)$  $45$ - $\mu$ mino-acid cytoplasmic tail of henipavirus  $\mu$  proteins  $\mu$  $c\mathbf{t}_1$  and  $c\mathbf{t}_2$  and  $\mathbf{t}_3$  the protoins the proteins the proteins the proteins the proteins the proteins the proteins  $\mathbf{t}_1$  $\mathbf{w}_i$ expressed on the cell surface into clathrin-coated vesicles  $\mathbf{w}_i$ for one of  $\mathcal{A}$  and  $\mathcal{A}$  on  $\mathcal{A}$  or  $\mathcal{A}$  and  $\mathcal{A}$  compared compared compared compared on  $\mathcal{A}$ Removal of the signal notation  $\mathbf{r}_i$  $t=\frac{1}{\sqrt{2}}\int_{0}^{\infty} \int_{0}^{\infty} \int_{0}^{\infty$  $\mathbb{R}^+$ (REFS 77,78).  $\mathbf{W}_i$   $\mathbf{A}$  for the finding that, although removal of the finding that, although  $\mathbf{A}$ endows single signal causes and concentrations  $\mathcal{L}^{\mathcal{A}}$   $\blacksquare$ of cellas  $\mathcal{L}$  is also caused a decreased a in the size of  $N_{\rm H}$  (  $\sim$  10  $\mu$  g/s  $\sim$  10  $\mu$  because  $\sim$  10  $\mu$  $t=\frac{1}{2}$  and  $t=\frac{1}{2}$  and  $t=\frac{1}{2}$  and  $t=\frac{1}{2}$  and  $t=\frac{1}{2}$  and  $t=\frac{1}{2}$ The subcellular location, specificity, sensitivity to  $\mathbf{H}_{\text{eff}}$ and decrease requirement for  $\mathbf{P}$  indicate that the proposition of the proposition  $\mathbf{P}$ tease responsible for proteins  $\mathcal{L}_\mathbf{r}$  proteins  $\mathcal{L}_\mathbf{r}$  proteins  $\mathcal{L}_\mathbf{r}$ differs from protecting the protection of  $\mathbf{f}$ in the the maturation of  $\mathbb{Z}^{76,78}$ . Furthermore, the state  $\mathbb{Z}^{76,78}$ . Furthermore, the state  $\mathbb{Z}^{76,78}$  $f: \mathbb{R}^n$  is a subset of a property the arginine of argining the argin  $\mathbb{R}^n$ the NiV  $\mathbb{R}^n$  for  $\mathbb{R}^n$  for  $\mathbb{R}^n$  a non-polar residue site  $\mathbb{R}^n$  for  $\mathbb{R}^n$  $\mathbb{R}$  and contrasts with the absorption of a boundaries with the absorption of absorption  $\mathbb{R}$ lute need for a basic residues in the F proteins in the F proteins in the F  $p$  $\blacksquare$  $f \blacksquare$ all  $\blacksquare$  $h \vdash \lambda$ .  $\ell$ <sup>0.</sup> Recently, it was shown that  $f$ the lysisses and cysteine proteine proteine proteine  $\mathcal{L}_\text{c}$ for the proteins of the HeV  $f$   $f$  and  $f$  proteins  $\mathbb{R}^n$ .

