an *in vitro* study that showed a reduction in both infectivity and viral replication when both drugs were used (Rothan *et al.*, 2015).

FILOVIRUSES

Ebola is not susceptible to ribavirin *in vitro*, as EC_{50} values were > 500 μg/ml (Huggins, 1989). Similarly, ribavirin is ineffective against Marburg virus (Andrei and De Clercq, 1993).

PICORNAVIRUSES

Replication of coxsackie B in human amnion cell cultures was inhibited by ribavirin when assessed by plaque reduction assay. Recombinant human leukocyte interferon alpha acted synergistically with ribavirin against this virus (Okada *et al.*, 1992). Myocardial titers of coxsackie B3 have been reported to be significantly lower in mice treated with ribavirin commencing either at the time of infection or up to 4 days postinfection (Kishimoto *et al.*, 1988). Ribavirin was inactive against poliovirus. Ribavirin treatment of cell cultures persistently infected with foot and mouth disease virus has reportedly eliminated infection (de la Torre *et al.*, 1987).

Ribavirin has modest activity against hepatitis A virus at a concentration of approximately 24 μg/ml (Widell *et al.*, 1986; Crance *et al.*, 1990).

ADENOVIRUSES

Ribavirin inhibited replication of adenoviruses in HeLa cells (Scheffler *et al.*, 1975; Murphy *et al.*, 1993). A laboratory study assessing ribavirin susceptibility of adenoviruses in Hep-2 cells showed that only serotype C was inhibited, with an EC_{50} of 48–108 μM. Serotypes A, B, D, E, and F were all resistant to ribavirin (Morfin *et al.*, 2005).

HERPESVIRUSES

Herpes simplex virus types 1 and 2 were very variably inhibited by ribavirin with EC_{50} values ranging from 0.32 to 100 μg/ml (Johnson, 1993). Ribavirin has been reported to potentiate the antiviral effect of aciclovir based on inhibition of cytopathic effect and viral yield reduction, but the synergistic effect of these two drugs was reversed by guanosine (Pancheva, 1991). Although ribavirin inhibits cytomegalovirus with an EC_{50} of 10–100 μg/ml (Johnson, 1993), the drug was considered clinically ineffective against this virus (Verheyden, 1988).

CORONAVIRUSES

There is controversy regarding the effect that ribavirin has on the SARS-related coronavirus (SARS–CoV). In one murine model, ribavirin was found to increase viral titers and duration of detection in lung parenchyma (Barnard *et al.*, 2006). Another more recent animal study used a novel highly virulent mouse-adapted strain of SARS-CoV to assess various antiviral compounds. Ribavirin treatment did not improve survival of affected mice or lower virus lung titers (Day *et al.*, 2009) Similarly, an *in vitro* study demonstrated no inhibition of viral growth, measured by cytopathic effect, plaque assay, and immunoblot analysis, at concentrations obtainable in humans (Stroher *et al.*, 2004). Other studies, however, support ribavirin inhibition of SARS-CoV, with *in vitro* data demonstrating a virustatic effect and synergy from combination ribavirin and interferon beta therapy (Morgenstern *et al.*, 2005; Saijo *et al.*, 2005).

Combination interferon and ribavirin therapy has also been studied in macaques infected with Middle Eastern respiratory syndrome (MERS-CoV). The animals receiving combination antivirals were found to have a significant reduction in viral genome copies within lung tissue, less systemic inflammation, and improved clinical parameters, including respiratory abnormalities and radiographic changes (Falzarano *et al.*, 2013).

FLAVIVIRUSES

Ribavirin has been reported to inhibit replication of dengue virus types 1–4 in monkey kidney cells, but not in human peripheral blood leukocytes (Koff *et al.*, 1982). The antiviral effects were completely reversed by the addition of guanosine. In another study dengue virus was susceptible to ribavirin *in vitro*, with an EC_{50} of 2–5 μg/ml as assessed by plaque reduction in the BHK-C15 cell line (Huggins, 1989). However, the drug did not prevent dengue virus infection in monkeys when given prophylactically, despite achieving peak ribavirin plasma concentrations of 7 μg/ml (Malinoski *et al.*, 1990). In human umbilical cord vein cells infected with dengue virus, ribavirin inhibited viral replication and modified cytokine production (Huang *et al.*, 2000).

There is currently insufficient data regarding the antimicrobial activity of ribavirin against Zika virus. High doses of ribavirin were found to inhibit the related West Nile virus replication and cytopathogenicity in human neural cells *in vitro* with an EC_{50} of 60 μM (Jordan *et al.*, 2000). Ribavirin improved survival in hamsters infected with yellow fever virus (Sbrana *et al.*, 2004).

OTHER VIRUSES

The replication of reovirus is inhibited by ribavirin at a concentration of 12.5 μM (Rankin *et al.*, 1989). Cytopathic effects induced by growth of vaccinia virus in vero cells are inhibited by ribavirin, with an EC_{50} of 19 μg/ml (Kirsi *et al.*, 1984), although other reports suggest less susceptibility, with an EC_{50} ranging from 3.2 to 320 μg/ml (Johnson, 1993). An *in vivo* model studied cowpox respiratory infection in mice, and ribavirin-treated mice had a survival benefit at low viral challenge doses (Smee *et al.*, 2000).

The *in vitro* activity of ribavirin against feline calicivirus (Povey, 1978b) is of interest because this virus is related to hepatitis C in humans (Di Bisceglie *et al.*, 1992). Oral ribavirin therapy commenced 1–4 days postinfection in cats with calicivirus failed to show clinical or virologic benefit (Povey, 1978a).

Although there are no published data regarding the efficacy of ribavirin against human papillomavirus *in vitro*, ribavirin administered intradermally has been found to reduce the growth of warts in rabbits at early stages of infection with cottontail rabbit papillomavirus (Ostrow *et al.*, 1992).