For clinicians, RESPITE encourages them to offer remifentanil PCA with the tested regimen to labouring women more readily than before, in case an effective, non-neuraxial analgesia method is sought. For researchers, there are ample opportunities to add to the body of evidence in distinct cohorts of patients and to assess the safety of this relatively new method on a broader basis, thus getting a clearer picture of the added value and the presumably most beneficial indication of remifentanil PCA in providing effective labour analgesia.

Finally, we are convinced that in an event that is heavily influenced by the variety of opinions regarding the ideal personal way of giving birth, agreement on the ultimate labour analgesic that fits both the expectations of the individual mother and also the caregiver remains unattainable. Accepting this dictum could mean that a definite answer might only be found for distinct cohorts of patients that share the same mindset. Nonetheless, in offering unbiased information according to preference, RESPITE is an important step in the right direction.

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Addressing the global challenge of snake envenoming

Joshua Longbottom and colleagues1 highlight once again that snake envenoming is a major health issue affecting remote and rural regions of the tropics. They use information about venomous snake distribution, health-care access, and availability of antivenom to identify the most vulnerable populations to snakebite. This modelling study1 reported in The Lancet identified about 92·66 million people living in regions vulnerable to snakebite, including sub-Saharan Africa, southeast Asia, and Indonesia. The major limitation of Longbottom and colleagues’ study1 is that they do not report actual snakebites—making a number of assumptions, such as different venomous snakes and different human populations living together. This assumption results in the same risk of snake envenoming across different geographical regions, which is unlikely to be true. They also used a Nigerian retrospective observational study,2 with more than 90% of bites from Echis ocellatus (saw-scaled viper), in which deaths are due to coagulopathy and bleeding, to estimate the effect of delay to antivenom on mortality. The effectiveness of antivenom is highly species specific and different for neurotoxic envenoming,2 and cannot be administered early enough to prevent early prehospital deaths from cardiac arrest.4 Reassuringly, Longbottom and colleagues identified the same geographical regions as did a previously published global study of snakebites, which reported between 421 000 and 1 841 000 additional envenomings occurring annually, and 20 000–94 000 deaths.5

15 years ago, Lalloo and colleagues6 called for the global health community’s attention to the problem of snake envenoming in Africa, highlighting the high cost and paucity of antivenom and the socioeconomic burden of snake envenoming. They stated the urgent need for research on the burden and economic effect of
snake envenoming, and the need to improve antivenom development and supply to Africa.

What progress has been made since then? In 2017, WHO categorised snakebite as a high-priority neglected tropical disease, and in May, 2018, WHO resolved to decrease the morbidity and mortality of snake envenoming, and “coordinate global efforts to control snakebite”. Although acute effects of snakebites are relatively well understood, morbidity and cost associated with long-term effects are poorly studied globally. Many snakebite survivors, once treated for acute illness, are never followed up. Recent research has provided good evidence for the psychological and economic burden of snakebite. For example, patients with snakebites in Sri Lanka have symptoms of depression and post-traumatic stress disorder, and 10% did not return to work, which is a substantial economic burden to the country.

Antivenom was first developed in the 1890s, along with the tetanus vaccine. Vaccines have been one of the greatest successes in public health, resulting in the eradication of some diseases and substantial reductions in morbidity and mortality. By contrast, there is a crisis for antivenom supply, and technology not dissimilar from early vaccines is still used to manufacture antivenom. Human monoclonal antibodies are the future for cancer treatment, but poorly purified equine polyclonal antibodies to treat snake envenoming still exists with high rates of adverse reactions.

There continues to be a paucity of evidence to support antivenom effectiveness for snake envenoming. This doesn’t mean antivenoms are ineffective as they bind to snake toxins in vitro. However, research must provide scientific and clinical trial evidence that antivenoms are clinically effective, because they can cause anaphylaxis and are expensive. More importantly, there is a need to identify for which snakes, what types of toxin effects, and what period of time antivenom will be effective.

It is clear that the earlier antivenom is administered, the more effective it is in preventing toxin effects and potentially reversing some effects. To make early administration possible, there must be immediate access to antivenom, requiring increased production, and bedside diagnostic testing to identify envenomed patients. With training and standardisation, whole blood clotting testing appears to identify coagulopathy in 80% of viper-envenomed patients. Simpler tests with greater diagnostic accuracy, which can also identify all forms of envenoming (eg, neurotoxicity), are required. Testing for common snake enzyme activity is one potential way forward, and the almost ubiquitous group of snake toxins, phospholipase A₂, might prove useful.

15 years on and progress is being made to improve the treatment of snake envenoming. As the Longbottom and colleagues’ study confirms, there is a clearer picture of the most vulnerable regions and the overall social and economic burden. Going forward, there is a need to increase research efforts and funding into improved, safer, and more universally available antivenoms. Finally, research must also now focus on prevention of snakebite, a neglected aspect of decreasing snakebite burden.

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We declare no competing interests.

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1 Longbottom J, Shearer FM, Devine M, et al. Vulnerability to snakebite envenoming: a global mapping of hotspots. Lancet 2018; published online July 12. http://dx.doi.org/10.1016/S0140-6736(18)31224-8
2 Habib AG, Abubakar SB. Factors affecting snakebite mortality in north-eastern Nigeria. Int Health 2011; 3: 50–55
3 Silva A, Maduwage K, Sedgwick M, et al. Neuromuscular effects of common krait (Bungarus caeruleus) envenoming in Sri Lanka. PLoS Negl Trop Dis 2016; 10: e0004368
4 Johnston C, Ryan NM, Page CB, et al. The Australian snakebite project, 2005–2015 (ASP-20). Med J Aust 2017; 207: 119–25
5 Kasturiratne A, Wickremasinghe AR, de Silva N, et al. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. PLoS Med 2008; 5: e218
6 Laloo DG, Theakston RD, Wallea DA. The African challenge. Lancet 2002; 359: 1527–29
7 Williams SS, Wijesinghe CA, Jayamane SF, et al. Delayed psychological morbidity associated with snakebite envenoming. PLoS Negl Trop Dis 2011; 5: e1255
8 Koff WC, Burton DR, Johnson PR, et al. Accelerating next-generation vaccine development for global disease prevention. Science 2013; 340: 1232910
9 Wagstaff SC, Lai K, Theakston RD, Papapetrides C, Harrison RA. Bioinformatics and multiplexed DNA immunization to design rational snake antivenom. PLoS Med 2006; 3: e184
10 Yang Y. Cancer immunotherapy: harnessing the immune system to battle cancer. J Clin Invest 2015; 125: 3335–37
11 Stone SF, Isbister GK, Shahmy S, et al. Immune response to snake envenoming and treatment with antivenom; complement activation, cytokine production and mast cell degranulation. PLoS Negl Trop Dis 2013; 7: e2326
12 Maduwage K, Buckley NA, de Silva H, Laloo DG, Isbister GK. Snake antivenom for snake venom induced consumption coagulopathy. Cochrane Database Syst Rev 2015; 6: CD011428
13 Isbister GK. Antivenom efficacy or effectiveness: the Australian experience. Toxcol 2010; 268: 148–54
14 Ratnavage I, Shihana F, Dissanayake DM, Buckley NA, Maduwage K, Isbister GK. Performance of the 20-minute whole blood clotting test in detecting venom induced consumption coagulopathy from Russell’s viper (Daboia russelii) bites. Thromb Haemost 2017; 117: 500–07
15 Maduwage K, O’Leary MA, Isbister GK. Diagnosis of snake envenoming using a simple phospholipase A, assay. Sci Rep 2014; 4: 4827