

COVID-19's Impact on The Sustainability of the LAL Supply and Horseshoe Crab Population

Brett Hoffmeister

*LAL Manufacturing Manager
Associates of Cape Cod, Inc.
East Falmouth, MA*

Allen L. Burgenson

*Lonza
Testing Solutions Global SME
Marketing-CDMB
Walkersville, MD*

John Dubczak

*Executive Director of Reagent Development
and Pilot Plant Operations
Charles River Laboratories Charleston, SC*

The COVID-19 virus has been impacting humans worldwide for nearly a year at this writing. Over this time there was a great deal of speculation regarding how the pandemic and vaccine production to combat the virus would affect the production of LAL, and possibly outstrip naturally sourced LAL availability. There was also speculation regarding the impact the potential increase in demand of LAL might have on American horseshoe crab populations. Multiple vaccines have been approved and millions of COVID-19 vaccines have been produced and are being utilized to inoculate human beings around the world. Not a single dose has been delayed because of insufficient LAL supplies to vaccine manufacturers. Vaccine production is underway with more expected to be released for use in the very near future. As representatives of LAL manufacturers, we wish to assuage concerns and provide assurance that the demands of LAL testing in support of COVID-19 vaccines doesn't adversely impacts its production, nor does it put product availability or the American horseshoe crab population at any increased risk.

Limulus Amebocyte Lysate (LAL) is a reagent produced from the white blood cells of the Atlantic horseshoe crab (*Limulus polyphemus*), which is utilized by pharmaceutical and medical device manufacturers in an FDA-mandated Bacterial Endotoxin Test (BET). Past and recent articles have given voice to concerns about the availability of the LAL supply to accommodate large scale vaccine testing. Other media suggest that single source-reliance on one species is an untenable risk with some have going so far as to suggest that LAL manufacturing jeopardizes the horseshoe crab population. The media attention has provided renewed opportunity for some to recirculate inaccurate and misleading information to the public about the impact of biomedical uses of horseshoe crabs and the status of the crab population in the US. It is important to have a discussion of the relevant factors involved. By reviewing some of the questions and issues recently expressed by the media and other platforms, we wish to educate the reader on the facts.

Is LAL-based product availability particularly fragile or easily interrupted by natural or manmade events?

No, the LAL industry has been manufacturing for over 40 years with no significant interruption of services resulting from hurricanes, floods, blizzards, oil spills, or other disasters. LAL manufacturers are geographically diverse, located along the East coast of the US: Associates of Cape Cod Inc. (Massachusetts), Charles River Laboratories (South Carolina), Lonza (Maryland) and Wako Chemicals (Virginia). This large geographical footprint helps avoid a natural or manmade disaster from interrupting product availability. LAL manufacturers all operate with contingency plans in place, and maintain inventory needed to meet customer demands. Millions of LAL

tests are performed annually. Production of COVID-19 vaccines is underway around the world and serves as a good example of the robustness of the LAL Bacterial Endotoxin Testing supply chain.

This is what we do.

Are horseshoe crabs endangered?

No. It is the duty of US Fish and Wildlife Service (FWS) to determine if an animal in the US is “threatened” or “endangered.” The FWS has made no such claims to the status of the American horseshoe crab. They are not endangered; in fact, it’s estimated that there are tens of millions of adult crabs in the Delaware Bay region alone.¹ In many areas, populations are growing considerably. However, in other parts of the world, horseshoe crabs are not so closely monitored. *Tachypleus tridentatus*, found in Southeast and East Asia, for instance, is used as food, fertilizer, and manufacturing for chitin and its LAL equivalent, TAL. In the US, American horseshoe crab harvest is regulated by state agencies and the Atlantic States Marine Fisheries Commission (ASMFC), which oversees the coast-wide fishery.

