to heroin prescription seem to often misunderstand existing clinical research, they more importantly seem to disregard the limitations of methadone maintenance and the subsequent individual’s health and community harms that happen when people discontinue methadone.

This state of affairs is sad because other medical specialties commonly embrace second-line therapies, even if only for a selected group who fail first-line treatments. In the era of evidence-based decision making, moving forward will probably need those embroiled in this debate to cast aside the stigma associated with heroin prescription, and recognise that the drug was once a pharmaceutical product with physiological and chemical properties similar to other opioids that are in common clinical use. The existing interference and non-evidence-based opposition from politicians and care providers, who refuse to acknowledge the limitations of methadone maintenance and the superiority of prescribed heroin in selected populations, is arguably unethical. Denying effective second-line therapy to those in need ultimately serves to condemn many users of illicit heroin to the all too common outcomes of untreated heroin addiction, including HIV infection or death from overdose.

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**Are we any closer to combating Ebola infections?**

In March, 2009, a scientist working in a high-containment laboratory in Germany pricked herself with a needle that had just been used to infect a mouse with the Ebola virus. Although rare, similar laboratory accidents with Ebola virus have been reported in the UK (1976), USA (2004), and Russia (2004), of which the one in Russia was fatal. Additionally, there have been at least three exposures to Marburg virus in laboratories, another member of the Filoviridae family, and again one of these exposures was fatal.

The incident in Germany once again caught the high-containment research community off guard because of the lack of prophylactic and treatment options in circumstances of exposure to highly pathogenic agents. This and previous incidents coincide with increasing filovirus outbreaks in Central Africa since the mid-1990s, with at least three imported cases of filovirus infection (South Africa, Netherlands, USA), of which one was fatal and one resulted in the death of an assisting medical worker.

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high-containment facilities and staff working in these facilities have increased the risk of potential exposures. The emergence and re-emergence of exotic and often highly virulent pathogens certainly justifies our attention, but also needs proper preparation to handle laboratory incidents and protect exposed populations in endemic areas, particularly family members, and medical and aid personnel.

Since the discovery of the Ebola virus in 1976, the research community has been active in developing treatments to counteract infections. Although there has been some success in vaccine development, development of effective treatments has been cumbersome.2 Thomas Geisbert and colleagues’ report in The Lancet today4 is long overdue and should be considered a milestone in what has been a difficult and frustrating specialty of filovirus research. The investigators improved their previously successful method of silencing the Zaire Ebola virus RNA polymerase L with small interfering RNAs (siRNAs) that protected guineapigs against lethal homologous challenge.5 Although rodents are valuable screening models for efficacy studies of filovirus drugs or vaccines, they often are not useful for prediction of the success in the gold-standard rhesus macaque model.6,7 Geisbert and colleagues used an siRNA targeting three genes of the Ebola virus (L, virion protein [VP] 24, and VP35) for postexposure treatment of macaques. Two groups of animals were intravenously injected 30 min after infection with a high challenge dose of Zaire Ebola virus followed by subsequent treatments on days 1, 3, and 5 (first group) or every day from days 1 to 6 (second group). The result was 66% and 100% protection, respectively—efficacies that had not been achieved previously.4

RNA interference as an effective treatment strategy to combat infection with Ebola virus is not novel and has been successfully applied in rodent models and for prophylactic treatment of non-human primates.12,13 Reliable delivery of the nucleic acid, however, has been a longlasting obstacle that obviously has been overcome by Geisbert and colleagues’ use of stable nucleic acid-lipid particles.4

Case management of Ebola virus is based solely on the principles of isolation and barrier-nursing procedures with mainly symptomatic and supportive treatment. Shock, cerebral oedema, renal failure, coagulation disorders, and secondary bacterial infection should be managed. There is no proof of any successful strategy for specific prophylaxis and postexposure treatment of Ebola-virus infections in human beings.10,11 The table summarises the most promising experimental approaches (postexposure). With the severe and rapid progression of this infection, combination therapy might be most beneficial, but proper efficacy studies are lacking.

