Epidemiol. Infect. (2009), **137**, 480–484. © 2008 Cambridge University Press
doi:10.1017/S0950268808001295 Printed in the United Kingdom

COMMENTARY
Subduing the hepatitis E Python

A commentary on: 'Outbreak of waterborne hepatitis E in Hyderabad, India, 2005', by Sailaja *et al.* (2008)

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(*Accepted 13 August 2008; first published online 17 September 2008*)

Key words: Jaundice, maternal mortality, water-borne hepatitis.

Inspired by the Ancient Greeks, past students of infectious diseases have often personified in that many-headed monster, Hydra, the terrifying effects of scourges such as cholera, scarlet fever, diphtheria, yellow fever and malaria [1–4]. Hercules-like, these pioneers laboured to prod and probe the beast, intending to identify its vulnerabilities and deliver the final, mortal blows [5]. They have largely been successful, although cholera and malaria remain as some of the few heads to slay.

Epidemic jaundice

Another monster affliction, epidemic jaundice, has been a menace since antiquity. Hippocrates, in the 37th chapter of his *Of Internal Affections*, called attention to a form of jaundice he termed 'epidemic'. Astute as he was, the state of knowledge in 4th century BCE was not sufficient for him to tease out its various aetiologies with any degree of precision [6]. Nor, for most of the ensuing centuries, could other medical practitioners. Legg, Hirsch and Cockayne, in their late 19th- and early 20th-century documentations of *icterus epidemius*, offered little more than broad speculations as to its causation [7–9]. Their descriptions nevertheless make tantalizing reading and, perusing them, modern students cannot help but generate hypotheses about the underlying nature of those outbreaks. Might the outbreak in the summer of 1859 in the central prison at Gaillon, Normandy – characterized, other than jaundice, by haemorrhages, nervous symptoms and acute yellow atrophy – be louse-borne relapsing fever? And the 1871 epidemic which made 799 Bavarian soldiers ill while laying siege to Paris – could that be hepatitis A?

In his review, Legg highlighted the demographic peculiarities of certain outbreaks. While some seemed to affect only adults, and others children, there were also those that pursued a more pernicious course in pregnant women:

> In other epidemics, it is the pregnant women who suffer; and whenever this epidemic jaundice attacks pregnant women, it seems to go hard with them, causing either serious symptoms, as delirium and coma, or death itself, although the non-pregnant women and the men recover without trouble [7].

Hirsch and Cockayne referred specifically to an outbreak in Martinique in 1858, and to another a year later in Limoges, France, where fatalities were observed only in pregnant women [8, 9]. Readers of this journal will have little hesitation in identifying these outbreaks as hepatitis E. Its causative agent, hepatitis E virus (HEV), has four genotypes circulating globally, two of which – genotypes 1 and 2 – are associated with present-day waterborne epidemics of hepatitis E in developing countries, with genotype 1 by far the more predominant [10]. HEV genotypes 3 and 4 are associated with hepatitis E in the more developed countries. However, it does not occur as epidemics, but sporadically or as small clusters, and its incidence is higher than previously anticipated [11].

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Epidemic hepatitis E

Scale

The scale of epidemic hepatitis E can be monstrous. In the 1955–1956 outbreak of waterborne hepatitis in Delhi, subsequently confirmed as hepatitis E, 29 600 icteric cases were reported [12, 13]. Khuroo estimated a total of 92 000 cases of jaundice from reports of waterborne epidemics that struck India, Nepal, Kashmir and Burma in the 1970s and 1980s [14]. Active case-finding conducted during an outbreak of jaundice in Dashoguz Province, Turkmenistan, revealed >16 000 cases of enterically transmitted, non-A, non-B (ET-NANB) hepatitis, later verified as hepatitis E [15]. A 1992 outbreak of hepatitis E at Kanpur, India, generated 79 000 cases [16]. By far the largest single outbreak was the one that occurred between 1988 and 1989 in Xinjiang Province, China, which affected >100 000 people [17]. These huge epidemics are not unique to Asia: an outbreak of ET-NANB hepatitis in Somalia in 1988 involved >11 000 cases from >140 villages [18].

Settings

Whether urban or rural, populations are vulnerable to periodic hepatitis E outbreaks if large segments of them live under poor sanitary conditions, and either accessibility to potable water is restricted [19] or piped water supply is inadequately maintained [20]. Triggering events have included seasonal heavy rainfall [21] and flooding [22], natural disaster, such as earthquake [23], and breakdowns in the integrity of the sewage disposal system and in the storage, disinfection and supply of water [24, 25]. The extent of outbreaks may not always approach the scale of the previously mentioned mega-epidemics. Nonetheless, many people can be affected especially if they live in dense metropolitan communities, as exemplified by a report of a 21st-century hepatitis E outbreak in Hyderabad, India. Sailaja *et al.* [26] reported that the outbreak gave rise to >1600 cases over a 10-month period in 2005, ascribing it to faecal contamination of poorly maintained water-supply pipes that crossed the city's open drains. The epidemic curve showed upsurges in the number of cases every 3–5 weeks until the interventions (enhanced chorination of reservoirs and repairs to damaged pipes) took effect. Such an interval falls within the incubation period of hepatitis E, suggesting that the structural defects that allowed sewage to leak from the drains to the water supply were generating fresh waves of HEV transmission from people who had been infected during the preceding wave.