The ASMFC is made up of members from the US Fish and Wildlife Service, academia, fisheries managers, statisticians, scientists, and representatives of industry, government, and others who work to regulate horseshoe crab fisheries and monitor populations on the East Coast of the United States. Current management of the fishery is robust, and science based. The most recent benchmark stock assessment (2019) determined the overall number of American horseshoe crabs appears to be stable and is increasing in some areas.¹⁻³ It is reasonable to say that there may be more horseshoe crabs today than there have been for decades.

Does biomedical use of horseshoe crabs threaten the population?

The simple answer is no. The data show clearly that even a complete cessation of the biomedical fishery would have a minimal impact on the overall fishery mortality of horseshoe crabs. In fact, the population is so healthy that there is a coast-wide quota, to be lawfully harvested for bait, of nearly 1.6 million crabs. Actual landings based on

market demand and state regulations are far less than that, at approximately 800,000 crabs annually. The biomedical mortality is roughly 10% of that of the bait industry.¹

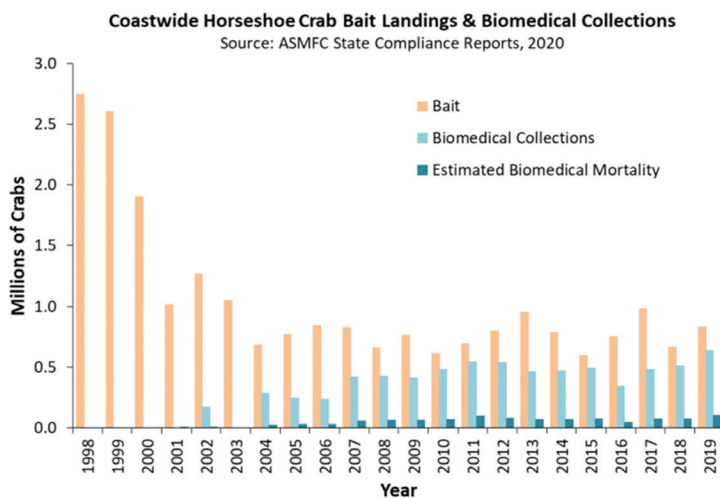
The 2019 stock assessment by the ASMFC states that the biomedical use of crabs has no impact on the population in the Delaware Bay region.¹ It is estimated that there are tens of millions of horseshoe crabs in the Delaware Bay region alone.⁴

It should be noted that in the areas where collection for LAL manufacturing exists, horseshoe crab populations are doing quite well and are stable and/or increasing. A recent study of nearly 175,000 crabs of which 68,000 were bled at LAL manufacturers over multiple seasons showed that long-term survival of those crabs, over multiple years, was as good or better than the survival rates of un-bled crabs.¹

Will COVID-19 vaccine production threaten the population of HSC because of increased need of LAL?

No. The LAL test is an important quality control measure, required by law, for anything injected or implanted into the human body. It is already used millions of times annually on raw material, intermediates, and final products. It is important to note that a very small amount of LAL is needed to perform these tests. Modern pharmaceutical manufacturing has significant scalability throughout the industry. It takes roughly the same amount of LAL to test 1,000 doses as it does to test 100,000 doses. This serves as a reminder that even a high and unexpected demand for vaccines and medical products can be managed with the proper safeguards and planning that are in place.

The demands of BET testing materials worldwide can and are being absorbed with available inventory and without significant negative impact on the pharmaceutical industry or supply chain. This ability to scale up production of pharmaceuticals alleviates any sudden and unexpected increase in testing demands and need for significant increases in LAL inventory. There is no



* Biomedical collection numbers, which are annually reported to the Commission, include all horseshoe crabs brought to bleeding facilities except those that were harvested as bait and counted against state quotas.

* Most biomedical crabs collected are returned to the water after bleeding; a 15% mortality rate is assumed for all bled crabs that are released. This number plus observed mortality reported annually by bleeding facilities via state compliance reports is noted in the above graph as 'Estimated Biomedical Mortality.'

