# Debate-Pro: manufacturers should assess the long-term stability of their antivenoms

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There is evidence that the actual shelf lives of some drug products are greater than their labelled expiration dates. When transported and stored correctly, many products have been found to remain stable for several months or in specific cases even years after reaching their labelled expiration date. In the USA, a shelf-life extension programme has been developed to generate stability data beyond labelled expiration dates.[1]

In their *EMJ* paper, Soopairin *et al* systematically review existing preclinical and clinical data on 20 different antivenom products after they have expired.[2] They find some evidence that antivenoms maintain preclinical efficacy for a considerable amount of time after the labelled expiration date. There is, however, much less evidence on safety and clinical effectiveness of expired antivenoms.

Not all antivenom products have the same stability profile, if only because some are lyophilised while others are liquid. The ad hoc batch-specific data reviewed by Soopairin *et al* should first and foremost be considered as a call for action for antivenom manufacturers to systematically undertake an assessment of the long-term stabilities of their products, including a thorough evaluation of their maintained safety, with the potential objective to extend and maximise their labelled shelf lives. The data, although incomplete, could also be helpful for national regulatory drug authorities to conduct a benefit-risk analysis and make informed decisions on a case-by-case basis about exceptional off-label use of expired vials, when non-expired antivenoms are unavailable. Obviously, use of expired antivenoms should be the exception, not the rule. It should not stop our collective efforts to build stronger supply chains and reduce risks of stockouts of non-expired antivenoms.

Situations of antivenom shortage are, however, sadly not uncommon. Antivenoms are complex bespoke biotherapeutics derived from the plasma of horses that have been immunised with selected snake venoms. The antivenom market is fragmented into multiple subregional markets, according to the local distribution of venomous snake species. Most antivenom producers around the world are small public companies focusing on serving their national needs. Under these circumstances, it is not unusual that only one single source of nationally specific antivenom product is available in a given country.[3] Temporary suspension or definitive discontinuation of production by its supplier can then lead to a situation of shortage, as illustrated in 2023 by a country-wide shortage of the locally produced antivenom in South Africa.[4] Under such circumstances, expired vials and ampoules, if available, could represent an exceptional therapeutic stopgap measure, if there are data to support that case. This is exactly what happened after Wyeth, in 2008, discontinued the production of its antivenom against the coral snake species endemic in the US territory; since then, based on reassuring ad hoc extended stability data, the US Food and Drug Administration has prolonged on several occasions the expiration dates of the known remaining vials.[5]

Finally, the encouraging long-term stability data for antivenom products justify calling for similar assessments for other antisera derived from equine hyperimmune plasma. Manufacturers of that class of biotherapeutics, under the supervision of their national regulators, should investigate the extended stability of their products. Equine diphtheria antitoxin (eDAT) used to treat diphtheria is an excellent example. Major diphtheria epidemics are rare, but when a large multicountry outbreak occurs, as is the case right now in West Africa, it may be severe enough to exhaust the existing stockpile of eDAT.[6] Storage of expired vials during interepidemic periods could represent a stopgap solution in preparedness for a possible major shortage during the next big multicountry outbreak of the disease, should the long-term safety and potency of expired eDAT products be proven.

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## REFERENCES

1 Lyon RC, Taylor JS, Porter DA, *et al*. Stability profiles of drug products extended beyond labeled expiration dates. *J Pharm Sci* 2006;95:1549–60.
2 Soopairin S, Patikorn C, Taychakhoonavudh S. Preclinical testing of expired Antivenoms and its uses in real-world experience: a systematic review. *Emerg Med J* 2024.
3 Potet J, Beran D, Ray N, *et al*. Access to antivenoms in the developing world: a multidisciplinary analysis. *Toxicon X* 2021;12:100086.
4 Ellis E. Grave warnings from snakebite experts as minister of health is asked to intervene in antivenom crisis. 2023. Available: https://www.dailymaverick.co.za/article/2023-04-05-grave-warnings-from-snakebite-experts-as-minister-of-health-is-asked-to-intervene-in-antivenom-crisis/ [Accessed 24 Jan 2024].
5 Hessel MM, McAninch SA. Coral snake toxicity. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2024. Available: https://www.ncbi.nlm.nih.gov/books/NBK519031/ [accessed 17 Feb 2024].
6 Balakrishnan VS. Diphtheria outbreak in Nigeria. *Lancet Microbe* 2024;5:e11.