*The henipavirus P gene products.* the first lines of inner of inner and infection  $\mathbf{f}$  $i$   $i$   $j$   $j$   $k$ organisms from the source of infection82–85. There are two  $t_{\rm F}$ stypes of IFN. Type I IFNs are produced in response to  $\mu$ and bacterial infection and comprise a family of relationships a family of relationships a family of  $\mathcal{L}$ IFN-α proteins and IFN-γ, is syn-γ, is s these of the immunes  $\mathbf{u}_i$  by certain cells of the immune system. Here,  $\mathbf{u}_i$ we focus solvent type I is the anti-viral type I  $\mathcal{H}^{\mathbf{N}}$  response I IFN responses. The transcription of the type  $\mathbf{A}$  activities  $\mathbf{A}$  and  $\mathbf{A}$  activities  $\mathbf{A}$  $\mathbb{E}\left\{x\right\}=\mathbb{E}\left\{x\in\mathbb{R}^{n}\mid\mathbb{R}^{n}\right\}$  and  $\mathbb{E}\left\{x\right\}=\mathbb{E}\left\{x\in\mathbb{R}^{n}\mid\mathbb{R}^{n}\right\}$  , i.e.,  $i$ .  $n$  ,  $n$  ,  $i$  or  $i$  of  $i$  or  $i$  or  $i$  or  $i$  or  $i$  and  $F(G, 3)$  and  $F(G, 3)$ leads to the synthesis of IFN- $\beta$ <sub>k</sub> and a subset of  $\alpha$ <sub>m</sub> if the  $\mathbb{R}^{84,86}$ . The IFN induction pathway can be activated by activated b **do**  $\pi$ <sub>k</sub> (d)  $e^{87}$  or by virus infection, in which  $\pi$  $\mathbb{E}[\mathcal{L}^{\mathcal{A}}]$  and dscribes of the responsibility of  $\mathcal{L}^{\mathcal{A}}$  $\mathbb{R}^8$ . For the sake of simplicity, we will refer here to the total refer here to the to th  $p$  is induced as the dsRNA-signalling as the ds $\mathcal{L}_{\mathcal{F}}$  $p(\lambda, \beta)$  is the second phase,  $p(\lambda, \beta)$  signalling (FIG. 4), the second phase,  $\alpha$ IFNS that are induced as a result of virus infection bind to virus infection bind to virus infection bind to  $t_{\rm eff}$  type-IFN receptors on the surface of both infected and  $\tau_{\rm eff}$  $\mathbf{E}$ uning activate hundreds of  $\mathbf{E}$  inducible  $\mathbf{E}$  inducible  $\mathbf{E}$ genes, some of which have anti-viral activity  $\mathbb{Z}$  and  $\mathbb{Z}$  and  $\mathbb{Z}$  activity  $\mathbb{Z}$  and  $\mathbb{Z}$  activity  $\mathbb{Z}$  and  $\mathbb{Z}$  activity  $\mathbb{Z}$  and  $\mathbb{Z}$  and  $\mathbb{Z}$  and  $\mathbb{Z}$  and  $\mathbb{Z}$  and  $\mathbb$ 

#### Box 2 | Henipavirus infection in flying foxes

Despite the high prevalence of antibodies to henipaviruses, particularly in Australian pteropids, neither Hendra virus (HeV) nor Nipah virus (NiV) has been associated with any naturally occurring disease of flying foxes. The subclinical nature of HeV infection of pteropids has been confirmed by experimental infection of several species of Australian flying foxes<sup>134,135</sup>. A comparison of the pathology observed in henipavirus-infected chiropteran and terrestrial mammals provides some insights into the different clinical outcomes of infection. The predominant lesion in natural and experimental henipavirus infection of terrestrial animals, including humans, is systemic vasculitis, which affects smaller vessels in many organs, with clinical symptoms arising predominantly from infection of the lung and/or the central nervous system<sup>21,136,137</sup>. Viral antigen is detected in syncytial cells in vascular endothelium and, in the case of NiV infection, in bronchial and alveolar epithelium. Henipaviruses are readily recovered from nasopharyngeal secretions, urine and internal organs including lung and brain<sup>21,138</sup>. By contrast, infection of flying foxes with doses of HeV consistently shown to be lethal in horses generated only sporadic vasculitis in the lung, spleen, meninges, kidney and gastrointestinal tract, and only in a proportion of infected bats<sup>134,135</sup>. Viral antigen is detected in the tunica media rather than endothelial cells. In infected pregnant flying foxes, antigen is observed in similar locations and in the placenta<sup>135</sup>.

Two observations might explain the lack of systemic disease in flying foxes. First, the presence of antigen in the tunica media rather than endothelial cells indicates that the latter might be spared from infection, therefore reducing the clinical effects associated with vasculitis. Second, the striking reduction in the level of antigen in flying foxes compared to horses and cats indicates that factors not found in terrestrial mammals that limit the ability of HeV to replicate could be at play in flying foxes. Indeed, after experimental infection of flying foxes with HeV, only half the animals show a rise in antibody titre, which is often low and sometimes of short duration (<3 weeks). Despite rigorous sampling regimes, virus has been isolated only infrequently, and where isolation was successful, positive sources included urine and the foetus, heart, placenta, kidney and spleen of two pregnant bats<sup>134,135</sup>.