Figure 1.

significant increase in the use of horseshoe crabs and no threat to the population because of COVID-19 vaccine production.

What are the threats horseshoe crabs face today?

According to the 2019 ASMFC Stock Assessment report, the following are the major sources of horseshoe crab mortality:

- Bait Harvesting
- Bycatch from other fisheries
- Loss of habitat due to erosion prevention measures (riprap, seawalls, etc.), and human encroachment on spawning grounds
- Stranding after spawning (estimated 10% mortality of entire Delaware Bay population, annually)

Like any sea creature, horseshoe crabs are dependent on a suitable environment where they can live and reproduce. Water quality is an important factor as is having suitable beaches in which to lay their eggs. Fertilizers, septic systems, and other forms of pollution can greatly reduce the quality of water the crabs depend on. Sea walls, rip-rap, and jetties can manipulate the natural movement of sand on beaches and affect spawning habitats. Beach nourishment, the practice of bringing in truckloads of sand to beaches to replenish what's lost, or make them look nice, can bury millions of eggs before they hatch if not carefully planned. We all have a part in protecting this valuable resource.

Is there any oversight of the manufacturing and collection processes?

Yes, LAL manufacturing is a highly regulated/audited and complex process that provides a critical lifesaving assay for the pharmaceutical and medical device industry. Manufacturers are regulated by the Food and Drug Administration (FDA) and must comply with strict regulatory standards to certify product quality, efficacy, and safety. In addition, routine audits of the process are conducted by the FDA, the International Organization for Standardization (ISO), fisheries managers, and customers. Fishers collecting crabs for LAL manufacturers are mandated to follow local regulations as a condition of permitting. In 2011, the ASMFC partnered with LAL manufacturers, citizens groups, fishers, and dealers to document industry best management practices (BMP). Many of these practices, such as a swift return to the water and careful handling practices, have been in place by manufacturers for over 40 years, and help to ensure quality product while minimizing the impact on the individual crabs. This in turn helps ensure survivability of the animal and the population. In most East Coast states there are regulations in place that help to protect the HSC populations.

What do LAL manufacturers do to support conservation?

LAL manufacturers have practiced conservation measures since the beginning of this process, long before regulatory bodies began managing the fishery. In addition to the decades-long catch and release policy, LAL manufacturers work closely with fisheries managers and have members on the advisory panel of the ASMFC. They have helped or initiated conservation measures such as closing areas to bait fishing,

participating the "rent a crab" program, which utilizes crabs from the bait industry, and supporting quotas and size limits. They support and have initiated aquaculture of HSC for release to the wild. LAL manufacturers financially support organizations such as The Ecological Research & Development Group (ERDG), aquariums, and the Virginia Tech trawl survey. Volunteers participate in spawning surveys, tagging studies, and the "Just Flip Em" campaign, which saves thousands of crabs each year. Many employees also routinely work with universities, schools, and citizen groups helping to increase public awareness and educate people about these remarkable animals.

Conclusion

The proposition that populations of horseshoe crab are declining because of their use in biomedical testing ignores the fact that there is a healthy and stable population of crabs in the US and that the impact of the LAL industry is minimal. The Review Panel consisting of representatives from academia, the National Marine Fisheries Service, and the Maine Department of Marine Resources, agreed with the ASMFC assessment team's approach, but noted:

...some covariates such as season of harvest, size/condition of crabs, and location that are worth investigating. However, additional data and analyses are not likely to significantly alter assessment results due to the modest magnitude of biomedical mortality. As such, while an uncertainty, the biomedical mortality rate should receive less focus in future assessments.

In conclusion it is reasonable to state that the horseshoe crab population in the US is viable and healthy, the biomedical industry does not impact this population negatively, and the supply of LAL is also robust and healthy. Alarmists who suggest otherwise do so by ignoring the scientific facts and without any true knowledge of the LAL industry, the horseshoe crab fishery, or population data.

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