On the basis of the success in non-human primate models, there were two promising experimental options for postexposure treatments that were offered to the German scientists: first, treatment with a nematode-derived anticoagulation protein,12 or second, treatment with a recombinant vesicular stomatitis virus expressing the Zaire Ebola virus glycoprotein,14 both of which have shown 33% and 50% efficacy, respectively, in postexposure treatment of rhesus macaques that were lethally infected with the virus. The second option was chosen in Germany in 2009. Other than initial unspecific mild symptoms (fever, headache, and myalgia), no adverse effects of the vaccination were reported. However, efficacy was hard to prove because we do not know whether infection had actually occurred.

The specialty of haemorrhagic viruses is in desperate need of approved countermeasures against Ebola-virus

<table>
<thead>
<tr>
<th>Antisense oligonucleotides</th>
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<th>Issues or concerns</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Phosphorodiamidate morpholino oligonucleotides</td>
<td>Yes (only pre-exposure)</td>
<td>Genetic variation, delivery</td>
<td>Warfield et al9</td>
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<td>Small interfering RNAs</td>
<td>Yes</td>
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<td>Geisbert et al4</td>
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<th>Coagulation modulators</th>
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<td>Tissue-factor-pathway inhibitors</td>
<td>Yes</td>
<td>Manipulation of coagulation</td>
<td>Geisbert et al12</td>
</tr>
<tr>
<td>Activated protein C</td>
<td>Yes</td>
<td>Manipulation of coagulation</td>
<td>Hensley et al13</td>
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<th>Postexposure vaccination</th>
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<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Vesicular stomatitis virus vectors</td>
<td>Yes</td>
<td>Genetic variation, safety</td>
<td>Feldmann et al17</td>
</tr>
</tbody>
</table>

*Only approaches that have shown in-vivo efficacy in macaque models are listed.

| Table: Promising treatment options for Ebola haemorrhagic fever* |
infections. To wait for the next incident to happen in a high-containment laboratory before any progress takes place seems intolerable. We also urgently need to improve outbreak support and go beyond transmission control, and actually provide specific care for affected individuals, which should be an ethical obligation for all of us. This provision can only happen in a timely fashion if existing experimental approaches, such as the siRNA strategy presented by Geisbert and colleagues, are investigated in clinical trials and are given at least approval as investigational new drugs that are ready to use in emergencies. Funding is needed, and could come from governmental and non-governmental agencies and industry.

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Age and the epidemiology and pathogenesis of tuberculosis

The mortality, morbidity, and disease diversity of tuberculosis varies substantially between different age groups (figure). These differences need clarifying because a better understanding of the immunological mechanisms underlying disease and protection are needed for rational vaccine design (see reference 4 and the review in this Series by Stefan Kaufmann and colleagues).

Disease risk after primary infection with Mycobacterium tuberculosis is greatest in infants (younger than 4 years), and declines slowly to a nadir at age 5–10 years. During adolescence (age 15–19 years), there is a rapid increase in risk with a second peak between the ages of 20–30 years. Age-related differences in disease risk are accompanied by differences in the response to infection and clinical features of disease. In early childhood, disseminated forms of disease, such as miliary tuberculosis and tuberculous meningitis, are common, and exuberant hilar lymph-node responses contribute to airway pathology. With increasing age, these features become less common, with a sudden shift in pathology noted during adolescence.

Tuberculosis at this stage shows features of so-called adult-type disease (previously called post-primary tuberculosis), the hallmark of which is tissue destruction and lung cavitation. Understanding the mechanisms that cause this sudden transition are fundamentally important because a better understanding of the immunological mechanisms underlying disease and protection are needed for rational vaccine design (see reference 4 and the review in this Series by Stefan Kaufmann and colleagues).

1 Tuffs A. Experimental vaccine may have saved Hamburg scientist from Ebola fever. 2009; BMJ 338 b2223.