Figure 3 | **I e** fe<sub>r</sub> (IFN) i **d c**<sub>i</sub> **d b**.e- **a ded (d)RNA ig a.i g.** The innate immune system depends on the ability of cells to detect the presence of unique, pathogen-specific molecules. The molecule considered most likely to be seen as foreign by virus-infected cells and activate the innate immune system is dsRNA, generated as a result of virus infection<sup>87</sup>. Several cellular sensors detect the dsRNA signal and respond by activating pre-existing transcription factors such as IFN-regulatory factor 3 (IRF-3) and the general transcription factor nuclear factor (NF)-κB83,97,144–146. Activated IRF-3 and NF-κB are redistributed to the nucleus, where they cooperate with other transcriptional activators to induce transcription of the interferon (IFN)-α/other 0 0 8.5 ron (IFN)-

 $\mathbb{C}^2$  and all  $\mathbb{C}^2$  and  $\mathbb{C}^2$  all  $\mathbb{C}^2$  all  $\mathbb{C}^2$  all  $\mathbb{C}^2$  all  $\mathbb{C}^2$ virus evolved ways to evade the IFN-induced ways to evade the IFN-induced ways to evade the IFN-induced ways to  $\mathbf{F}_i$ antiviral responses of the  $\mathbb{R}^3$ ,  $\mathbb{R}^3$ ,  $\mathbb{R}^3$ ,  $\mathbb{R}^3$ ,  $\mathbb{R}^3$ ,  $\mathbb{R}^3$  mechanisms of the mechanisms of the  $\mathbb{R}^3$ nisms include the inhibition of host-cell transcription and translation and the consequent failure to synthesize to synthesize to synthesize to synthesize to synthesize IFN, in high  $\mathbf{N}$  and  $\mathbf{N}$  signalling and IFN-signalling and  $\mathcal{P}_1$  induced and anti-induced anti-induced and anti-induced anti-induced anti-induced anti-induced anti-induced antieffects. The anti-IFN activities of parameters of parameters of  $\mathbb{R}$  activities of  $\mathbb{R}$ virus encoded by the viral  $1/2$  and NS2  $r_1 \rightarrow r_1 \rightarrow r_1$  1 **v**. Pneumovirinae **preumoviring**  $\Lambda$ <sup>91,92</sup>, and by the *Paramyxovirinae*. **Products of the P generalling in**  $P$  generalling  $P$  signalling  $P$  s and IFN signalling  $\frac{97-99}{\pi}$  strategies used by anti-IFN strategies used by parameter vary, both between  $\mathcal{U}$  and  $\mathcal{U}$ virus especification and specific genus. This is primarily because  $\mathfrak{g}_{\mathcal{A}}$   $t_{\rm eff} = \frac{1}{2}$  general and its encoded proteins are both organisms  $(BOX 3)$ .  $\mathbf{R}^2 \rightarrow \mathbf{R}^2 \rightarrow \mathbf{R}^2$  and unique way in which unique way in which was in which was in which way in which was  $\mathcal{F} = -\frac{1}{2}$  and  $\mathcal{F} = \frac{1}{2}$  and  $\mathcal{F} = \frac{1}{2}$  and  $\mathcal{F} = \frac{1}{2}$  and  $\mathcal{F} = \frac{1}{2}$ determinants by antagonizing the IFN  $\alpha$  response of  $\mathbb{R}^n$ infected cells.

**Inhibition of dsRNA signalling.**  $\partial \bullet$  signalling is inhibited not only by the access $s$ sory V protein, as observed for  $\mathcal{U}$ respirovirus este  $P$ <sup>33–95,100,101</sup>, but surprisingly also by the surp  $(FIG. 3)$ .  $t$ as encoded by the melanoma difference encoded by the melanoma difference  $t$  $\epsilon$  5 (*MDA5*), j  $\ldots$  **:** virus and respirovirus counterparts  $\mathbf{u}$  and  $\mathbf{v}^{102}$ . When the thermal



#### Box 3 | The henipavirus P gene

The paramyxovirus P gene encodes several proteins by means of internal translation-initiation sites, overlapping reading frames and an unusual transcription process in which one or more nontemplated G nucleotides are inserted at a conserved editing site, resulting in a shift of reading frame during translation<sup>127</sup>. The figure shows a schematic representation of mRNAs transcribed from the P gene of henipaviruses compared with those of morbilliviruses, respiroviruses and rubulaviruses. In henipaviruses (**a**) and respiroviruses and morbilliviruses (**b**), the unedited P-gene transcript encodes the P protein, and the V protein is generated by a separate transcript containing a single G nucleotide inserted at the editing site. Insertion of two G residues generates a transcript encoding a protein usually called W. V and W proteins share their amino termini with the P protein. Compared with morbilliviruses and rubulaviruses, henipaviruses have an N-terminal 100–200-amino-acid extension that might have evolved to better equip the viruses to antagonize the cellular interferon response (see text). The P. V and W proteins have unique C-terminal domains. In the P protein, this region is essential for viral

