Vaccines for a more sustainable future

Climate change is upon us, and we don't have to look far to find its fallout. Summers are warmer, sea levels are rising and it's almost impossible to look at the news without encountering a new case of severe weather damage. Heat waves, storms, floods, and wildfires are occurring more often - and with greater intensity. Global temperatures have steadily been climbing and are up to 1.2°C higher than at the end of the 19th century. In fact, 2022 was the hottest summer and second warmest year ever[1].

Clearly, we can't look away. We must act, but how?

The challenge of protecting our planet goes beyond the climate to nature. Recently, G7 leaders announced that "our world must not only become net zero, but also nature positive, for the benefit of both people and the planet.[2]" A nature positive approach enriches the resilience of our planet and societies. This disruptive idea forces us to think differently about our place in the world.

Nature is the backbone of our universal well-being and has inextricable ties to our economic foundation[3]. When we continually tap into these resources in an unsustainable way, we will inevitably run out. This will have dire consequences for the systems we've built that depend on them. We need collective action and dual focus to stabilise the climate and preserve our natural resources for our common future, particularly as our global demographics continue to shift due to population ageing and overall growth.

Ten percent of our growing global population is over 60 years old[4]. This worldwide trend presents an important opportunity for

sustainable development. The changing landscape of our society relies on active participation from older generations. We must prepare for the social and economic transformations associated with ageing, developing the necessary conditions to enable these generations to lead self-determined, healthy lives. For this, we rely on fundamental shifts in policy and universal attitudes to older persons and their part in society. Luckily, the global community is reacting.

Recognising the need for dramatic change to slow this trajectory, the United Nations adopted 17 Sustainable Development Goals (SDGs) in 2015, as a universal call to protect the planet, end poverty and ensure that all humans enjoy peace and prosperity by 2030[5]. The 17 SDGs are interlinked, emphasising the importance of addressing them all.

The third UN SDG describes how good health is pivotal to sustainable development. As the global population continues to rise, and as we're all living longer, it's important to ensure good health continues in our later years. Preventative care is one of the best ways to support this reality. A continual threat is the burden of infectious diseases: millions of lives are lost to diseases that are largely preventable. Global immunisation is the key. That's where vaccines get to work. Vaccines are not only protecting us from direct pathogens, but also paving the way for a more sustainable future.

How vaccines promote planetary health and sustainability

Major historical events have evidenced the criticality and importance of vaccines for global health. Vaccines have helped prevent cervical cancer in women, as well as reduce pneumococcal and meningococcal diseases in children, and edge us closer to eradicating polio. Since 1988, the number of children affected by polio has reduced by 99 percent[6]. Thanks to the measles vaccine alone, 23 million deaths were averted between 2010 and 2018[7]. Meanwhile, more recently, the significance of vaccines was crystallised during the COVID-19 pandemic, whereby vaccines averted 20 million deaths, saved the global economy trillions, and helped restore free movement in society[8]. Vaccination has enabled us to prevent over 20 life-threatening diseases. This means more people are living longer, healthier lives.

However, political, economic, and cultural hurdles have meant that many are losing out on vaccinations. In 2020, 22.7 million children missed basic vaccines – almost 4 million more than the year before[9]. Much of this is attributed to the repercussions of the pandemic, with countries falling backwards on other vaccinations. Not only does this widen the inequalities in vaccine access, but it also leaves certain populations more vulnerable to future threats. For instance, WHO reported that only 82% are now fully vaccinated against DTP (diphtheria, tetanus, and pertussis) in the Americas, down from 91% in 2016[10].

The types of vaccines we use are equally important as our access to them. Sustainable vaccine development relies on access to a diverse, strong range of technologies such as live-attenuated, inactivated, subunit, and RNA-based vaccines. In this way, we can create new vaccines that tackle different antigens and diseases, protecting even more people against conditions that can otherwise be very difficult to treat.

Still, there's another piece of the puzzle. Vaccine development is a complicated, time-intensive process. Once a winning formula is made - and passes through the various intensive stages of clinical approval - it's important to ensure it continues to be available and isn't delisted due to the lack of commercially available sustainable ingredients. This is why designing vaccines using sustainable ingredients is critical. Sudden surges in demand could quickly lead to shortages, bringing consequences that would derail our vaccine access a decade or two from now. Given the long development pipelines waiting until then to find sustainable alternatives will be too late.

Vaccines are a key tool for protecting the planet and meeting our sustainability goals. The responsibility is on us all to not only select sustainable ingredients, but to secure supply chains and sources that will not deplete in the future. It's therefore essential that our efforts are prioritised, to help ensure that everyone gets the vaccines they need.

