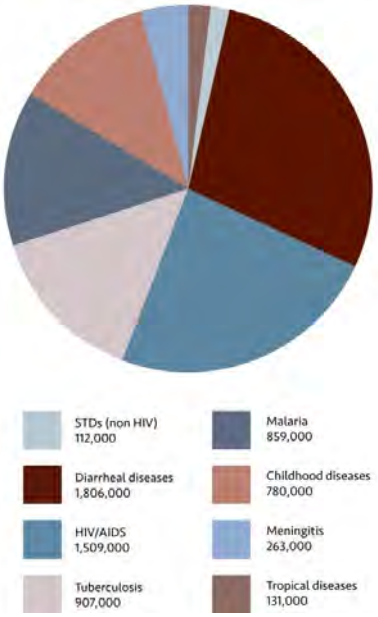
Advanced adjuvants for novel vaccines

Expanding access to technology in the fight against infectious disease

HEALTH NEED

Every year vaccinations against infectious diseases save the lives of 2.5 million children and protect over 100 million more from illness and disability.[1] However, millions of children remain at risk in developing countries, where the global infectious disease burden is highest (Figure 1), because vaccines that protect against specific infectious diseases are either too expensive or they are not yet available.

FIGURE 1: Mortality due to infectious diseases in low-income countries in 2004.[2]



For other vaccine targets, some antigens (Table 1) elicit an insufficient immune response on their own. Successful vaccines for certain pathogens will likely require enhanced immune responses, including cellular-mediated immunity (CMI) (Th1) and mucosal immunity or a more robust humoral (Th2) response. Advanced adjuvants that improve vaccine efficacy and reduce the cost per dose of vaccine could potentially address these gaps and help to accelerate the development, coverage, and impact of many vaccines of critical importance to developing countries.

BENEFITS OF ADJUVANTS

Depending on the profile of the antigen and adjuvant, the positive impact of adjuvants on vaccination can be functional and practical (Table 2). When properly formulated, adjuvants can help to augment the breadth and magnitude of protective immune responses to vaccines.

A handful of adjuvants are currently licensed for human vaccination (Table 3), and a number of new adjuvants have reached advanced development stages (Table 4). These adjuvants have the potential to address previous development barriers by enhancing otherwise poorly immunogenic antigens or biasing the immune response toward the type of response needed to protect against specific pathogens. Some adjuvants have also been shown to reduce the dose required per person, helping to decrease vaccine costs, but broad effects on affordability have yet to be confirmed.

ONGOING CHALLENGES

Major developments in antigen discovery over the past decade have accelerated the vaccine development process for a number of new indications, but because vaccine development is expensive, manufacturers still tend to focus on products needed by wealthy countries to ensure an adequate return on investment.

PATH collaborates with partners, including developing-country vaccine manufacturers, to research and develop vaccines that will meet the unique needs of immunization programs in low-income countries. Yet, hurdles remain, including:

INTELLECTUAL PROPERTY RESTRICTIONS

Most adjuvant intellectual property (IP) is held by a small concentration of pharmaceutical and biotech companies. As a result, many developing-country vaccine manufacturers, vaccine development programs and product development partnerships (PDPs) do not pursue proprietary adjuvants, or if they have succeeded in negotiating access, they must evaluate performance one adjuvant at a time, which can be inefficient, costly, and time consuming.

LIMTED DATA

Typically, the opportunity for selecting the most suitable adjuvant is missed because head-to-head comparisons of different adjuvants are not permitted by the adjuvant developers. Without head-to-head comparisons, vaccine manufacturers and PDPs cannot assess data that are relevant to the formulation and evaluation of candidate antigens, hindering the identification of appropriate characterization methods and other conditions under which an adjuvant will fail to elicit its desired effect.

ADDITIONAL CONCERNS

Aluminum salts, also known as alum, are the primary adjuvants used in vaccines worldwide; however, alum is not optimally effective for vaccines against diseases where CMI[3] or mucosal immunity is likely required for protection. Alum-adjuvanted vaccines are also more sensitive to extreme cold. When exposed to freezing temperatures, the aluminum salts agglomerate, permanently compromising vaccine efficacy.

PATHWAY FORWARD

In addition to our work with **alum**, **oil-in-water emulsions**, **dmLT**, and **PCPP**, PATH is working to expand access to other proprietary and nonproprietary adjuvants as well as relevant formulation technologies to facilitate their successful exploration and use by PDPs and developing-country vaccine manufacturers. Project tasks center on:

- Improving existing adjuvanted formulations.
- Identifying and engaging with adjuvant developers.
- Evaluating and prioritizing advanced adjuvants and integrating the best-performing adjuvants in early stages of vaccine development.

BROADER GOALS INCLUDE:

- Creating global access by helping to improve IP access to adjuvants and facilitating access to adequate supplies of GMP-produced adjuvants, enabling the development of vaccines of importance to developing countries.
- Encouraging data sharing to build technical capacity and expand the evidence base, especially benchmarking studies that compare the efficacy of multiple adjuvants for a specific antigen in preclinical models.
- Fostering synergies and strategic partnerships to facilitate the broader development and advancement of adjuvanted vaccine formulations through the transfer of technology, data, and expertise among adjuvant developers, PDPs, vaccine producers, and other stakeholders.