RNA synthesis and contains sites for binding to the



N and L proteins in ribonucleoproteins. The C-terminal domain of the V protein is highly conserved among paramyxoviruses and contains seven perfectly conserved cysteine residues. The C-terminal domain of the W protein is frequently short because of the presence of a stop codon soon after the editing site, but in henipaviruses the W-specific domain is 43 amino acids in length, compared with 55 for the V-protein C-terminal domain<sup>10</sup>. The P genes of henipaviruses, morbilliviruses and most respiroviruses contain a second short discrete overlapping reading frame upstream of the editing site, which in P, V and W mRNAs encodes the C protein. The structure of the P gene differs in rubulaviruses (**c**), where the primary transcript encodes the V protein, and transcripts with two G nucleotides inserted at the editing site generate the P protein. Note the long 3′ untranslated region of the henipavirus P gene RNAs.

 $B = \frac{1}{2}$  contrast, respirovirus such as  $\frac{1}{2}$  and  $\frac{1}{2}$ and more such as  $\mu$  as  $\mu$  use  $\mu$  use  $\mu$  as  $\mu$ egies to block IFIG. 4). Severally signalling  $\frac{1}{4}$  and  $\frac{3}{4}$ inhibit tyrosine phosphorylation of  $\mu$  and  $\mu$  and  $\mu$  in  $\mu$ or  $\mathbf{y} \mathbf{I} \mathbf{2}$ , and the access that  $\mathbf{p}$  is a contracted that  $\mathbf{y}$ tein 95,100,101,116. Several anti-IFN-signal  $\mathbf{A} = \mathbf{A} \mathbf{A} \mathbf{B} + \mathbf{A} \mathbf{A} + \mathbf{A} \mathbf{A}$ intact but prevent their translocation to the nucleus  $\mu$  is the nucleus  $\mu$  $\mathbf{x}$  in the cells, type phosphorylatic phosphorylatic cells, the  $\mathbf{y}$ and STAT2 is in the V protein and STAT1 is in the V protein and STAT1 is in the V protein and STAT1 is in the reference in a complex with the IFN receptor  $\mathbf{A}$  $\mathbf{A} = \mathbf{p} \cdot \mathbf{A} \mathbf{I} + \mathbf{P} \mathbf{C} \mathbf{A} \mathbf{I} + \mathbf{I} \cdot \mathbf{A} \mathbf{A} \mathbf{P} + \mathbf{P} \mathbf{C} \cdot \mathbf{A} + \mathbf{I} \cdot \mathbf{A} \mathbf{A} \mathbf{P}$ tor of  $I = \{x_1, x_2, \ldots, x_n\}$  single signalling, but its precise role  $r$  $\ell$  mediate  $1^{118,119}$ .

 $T_{\text{max}}(t)$  is denoted the other hand, broaden the o  $p$ argeting strategies by sequestering strategies by sequestering strategies by sequestering strategies by sequestering  $p$  $\frac{1}{\sqrt{2}}$  in  $\frac{1}{\sqrt{2}}$  is  $\frac{1}{\sqrt{2}}$  in  $\frac{1}{\sqrt{2}}$  in  $\frac{1}{\sqrt{2}}$  and  $\frac{1}{\sqrt{2}}$  (FIG. 4).  $\mathbf{R}$ rkably, this activity does not resident in the cycle reside rich C-terminal domain of the V protein, but in an area  $\mathbf{A} = \mathbf{A} \cdot \mathbf{A} + \mathbf$ provides hencipality with a multi-IFN  $p$  multi-IFN  $p$ response in which STAT proteins are sequestered in complexes, consequently abroad the sequence of  $\mathbf{R}$  biological theorems above  $\mathbf{r}$  $\alpha$  activity<sup>104,122</sup>. The most efficient is the most efficient, and the most efficient is the most efficient, and the most efficient is the most efficient is the most efficient in  $\mathbb{R}^n$ **P** protein the least effect and  $P_1$  and  $P_2$  and  $P_3$ proteins of  $\mathbf{N} = \{x\}$  . The showed is a time  $\mathbf{N} = \{x\}$  $\mathbb{R}^n$  when the C generator  $\mathbb{R}^n$ downstrate the edition of the edition  $\mathbb{R}^2$ .

