

therapy. Unfortunately, despite early promising reductions in severe anemia, in a phase III study the combination of viramidine and interferon failed to meet noninferiority criteria when compared to the pegylated interferon-ribavirin standard of care and consequently viramidine has not been pursued for further development (Benhamou *et al.*, 2009).

## 2. ANTIMICROBIAL ACTIVITY

### 2a. Routine susceptibility

The susceptibility of a range of viruses to ribavirin is summarized in Table 259.1.

#### PARAMYXOVIRUSES

##### *Pneumoviruses*

The concentrations of ribavirin required to reduce the replication of the pneumovirus RSV by 50% (a 50% effective concentration [EC<sub>50</sub>]) are 1.38–5.82 µg/ml, well below the threshold for cellular toxicity (Browne, 1981; Hruska *et al.*, 1980; Kawana *et al.*, 1987; Shigeta *et al.*, 1988; Shigeta *et al.*, 1992; Watanabe *et al.*, 1994). Some strains are less susceptible, with the EC<sub>50</sub> values as high as 16 µg/ml (Johnson, 1993). Aerosolized ribavirin protects cottontail rats from RSV and influenza B virus infections (Wyde *et al.*, 1987). Resistance to ribavirin has not been observed in RSV isolates from people treated with ribavirin for up to 55 days (Hall *et al.*, 1983a; McIntosh *et al.*, 1984; Hall *et al.*, 1985). It has also not been possible to generate resistant variants of RSV through passage in ribavirin-treated cell cultures (Hruska *et al.*, 1980).

Ribavirin inhibits replication of human meta-pneumovirus (a virus closely related to tRSV) *in vitro* at concentrations similar to those that inhibit RSV (Wyde *et al.*, 2003). In a mouse model of meta-pneumovirus infection, ribavirin treatment reduced pulmonary virus titers by 5.0 log<sub>10</sub> (Hamelin *et al.*, 2006).

##### *Other paramyxoviruses*

The activity of ribavirin against the measles paramyxovirus was first reported in 1978 (Murphy, 1978). In general, parainfluenza virus and measles and mumps viruses are relatively less susceptible to ribavirin *in vitro* than the pneumovirus RSV, with the former viruses having EC<sub>50</sub> values in one study of 8.6–67 µg/ml, determined by plaque reduction in HeLa or Vero cell lines (Shigeta *et al.*, 1992), and of 21–32 µg/ml as assessed by inhibition of the cytopathic effect in the same cell lines in an earlier report (Kirsi *et al.*, 1984). However, some strains of measles virus are apparently inhibited by 0.003 µg/ml ribavirin (FDA, ribavirin product information, 2011). Ribavirin inhibits subacute sclerosing panencephalitis (SSPE)-related strains of measles virus *in vitro* (Hosoya *et al.*, 1989) at concentrations of 10–50 µg/ml, and although the drug did not improve the survival of hamsters when administered intraperitoneally, it improved survival in a dose-dependent manner when given by the intracranial route (Honda *et al.*, 1994). In hamsters, treatment of SSPE infection

Table 259.1. Activity of ribavirin against selected viruses *in vitro*.

DNA viruses		RNA viruses	
Virus	IC <sub>50</sub> (µg/ml)	Virus	IC <sub>50</sub> (µg/ml)
Herpesvirus		Paramyxoviruses	
HSV-1	0.32–100	RSV	1.3–16
HSV-2	1–100	Parainfluenza	3.2–67
CMV	10–100	Measles	0.003–67
		Equine morbillivirus	45
		Mumps	0.1–10
Adenovirus	3–200	Orthomyxoviruses	
		Flu A, flu B	0.05–12
Pox viruses		Retrovirus	
Vaccinia	3–320	HIV	50
		Arenaviruses	
		Lassa	10–32
		Junin	3–32
		Bunyaviruses	
		Hantaan	15
		Crimean Congo	4–10
		Rift Valley	76–80
		Sandfly	75–80
		Punto Toro	2–10
		Flaviviruses	
		Dengue	2–5
		Filoviruses	
		Ebola	> 500

Abbreviations: IC<sub>50</sub>: half-maximal inhibitory concentration; HSV: herpes simplex virus; CMV: cytomegalovirus

Source: Modified with permission from Johnson (1993).

with combination intracranial interferon alpha and ribavirin (1.0 mg/kg daily) completely prevented mortality (Takahashi *et al.*, 1998). Mumps virus is inhibited by ribavirin concentrations of 0.1–10 µg/ml (FDA, ribavirin product information, 2011).

Equine morbillivirus is moderately susceptible to ribavirin *in vitro* when tested in a variety of cell lines with EC<sub>50</sub> values of approximately 188 µM (45 µg/ml) (C. Birch, personal communication, 2016).

*In vitro* ribavirin also inhibits replication of Nipah and Hendra viruses (members of the new henipaviruses genus, part of the paramyxovirus family). For Nipah virus, the minimum effective concentration of ribavirin was 100 µg/ml, and in a hamster model, ribavirin at best delayed death from Nipah virus by < 2 days (Georges-Courbot *et al.*, 2006). *In vitro* ribavirin inhibited RNA production of Hendra virus at concentrations > 12 µM, and at 50 µM RNA synthesis was reduced 9-fold and viral yield 58-fold (Wright *et al.*, 2005). A hamster study of combined chloroquine and ribavirin for Nipah and Hendra Viruses again demonstrated effective antiviral activity *in vitro* but had with no effect on overall mortality *in vivo* (Friberg *et al.*, 2010).