effectiveness of muscle training, the trial also shows the potential for prevention of prolapse symptoms through lifelong attention to pelvic floor muscle exercise, and possibly intentional use of muscles to protect the pelvic floor during physical strain, such as that inflicted by heavy lifting. The results of this trial should encourage clinicians to refer women to physiotherapists, and to other health-care professionals who can implement behavioural and physical therapies for prolapse in a range of health-care settings.

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I declare that I have no conflicts of interest.

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Melioidosis: refining management of a tropical time bomb


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Burkholderia pseudomallei

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See Articles page 807

Melioidosis, dubbed the Vietnamese time bomb[1] after reports of lengthy disease latency in war veterans, is caused by *Burkholderia pseudomallei* and manifests as acute, subacute, or chronic disease. Bacteraemic disease especially when associated with pneumonia is the most lethal form, especially if associated with septic shock, but infection with or without abscess formation can occur in any organ system. Although most presentations occur soon after exposure, the organism's ability to evade host immune mechanisms and to survive and multiply in phagocytes[2] gives rise to latency—latency of up to 62 years has been reported.[3] Seroprevalence rates vary widely but are highest in northeast Thailand, where most children show evidence of exposure.[4] It remains unclear how many of those with serological evidence of exposure harbour latent *B pseudomallei* with the potential for subsequent activation. Several risk factors cause some people to have an increased risk of melioidosis, with diabetes being the most common.[5]

For those with culture-confirmed melioidosis, treatment recommendations include an initial intensive intravenous course of at least 10 days with ceftazidime or a carbapenem.[5] This course is followed by a so-called oral eradication phase of at least 3 months. The initial clinical response might indicate a need to modify the duration of the intensive phase, but the optimum antibiotic regimen and duration for eradication are uncertain. Recurrent melioidosis was noted in 13% of patients treated in Australia,[6] but its prevalence has fallen over the past decade, possibly attributed to improved compliance, choice, and dosing of antibiotic regimens.[7] Higher rates of recurrence in Thailand have been associated with inadequate duration of treatment.[8]

In *The Lancet*, Ploenchan Chetchotisakd and colleagues present findings from the MERTH trial,[9] in which they enrolled 626 patients with melioidosis, randomly allocating them to receive trimethoprim-sulfamethoxazole alone (the recommended regimen in Australia) or trimethoprim-sulfamethoxazole

plus doxycycline (the recommended regimen in Thailand). During follow-up, they recorded no between-group difference in the occurrence of culture-positive recurrent cases (16 in the single-drug group, 21 in the combination group; hazard ratio 0·81, 95% CI 0·42–1·55), suggesting non-inferiority of the single-drug treatment (p=0·01). Furthermore, toxicity was higher in the combination group.

The study's power calculations probably did not take into account the high rate of re-infection by a different genotype from the initial infection, rather than true relapse. Of recurrences with paired isolate typing undertaken (29 [78%] of 37 patients with culture-confirmed recurrent melioidosis), 15 (52%) were due to a different genotype, which is much higher than previous reports—in a study of 921 patients in which detailed typing was used to characterise paired isolates from relapse cases, 26% were shown to be new infections.[10] It is tempting to postulate that at least some of these re-infections were actually recurrence from an original polyclonal infection, but the pronounced difference in median time to re-presentation of 7 months (for relapse) versus 29 months (for reinfection) suggests otherwise. Previous work has also shown polyclonal infection to be a rare occurrence, happening in only 1·5% of patients.[11] Despite this unexpected finding, even a subgroup analysis of same-genotype relapses lends support to the investigators' conclusions.

MERTH had a treatment duration longer than generally recommended—20 weeks. Advocates of combination antibiotics for 3 months might therefore remain unconvinced without further research clarifying the optimum duration. However, several points support the study's findings. Doxycycline might antagonise the effects of trimethoprim-sulfamethoxazole in vitro.[12] Also, doxycycline monotherapy is associated with high rates of relapse.[13] For many years, single-drug treatment with trimethoprim-sulfamethoxazole has been used effectively as eradication treatment in Australia.[6] In view of the extended duration of eradication treatment necessary, compliance might be hampered by adverse events as reported in the combination treatment group in this trial. Patients in this group had a 40% rate of switching to second-line regimens due to adverse events.