with its nuclear-localization signal in the W-specific signal in the W-specific signal in the W-specific  $\mathbf{c}\in\mathbb{R}$  in the  $\mathbf{c}\in\mathbb{R}$  in the  $\mathbf{c}\in\mathbb{R}$  in the station station station station station station  $\overline{103,105}$ The height para-value is larger than any of its para-value is  $\mathcal{N}$  $\begin{pmatrix} 0 & \text{mm} & \text{m} & \$  $\mathbf{p}=\mathbf{p}\cdot\mathbf{p}=\mathbf{p}\cdot\mathbf{p}=\mathbf{p}\cdot\mathbf{p}$  . We will approximately of a 100–200 $\Lambda$   $\mathbb{R}$ the subfamily  $1^{12,20}$  (BOX 3). The minimum domain  $\mathbf{I}$  of  $\mathbf{I}$  in  $1$  is a contactivity and  $\frac{1}{2}$  for  $\Delta$  $t_1 = 150$  (REF. 105). The Niv C protein also displays modest in  $\mathbb{R}^n$  and  $\mathbb{R}^n$  inhibition of IFNN  $\mathbb{R}^n$  $s_{\rm eff}$  (providing to the multipaceted to the multipaceted multi hencipavirus strategy to abrogate  $\mathbf{E}_k$  strategy to abrogate IFN signalling, although  $\mathbf{E}_k$ the mechanism and target are unknown  $\frac{1}{\sqrt{2}}$  $N \cdot \mathbf{A} = \mathbf{A} \cdot \mathbf{A} + \mathbf{A} \cdot \mathbf{A} +$  $P=\mathbb{P}^{\mathbb{P}}$  and paramyxovirus of paramyxovirus  $\mathbb{P}^{\mathbb{P}}$  $s$  in the virulence and host-range determinants. The virulence and host-range determinants.  $\mathbb{R}$  and  $\mathbb{R}$  and disease virus (NDV) depends on virus inhibition of the virus inhibition of the theorem of the theorem of the theorem of the  $\alpha$ IFN response, and mutations in proteins in proteins in proteins in proteins  $\mathbf{r}_1$  $\alpha$  anti-signalling activities activities alter the virus–host relationship in favour of the host  $\mathbf{u}_s = \mathbf{u}_s^{-123-126}$ , is such that  $\mathbf{u}_s = \mathbf{u}_s = \mathbf{u}_s$ 

information on the function of the function of the  $f$  $\mathbf{C} = \mathbf{C} \mathbf{C} \mathbf{C}$  with cells transiently over- $\mathbf{C} \mathbf{C}$  $\mathbb{R}$ expressing the proton is not known if they are know

tyrosine phosphorylation is also inhibited by all three inhibited by all three inhibited by all three inhibited by a  $\mathcal{A}$  and  $\mathcal{A}$   $\mathcal{A}$  below. The V and P proteins interact with  $\mathcal{A}$  and  $\mathcal{$  $\mathbf{S}=\begin{bmatrix} 1 & \cdots & \mathbf{S}_n \end{bmatrix}$  in the cytoplasm, whereas the W protein, armed whereas the W protein, armed whereas the W protein, and  $\mathbf{S}=\begin{bmatrix} 1 & \cdots & \mathbf{S}_n \end{bmatrix}$ 

 $\mathbf{W}_k$ eted in virus-infected cells. In  $\mathbf{W}_k$  of an allowing analysis  $\mathbf{W}_k$  $\mathfrak{p}_\infty = \frac{1}{2}$  . It is the unique to the unique values of unique to the unique values  $\mathfrak{p}_\infty$  $g_{\text{eff}}(x) = \frac{1}{2} \int_{0}^{\infty} \int_{0}^{\infty} \left[ \int_{0}^{\infty} \left[ \int_{0}^{\infty} \left[ \int_{0}^{\infty} \right]_{0}^{\infty} \right]_{0}^{\infty} \right]_{0}^{\infty} dx$ reverse generation and the study of mutant-virus patho-virus patho-virus patho-virus patho-virus patho-virus p  $\ldots$  in vivo. Nevertheless, it can be speculated that  $\ell \to \ell$  $\mathbf{q}(\mathbf{A},\mathbf{R}) = \mathbf{q}(\mathbf{A},\mathbf{R}) \times \mathbf{q}(\mathbf{A},\mathbf{R}) \times \mathbf{q}(\mathbf{R}) \times \mathbf{q}(\mathbf{R})$  $s$  species, compared with the subclinical replication in  $\mathcal{S}_\mathcal{P}$  $\mathbb{E}[\mathcal{M}_\mathcal{D}]$  and ability of the ability of the virus of t  $\mathbf{t}[\mathbf{t}]\in\mathbb{R}^{n}$  and it will be obtained the host it will be of  $\mathbf{t}$ interest to determine the anti-IFN activities of the  $I$  $\chi$  -general products in chiropteran cells.