Emerging technologies

Key formulation ingredients increase the likelihood of vaccine success. For example, modern vaccines often incorporate adjuvants and adjuvant systems, which are ingredients that are used to help induce a stronger immune response. Adjuvants can amplify vaccine efficacy by helping to raise an early, long-lasting, and efficient immune response to a vaccine. In turn, this can provide significant protection against the disease being targeted. When combined with immunostimulatory molecules, the resulting adjuvant systems can help reach the same level of immune protection with fewer injections or a lower dose than when vaccinating with the non-adjuvanted antigen alone. Adjuvant systems stimulate immunity at various stages of the immune response, for instance, by activating chemokine signalling and targeting specific types of immune cells, such as dendritic cells and T-helper cells (typically Th1, Th2, or others).

However, some vaccine formulations do not result in optimal antigen delivery and presentation, reducing vaccine efficacy as a result. Thus, a diverse repertoire of adjuvant systems is necessary to create better vaccines. Modern vaccine development is focusing on discovering and incorporating new adjuvants to help address those countless conditions without current vaccine solutions. Establishing new adjuvants empowers us to achieve new pathways of immunisation that unlock new therapies – and therefore help even more people. As ongoing research continues to establish a more extensive portfolio of adjuvant system technologies, this enables us to not only address more diseases, but helps us also potentially improve the efficacy of existing vaccines.

Aluminium salts are the most well-known and widely used class of adjuvants. Generally referring to aluminium phosphate and aluminium hydroxide, they adsorb the protein antigen and mediate its presentation to innate immune cells[11,12]. Certain oil-in-water emulsions (eg. MF59 and AS03) mediate local inflammatory responses[13]. Saponin-based adjuvant systems, including Matrix-M and QS 21, offer multiple effects that support humoral and cellular immune responses[14]. Certain components such as squalene are used in combination with surfactants in specific adjuvant formulations. Meanwhile, neo-antigen vaccines that tackle cancer are being explored as therapeutic vaccines using the CAF family of adjuvants, such as CAF09b.

Scientists and vaccine manufacturers are continuously innovating to expand the repertoire of available adjuvant options. While we work to discover novel adjuvant formulations, we must use existing options responsibly. The SBTN (science-based targets for nature) high impact commodity list has highlighted the need for more awareness around the material impact on nature of certain supply chains. The use of raw materials derived from these commodities as key ingredients in vaccines will, in the future, need to be better understood and managed by raw material suppliers, adjuvant producers, and vaccine developers.

Beyond this, as we'll share below, the use of some of the most prominent and promising components, saponins and squalene, has been affected by other sourcing challenges – once again highlighting the need for sustainable supplies.

Saponins: sustainable sourcing from tree bark

Saponins, coined from the Latin word *sapo* (meaning soap), are plant-derived chemicals with the ability to form foams in water[15]. They have primarily been sourced from *Quillaja saponaria* Molina, a type of tree known for its saponin-rich bark. Otherwise called quillay trees, they are commonly found in Chile and other parts of South America.

Traditionally used as foaming agents, *Quillaja* saponins are also used in cosmetics, food products, and vaccines. Their strong immunostimulatory activity, and capacity to stimulate both cell-mediated and humoral immunity, have led to their popularity as vaccine adjuvants.

Quil-A is a crude quillay extract containing a heterogeneous mix of over 100 saponin components that is exclusively used in veterinary vaccines. To make the most of its potent immunogenicity, a purified fraction of Quil-A was created to be used in human vaccines. Known as QS 21, this adjuvant has recently been the subject of multiple success stories in the pharmaceutical industry, as a component of vaccines against shingles and malaria – the world's first!

This has inspired a new wave of increasing interest and put a spotlight on a looming shortage. For decades, Chile has been harnessing quillay trees to meet demand and deliver exports. However, these trees only yield bark with economic and clinical merit when they are over 25 years of age[16]. This has led to subsequent ecological damage and stricter regulations. Chilean law prohibits the deforestation of *Quillaja saponaria*. Thus, special permits are required to cut down the trees[17]. Since landowners are allowed to prune 35% of their biomass every five years, the market is moving away from bark to biomass.

Although bark extract still exists, quantities are reducing, access is limited, and prices are rising[18]. These limitations are having an immediate effect on vaccine access: it has been reported that waiting times for shingles vaccines using QS 21 in their formulations can even exceed a year[19].

Deforestation has a dramatic effect on nature, and the cascading threat of consequences must be prevented to preserve and protect our planet. Thus, it is critical that we find alternative technologies and sustainable solutions.