B pseudomallei is an environmental saprophyte found in the soil and fresh surface water of tropical regions. Clinical trials in such settings are often difficult, meaning that conditions of treatment are necessarily real-world. Melioidosis endemicity has been reported in dozens of tropical regions and cases are also imported to non-tropical areas, but numbers are generally small. Adequately powered clinical trials can be done only in highly endemic areas such as Thailand, with support from international organisations experienced in clinical trials. It is a disease of major public health importance in northeast Thailand, and is possibly the third most common cause of death due to an infection after HIV and tuberculosis, accounting for roughly 20% of community-acquired bacteraemia.[5] The findings of MERTH should prompt a change in standard recommendations for the eradication treatment phase of melioidosis toward trimethoprim-sulfamethoxazole alone. However, many questions about optimum doses and duration remain, with some even suggesting that an extended intravenous phase might decrease the rate of relapse. Because *B pseudomallei* has such complex interactions with host immunity resulting in latency, diverse presentations, and high risk of disease relapse, future treatment guidelines might be equally complex and possibly stratified, related to disease site and severity, as well as host factors and initial treatment response.

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Safer countries through global health security

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Countries around the world face a perfect storm of converging threats that might substantially increase the risk from infectious disease epidemics, despite improvements in technologies, communication, and some health systems. New pathogens emerge each year, some of which have high mortality and the potential for efficient transmission—eg, severe acute respiratory syndrome (SARS),[1] Middle East respiratory syndrome coronavirus,[2] and avian influenza A H7N9.[3] Existing pathogens are becoming resistant to available antibiotics and several are now resistant to virtually all available treatment.[4] There is also the potential threat of intentional release of biological agents, which can be developed or synthesised biologically and disseminated at low cost and with little scientific expertise. Moreover, the accelerated pace of globalisation amplifies these risks: a disease is just a plane trip away, and an outbreak anywhere is a threat everywhere.

One of the primary responsibilities of any government is to protect the health and safety of its people. There are three key elements of health security: prevention wherever possible, early detection, and timely and effective response. Although many countries are now better able to manage infectious disease threats than in the past, these improvements have often been small in scale and limited in scope. The International Health Regulations (IHR), revised by WHO in 2005 to more directly address new and emerging epidemic threats,[5] require all 194 signatory countries to improve capacity in these and other areas as part of their commitment to protecting health.[6] Yet, at least 80% of countries did not report full IHR compliance by the 2012 deadline.[7]

There is a perception in some quarters that tackling epidemic threats is less important than addressing major killers, such as HIV, tuberculosis, and malaria, and that international efforts to stop outbreaks might be more in the interest of high-income than of low-income and middle-income countries.[8] In fact, epidemic threats are potentially devastating to development through economic dislocation, decreased productivity, avoidable medical costs, loss of revenues from tourism and travel, and negative incentives for investment. The effective implementation of measures to ensure global health security builds a firm, broad-based public health foundation that promotes country self-sufficiency and can sustain health progress in any area in which a country decides to focus. Most fundamentally, addressing epidemic threats saves lives.

Rapid progress in health security is feasible if there is high-level political motivation, adequate investment, and technical expertise. After the devastating impact of SARS in 2003, China launched an ambitious programme to improve detection of new threats, strengthen response capacity, and report more transparently. The number of influenza surveillance laboratories grew to more than 400, the Chinese National Influenza Center was designated as the world's fifth WHO Collaborating Centre for Reference and Research on Influenza,[9] the Chinese Center for Disease Control and Prevention (China CDC) was greatly strengthened with training of field epidemiologists and establishment of an Emergency Operations Centre, and mechanisms for rapid reporting to WHO were put in place. When the influenza A H7N9 virus began causing human illness in February, 2013, China was quickly able to identify and sequence the genome, and share the sequence globally within days of the first report, which enabled a rapid start on development of diagnostics and a vaccine.

Many countries have improved health security by preventing avoidable epidemics, detecting outbreaks