#### **Conclusions**

The routes by which hence  $\mathbb{R}^n$  and  $\mathbb{R}^n$  avisations emergencies emergencies emergencies emergencies  $\alpha$  and  $\alpha$  remain obscure  $\mathcal{A}$   $\alpha$  . our in ance of virus ecology is equal to  $\mu$  $f(x) = \sqrt{2\pi} \int_{0}^{x} f(x) dx$  on  $f(x) = f(x)$  are few data on  $x$  $\mathbb{P}_{\mathcal{L}}[f]$  and diseases for control of the diseases caused of diseases caused of  $\mathcal{L}[\mathcal{L}]$ 

by hencipal  $\mathcal{L}$  in the future of the future. The high virulence of  $\mathcal{L}$ hence of the absence of the  $\mathbf{A}$ strategies and vaccines and the transformation as  $4\leq 4$  $p$ andoubtedly in pathogens have under the rate at  $p$ information has been generated on the biology and biology and biology and biology and biology and biology and  $\mu$  $p$ and  $p$  and  $p$ . Here, recent investigation is  $p$ tigations into the structure and function of  $\mathcal{A}$  $\mathbf{p}=\mathbf{p}=\mathbf{p}$  and  $\mathbf{p}=\mathbf{p}=\mathbf{p}=\mathbf{p}$  and  $\mathbf{p}=\mathbf{p}=\mathbf{p}=\mathbf{p}$ cells have provided values on the nature information on the nature  $\rho$  $\mathbf{0}$ of the relationship between hencipality  $\mathbf{0}$  and the cells  $\mathbf{0}$  $t_{\rm eff}$  infections for the observed explanations  $\mathbf{r}_{\rm eff}$ interaction between henipaviruses and their terrestrial  $\mathbf{u}, \ldots$ 

 $T$  of the biological criteria that differentiate  $\mathcal{L}$ and  $\mathbf{y} = \mathbf{y} = \mathbf{y}$  from  $\mathbf{y} = \mathbf{y}$  from other wide host wide host wide host wide host wide host range and the virulence that they display in their hosts. The susceptibility to hence  $\mathbf{A}$  is a substitution of a range o  $m_1 + m_2 + m_3 + m_4 + m_5 + m_6$  sus-species and the similarity in patterns of subceptibility to infection by HeV and NiV and NiV are now known by HeV and NiV are now  $\mu_{\rm{max}}$  $\mathbf{t} = \mathbf{b} \cdot \mathbf{b}$  in part, to the fact that both viruses  $\mathbf{t} = \mathbf{t}$  $u = \mathbf{a} \mathbf{a} = 2 \rho_1 \rho_2 \cdots \rho_m \mathbf{a} \mathbf{a} \rho_1 + \gamma_2 \mathbf{a} \rho_2 \cdots$  $s$ urface glycoprotein of and widespread and  $\mathbf{v}$ distribution among vertebrates. The widespread cel- $\psi$  $\mathcal{L}_1$  is distribution of equation  $\mathcal{L}_2$  equation in variable in variable endothelial cells, and provides an explanation for  $p$  $t = \frac{1}{2}$  in the most frequently observed outcomes of the  $\frac{1}{2}$ in terrestrial involvement of endothering  $\mathbf{r}_i$  and  $\mathbf{r}_i$  also be determined by determining  $\mathbf{r}_i$ cells. However, it remains to be seen if  $\alpha$ the universal hencipal hencipavirus receptor  $\mu$  and  $\mu$ and all natural lines of variable  $\mathcal{A}$  and  $\mathcal{A}$  strains, or variable  $\mathcal{A}$  strains, or variable  $\mathcal{A}$ and as the contribution in the outbreaks of disease in the outbreaks of disease in the outbreaks of disease in  $\mathcal{A}$ in Bangladesh where human-to-human-to-human-to-human-to-human-to-human-to-human-to-human-to-human-to-human-to- $\mathbf{u}$  documents of  $\mathbf{u}$ 

 $T_{\rm eff}$  investigations investigations have also have also have also have also have also have a second information of  $T_{\rm eff}$ revealed several other factors that probability is a shock of the nearest  $\mathcal{L}$  $\mathbf{u}$  is a clear proton by cathering by cathedral by catherines in treating or novel approaches in treating or novel  $\mathbf{u}_i$  $\mathcal{L} = \mathcal{L}(\mathbf{A} \cdot \mathbf{D})$  in the clear proteins infection. The cleaval proteins infection. The clear proteins infection.