Epidemic hepatitis E has also been reported, particularly after heavy flooding, in communities that use river water for drinking, bathing and disposal of human excreta [27], although the extent of an outbreak may be constrained by the low density and wide dispersal of the population. Nonetheless, attack rates in the 1988 epidemic in Somalia were significantly higher in villages supplied with river water than those supplied with well or pond water [18]. The emergence of large hepatitis E epidemics is also favoured by forced displacement of human populations. Armed conflicts can compel large swathes of populations to flee to regions with no pre-existing sanitation and where access to safe drinking water is severely restricted. Civil war in Somalia led to a hepatitis E outbreak in 1991 involving 1700 cases in refugees arriving in neighbouring Kenya [28]. In 2004, a similar war in Darfur, Sudan, resulted in close to 3000 cases in those living in refugee camps [29]. Even more contemporary is the hepatitis E epidemic now breaking out among internally displaced people in northern Uganda. It began in October 2007 [30], and currently, has given rise to >6000 reported cases.

Susceptibility of pregnant women

Also fitting the descriptions by Legg and Hirsch is the disproportionate number of case-fatalities in pregnant women [14, 16, 21, 25, 31–34]. While for the general population the case-fatality rate seldom rises above 3% in epidemics of hepatitis E, for pregnant women it has been reported to be between 11% and 31%. This wide range reflects differences in sample sizes, characteristics of the denominator sample and methods of data collection. Morbidity and mortality in pregnant women are overwhelmingly associated with fulminant hepatic failure (FHF), with deaths primarily occurring during the third trimester of pregnancy [21, 31, 34]. Incidence data in pregnant women during epidemics are scarce, but a sample survey conducted during the Delhi outbreak revealed that the clinical attack rate was 3% in pregnant women compared to 1·5% in non-pregnant women [31]. A later study conducted during a 1978 outbreak of ET-NANB hepatitis in Kashmir found the attack rates in pregnant women, non-pregnant women and men to be 17%, 2% and 3%, respectively [34]. Thus, in epidemic hepatitis E, not only are pregnant women more likely to develop

https://doi.org/10.1017/S0950268808001295 Published online by Cambridge University Press

severe illness or die compared to the general population, but they also are more prone to become ill. The disparities in incidence, severity and mortality between pregnant women and the rest of the population are maintained in inter-epidemic periods during which sporadic hepatitis E remains rife [35–46]. A study that investigated the pathogenesis of FHF in HEV-infected pregnant women revealed a more pronounced T-helper-2 bias in the cellular response to HEV in them compared with non-pregnant women [47]. More recently, HEV-infected, pregnant patients with FHF were shown to have lower CD4 but higher CD8 lymphocyte counts in peripheral blood, and higher circulating levels of pregnancy-associated steroid hormones, compared to non-HEV-infected, pregnant patients with FHF or non-pregnant controls [48]. Moreover, pregnant women with FHF have been observed not to express the p65 subunit of the dimeric transcription factor NF-κB, although the ability to express its p50 subunit remains intact [49]. How these factors interact to heighten hepatocytic destruction remains to be determined.

Obstetric and fetal outcomes in pregnant women with hepatitis E are also often adverse. In 1880 Legg noted from reports of the outbreaks in which pregnant women were particularly afflicted that, for these cases, 'Premature labour usually comes on, and the child is born dead, but not yellow' [7].

Strikingly consistent with such an assessment is Naidu & Viswanathan's terse description of what, during the 1957 Delhi epidemic, befell a jaundiced and comatose pregnant woman on the 31st day of hospital admission: 'In the evening, she had premature delivery. Membranes were bile-stained. Foetus was dead, but not jaundiced' [31].

Such outcomes have been investigated more formally. A case-control study conducted during an outbreak in Kashmir in 1978 showed that the risks of premature delivery and fetal death were significantly higher among pregnant women with FHF than in those without FHF or without jaundice [34]. Similar observations were made in pregnant women with sporadic hepatitis E during inter-epidemic periods, which also showed that the risks of miscarriages and neonatal deaths were higher [37, 45, 46].

Towards eradication

Having considered these various features of epidemic hepatitis E, it would seem appropriate to personify its ravaging and waterborne nature – and its unusual predilection to harm pregnant women – not in Hydra, but in another monster in Greek mythology, Python. This serpent, which emerged from the earth after The Great Deluge, pursued and harried the pregnant Leto after she was forced by Hera, the wife of Zeus, to roam the earth (Hera had discovered that Leto, a descendant of the Titans, was Zeus' paramour). Leto managed to give birth to twins. One of them, Apollo, then took vengeance on Python for having tormented their mother, killing it with his arrows [50].

Subduing the hepatitis E Python will certainly require more than an arrow shot. Sailaja *et al*. [26] allude to a recombinant vaccine that has recently completed phase 2 trials [51]. While its safety and efficacy in preventing hepatitis E in young adults have been determined, questions remain as to how long protection will last, whether it will prevent HEV infection rather than disease, especially in pregnant women, and, should these women become infected after having been vaccinated, whether they would be protected against FHF [52]. Sailaja *et al*. also made reference to the United Nations' Millennium Development Goals (UNMDG). One of its targets is to halve, by 2015, the proportion of the world's population without sustainable access to safe drinking water and basic sanitation. The specific provision of purified water might, additionally, play an important role in directing the evolution of enterically transmitted pathogens towards lesser virulence [53]. Political will and resources permitting, the UNMDG's target may well be reached. Even so, the population left without access to safe water will still remain considerable. It is within such populations that Python lurks, and at times rises up to wreak havoc.

ACKNOWLEDGEMENTS

The views expressed in this paper are the author's and do not necessarily represent those of the Centers for Disease Control and Prevention.

DECLARATION OF INTEREST

None.

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