To address this, biotech corporations like Desert King and Botanical Solution Inc. (BSI) are pioneering innovations in the field. Desert King has cultivated their own bark-enrich quillay trees that generate greater yields and are naturally more sustainable. Meanwhile, BSI has developed a patented R&D platform based on plant tissue culture that is able to create sustainable botanical products. One of these is ABM-01, based on *Quillaja spaonaria*, which is planned to act as a replacement in the production of QS 21. In this way, a scalable and truly sustainable supply of QS 21 is possible, helping create the next generation of adjuvants in vaccine development.

Squalene: from shark oil to a sustainable source

Squalene is an organic compound with powerful bioactive properties[20]. As a naturally occurring oil, it has been used in skincare products, and cosmetics, as well as in various vaccine adjuvant formulations. For instance, the squalene-based emulsions MF59, AS03, and AF03 have been successfully utilised in flu vaccines, helping initiate potent innate and adaptive immune responses[21]. Developing effective flu vaccines is an ongoing challenge, given that reduced potency has been demonstrated in certain demographics, such as the elderly and young children, and that their success depends on how well the vaccine strains match those circulating during the season[22]. History has shown us how the influenza virus can rapidly turn pandemic, highlighting how imperative it is to have a repertoire of efficacious vaccines on hand. Clearly, components like squalene can be valuable in vaccine development. This interest has shed light on the need for alternative and more sustainable sources that can consistently meet demand.

Squalene is found in most living microorganisms – but in very trace amounts. Sharks are an exception. Sharks store most of their lipids in their livers, the majority of which is made up of squalene. Harvesting squalene from shark liver oil is a relatively straightforward process – a single distillation – such that this has become the predominant source. However, there are dramatic environmental

consequences. Oceanic shark populations have dropped by 71.1% from 1970 to 2018[23]. In fact, half of oceanic shark species are now endangered[24]. Sourcing shark liver oil is furthering this state of peril. Not only is this threatening shark populations, putting pressure on their already long reproductive cycles, but it also means that squalene is in short supply.

This has inspired the search for sustainable alternatives. Some organisations are advancing plant-derived squalene, such as that made from amaranth. Meanwhile, Amyris, a biotech company focused on clean chemistry, uses fermentation to ensure high purity for their pharmaceutical-grade squalene. Using yeast isoprenoid pathway engineering, their sugar-derived squalene is molecularly identical to that harvested from sharks.

Creating the sustainable vaccines of tomorrow

Sustainability is a challenge that needs to be at the forefront of R&D for vaccines today. The threat is two-fold: overlooking the importance of prioritising sustainable supplies can affect our access to existing vaccines – through depleted sources and unreliable supply chains – and put future vaccines at risk for decades to come. The time it takes for vaccines to be market-ready means that every delay in developing new sustainable ingredients will lead to significant repercussions for the health of subsequent generations. Failing to act now threatens our vaccine access and technologies – effects that will only truly crystallise after the 10 to 20-year-long development pipelines.

Success in this realm relies on global collaboration. Thus, investment in worldwide vaccine R&D, to develop better vaccines – for known diseases, new vaccine platforms, and potential pandemic threats – must be prioritised. By supporting high-quality sustainable vaccine production in local communities and countries of different means, we can strengthen the overall vaccine landscape. Our health security depends on solutions that are not only sustainable, but also adhere to good manufacturing practices (GMP) standards.

The vaccines of tomorrow revolve around sustainable supply chains and access to scalable commercial supplies that do not put undue pressure on the natural environment. It is our responsibility to future-proof vaccines by focusing on longevity in our processes. With combined global efforts, we can enhance the global health infrastructure, leading us to develop better vaccines against more diseases and supporting our preparedness for future outbreaks.

We believe that global collaborations are the cornerstone of creating a greener planet. Let's do all we can today, to generate a sustainable future we're proud of.

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ABOUT CRODA

At Croda, we are committed to using our smart science to promote healthy lives and well-being through the development and application of our ingredients and technologies, most notably with our excipients and vaccine adjuvants in the development of novel vaccines.

By being the most sustainable supplier of innovative ingredients, we will provide solutions to some of the world's biggest challenges while helping our customers achieve their sustainability goals.

In 2022, Croda announced our ambition to be Net Nature Positive by 2030. Guided by the principles set out by the Science Based Targets for Nature (SBTN) we are working to better understand the ways that our manufacturing sites, raw materials, and finished ingredients impact or depend upon biodiversity and nature, including prioritising those materials on the High Impact Commodity List.

Croda's partnerships with Amyris and BSI will expedite the commercial availability of squalene and QS 21, and are two examples of putting our commitment, to be Climate, Land, People, and Nature Positive by 2030, into action. We are excited to be able to offer sustainably sourced squalene and saponins soon.

Change happens when we each take small steps forward and do the best we can – with the planet in mind.