 $\mathfrak{so}(\mathbb{R}^d)$  and  $\mathfrak{so}(\mathbb{R}^d)$  and  $\mathfrak{so}(\mathbb{R}^d)$  and  $\mathfrak{so}(\mathbb{R}^d)$  and  $\mathfrak{so}(\mathbb{R}^d)$ in infected cells  $\mu$  . Any correlation between the virus with an and between the virus within and between  $\mu$ if the wide range of the wide range of anti-IFN strategies. It is temperature that the virulence of  $\mu$  $s$ ite that is unique among viral glycoproteins, facilitates  $\mathcal{J}_1$  and  $\mathcal{J}_2$  and  $\mathcal{J}_3$  and  $\mathcal{J}_4$ virus dissemination in vivoral  $\mathbf{v}$  and  $\mathbf{v}$ hence it due at least in part to the multipart to the multipart of the multipart of  $\mathbb{R}^n$ P-gene strategy that these viruses have developed to in his the IFN system, a strategy that is not  $\mathbb{I}^{\mathbb{I}}$  that is not is not is not in the parameters of the parameters  $\mathbf{f}$  and  $\mathbf{f}$  and  $\mathbf{f}$  and  $\mathbf{f}$  and  $\mathbf{f}$ nuclear components.

rity in flying for  $\mathbf{a}$  and  $\mathbf{a}$  pathogens in the ecosystem basis in the ecosystem in the ecos nisms of transmitted from batter  $\mathbf{f}(\mathbf{z}) = \mathbf{f}(\mathbf{z})$  . The  $\mathbf{f}(\mathbf{z}) = \mathbf{f}(\mathbf{z})$  $\alpha$  relation of  $\alpha$  and risk-virus transmission or risk-viruses use the same range of  $\alpha$  and  $\alpha$  $\mathbb{R}$  important  $\mathbb{R}$  important  $\mathbb{R}$  by a ratio by the properties have been raised by the properties of  $\mathbb{R}$ recent and  $\alpha$  in vitro  $\alpha$  **i**  $\alpha$  **i**  $\alpha$  **i**  $\alpha$  $A = \{A \mid A \in \mathbb{R}^n : A \subseteq A \cup A \neq A \}$ virulence of  $\mathbb{R}^n$  and  $\mathbb{R}^n$  in terrestrial hosts versus in terrestrial hosts versus  $\mathbb{R}^n$  $t_{\rm c}$  , outcome of  $\mathbf{u}$  in  $\mathbf{u}$  in  $\mathbf{u}$  and  $\mathbf{u}$  and  $\mathbf{u}$  in  $\mathbf{u}$  and  $\mathbf{u}$  in  $\mathbf{u}$ provide crucial clusters. In example, in the receptor in  $\mathbf{A}$  $\beta$  in light of the highly conserved nature of  $\beta$  murine of murine of murine of  $\beta$ domain, there will probably be simply be significant functions of  $\mathbf{r}$  and  $\mathbf{r}$ in the ephric B2 of the ephric flying flying for  $\mathbf{R}^2$  $\mathbb{B}_1$  , we are  $\mathbb{C}_1$  cells and time of tisproducts to inhibit IFN in bats. In the  $\mathcal{P}_\text{max}$  $\mathcal{A}$  single and IFN signalling in chiral  $\mathcal{A}$ cells, the limited replication observed in  $\mathbf{u}$ could be due to other factors such as the nature, density  $\mathcal{L}_\text{c}$  $\alpha$  and the battle battle battle receptors or the ability of the abili viral C protein to inhibit viral  $\alpha$ more effectively than has been observed in  $\mathbb{R}^n$ lian cells<sup>127</sup>. The cells of  $\mathbf{1}$  the respirovirus  $\mathbf{1}$  and  $\mathbf{1}$  the respirovirus  $\mathbf{1}$  $P = \{p \in \mathbb{R} \mid \mathbf{R} \cup \mathbf{R} \mid \mathbf{R} = \mathbf{R} p \mid \mathbf{R} = \mathbf{R} \}$  $A = 127,130$ .

 $A = \{x \in \mathbb{R}^n : x \in \mathbb{R}^n : y \in \mathbb{R}^n :$  $\phi$  to the total virus to the range of viruses infection with a wide range of viruses in  $\phi$  $t\in\{1,\ldots,N\}$  symptoms, and  $\mathbf{y}$  and  $\mathbf{y}$  and  $\mathbf{y}$  and  $\mathbf{y}$  and  $\mathbf{y}$  $\mathcal{L}(\mathbf{U}) = \mathbf{U}_{\mathbf{q}} \mathbf{Y}_{\mathbf{p}}$ s the inhibition of virus replies  $\mathbf{V}_{\mathbf{p}}$ cation by leading as mannoses-binding protein and protein and protein and protein and protein and protein and  $\rho$  $\gamma$  and  $-1$  (REFS 131,132).  $\gamma$  and  $-1, \gamma$  and  $\gamma$ leaten secreted by various cell types, has been shown to  $\mathbf{A}$ to inhibit hence  $\mathbf{h}_0$  to  $\mathbf{h}_0$  and  $\mathbf{h}_0$  and  $\mathbf{h}_1$  and  $\mathbf{h}_2$ cell fusion, probability by aberraising  $\mathbb{R}^n$  function,  $\mathbb{R}^n$  function,  $\mathbb{R}^n$  functions  $\mathbb{R}^n$  functions  $\mathbb{R}^n$  functions  $\mathbb{R}^n$  functions  $\mathbb{R}^n$  functions  $\mathbb{R}^n$  functions  $\mathbb{R}^n$  fu and G glycople  $\mathcal{A}^{132}$ . In addition to this direct effect  $\mathbf{u} = \mathbf{x} - \mathbf{u} \mathbf{a}_F \mathbf{u}$  ,  $q = \mathbf{u} - \mathbf{1}$  might also act indirectly to limit  $\mathbf{A}_i$  it enhances it enhances it enhances denote it enhances  $\mathbf{A}_i$ cell production of production of probability  $\rho$ interleuking 6 (I-6), which has an essential role in the sential role in the sent  $f_{\rm eff}$  and differentiation of B cells into antibody-secreting into antibody-secreting into antibody-secreting  $f_{\rm eff}$ cells<sup>132</sup>. The capacity of  $\mathbf{A}$  and  $\mathbf{A}$  is  $\mathbf{A}$  and  $\mathbf{A}$  and  $\mathbf{A}$ abrogate the STAT-dependent IL-6-signalling pathway  $\mathbb{R}^n$  mined. The development of a range of anti-IFN strate-IFN strategy in the strategy of  $\mathbb{R}^n$  $\mathbb{R}^n$  by hencipavirus evolved to maximize the might have  $\mathbb{R}^n$ virus replication under conditions of restricted growths  $\mathbf{u}_i$ in bats. Finally, the ability to conduct the ability to conduct the studies  $\mathcal{L}_\mathcal{F}$  $u_1, \ldots, u_{n-1}$ ising recombinant molecular biological techniques on  $\mathbb{R}^n$ otherwise highly pathogenic and dangerous viruses  $\rho$ 

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**Competing interests statement** The authors declare no competing financial interests.

#### **DATARASES**

The  $f(x)$  ige ihia iceae iked ie... Entrez: http://www.ncbi.nlm.nih.gov/Entrez canine distemper virus | HeV | hPIV2 | hPIV3 | MDA5 | MeV | mumps virus | Newcastle disease virus | NiV | NS1 | NS2 | rabies virus | respiratory syncytial virus | SeV | SV5 | SV41 |

Tioman virus | Tupaia virus | vaccinia virus

Uni**ProtKB:** http://us.expasy.org/uniprot<br>cathepsin L | CD64 | ephrin B2 | IFN-β | IFN-γ | IL-6 | IRF-3 | SLAM | STAT1 | STAT2 | STAT3 | TLR3 | TYK2

#### FURTHER INFORMATION

Bryan T. Eaton, Deborah Middleton and Lin-Fa Wang's homepage:

http://www.csiro.au/aahl Acce<sub>rs</sub> hii eacie ik b<sub>u</sub> if ee<sub>.</sub> ie.