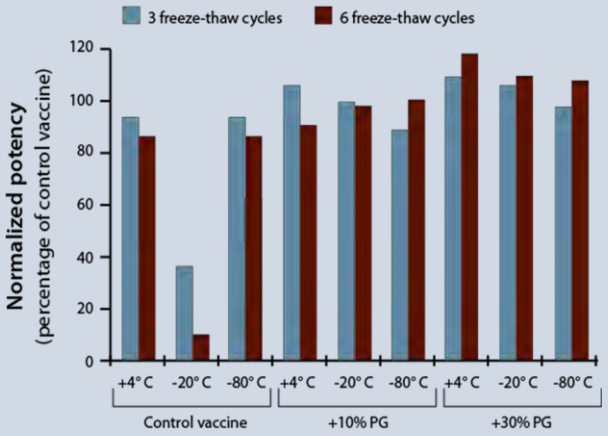
One example of our work is the evaluation of advanced adjuvants for potential use in the development of an effective and affordable adjuvanted formulation of inactivated poliovirus vaccine. Later phases of the work may involve the development of adjuvanted formulations for malaria, rotavirus, HIV, or tuberculosis.

Improving alum-adjuvanted formulations

A growing body of evidence indicates that cold chain storage facilities and transportation methods in both developing and developed countries often expose vaccines to freezing temperatures.[4] PATH recently identified a method to protect liquid formulations containing an aluminum salt adjuvant or its equivalent (e.g., aluminum hydroxide, aluminum phosphate, or calcium phosphate) from freeze damage.

By adding low-cost excipients (e.g., propylene glycol) to hepatitis B (Hep B) vaccine, PATH and research partners successfully protected the adjuvant and the protein-adjuvant bond despite repeated exposure to temperatures well below the vaccine freezing point (Figure 2). The adjuvant proved stable against agglomeration or sedimentation upon thawing.

FIGURE 2: Propylene glycol protects hepatitis b vaccine from freeze damage.[5]



All excipients involved in the methods are generally recognized as safe by the US Food and Drug Administration (USFDA) and commonly used in parenteral drugs approved by the USFDA and other drug regulation agencies. The cost of adding the excipients to vaccines is negligible.

In addition to Hep B vaccine, PATH has applied this freeze-protection method to diphtheria-tetanus-pertussis (DTP), and DTP-Hep B-*Haemophilus influenzae* type B vaccines—with demonstrable results.

To facilitate widespread adoption, all relevant IP has been placed within the public domain.

TABLE 1: Vaccines in development.

Disease	PDP	Lead Vaccine Candidates	Desired Immunity
Tuberculosis (TB)	Aeras	• Heparin-binding hemagglutinin (HBHA). • *Mtb39a Mtb32a* fusion protein (M72). • Ag85 TB10.4 fusion protein (H4). • Ag85, ESAT6, and rv2660 fusion protein (H56).	• CMI. • Broadly neutralizing antibodies.
HIV	International AIDS Vaccine Initiative	• HIV envelope immunogens.	• Broadly neutralizing antibodies. • Antibody affinity maturation.
Malaria	PATH Malaria Vaccine Initiative	• Modified circumsporozoite protein (RTS, S). • *Pfs25*, *Pfv25*. • *Pv*DBPII.	• CMI. • Broadly neutralizing antibodies.
Diarrheal diseases • Enterotoxigenic *E. coli* (ETEC) • *Shigella*	PATH Enteric Vaccine Initiative	• ETEC inactivated whole-cell vaccines. • Purified ETEC colonization-factor antigens. • *Shigella* conserved, surface-expressed proteins.	• Mucosal antibodies.
Diarrheal diseases • Rotavirus	PATH Rotavirus Vaccine Program*	• VP8-subunit. • VP8-VLP. • Inactivated whole virion.	• Broadly neutralizing antibodies.

*Non-replicating rotavirus vaccine.

TABLE 2: The positive impact of adjuvants on vaccination.

Practical	**Improve the immunization schedule**
	Accelerate the onset of the immune response.
	Potentially reduce the need for a boost.
	Diminish the dose of Ag (i.e., dose sparing).
Functional	**Increase the magnitude/efficacy of the immune response**
	Enhance functional antibody titers.
	Allow greater breadth of antibody cross-reactivity.
	Prolong the duration of the immune response.
	Enable memory of the initial immune response.
	Facilitate the mucosal homing of immune effector cells through the upregulation of the cells' homing markers.
	Overcome extrinsic constraints related to poor nutrition or immunocompromised influences.
	Surmount intrinsic restrictions such as immunogenic limitations on Ag presentation due to major histocompatibility complex haplotype heterogeneity.

TABLE 3: Adjuvants in licensed vaccines.[6]

Adjuvant	Class	Company	Indications	Coverage	Rationale
Alum	Mineral salts	Various	Various	Global	• Antigen (Ag) delivery. • Improves humoral response and Ag stability.
MF59®	Oil-in-water emulsion	Novartis	Influenza	Europe	• Ag delivery. • Improves humoral response and CMI. Dose sparing demonstrated.
AS03	Oil-in-water emulsion	GlaxoSmithKline (GSK)	Influenza	Europe	• Ag delivery. • Improves humoral response and CMI. Dose sparing demonstrated.
AS04	Alum + TLR4 antagonist	GSK	Hepatitis B virus, human papillomavirus	Europe, United States	• Immunostimulant. • Improves humoral response and CMI.
Virosome	Liposome	Crucell	Hepatitis A, influenza	Europe	• Ag delivery. • Improves humoral response and CMI.

TABLE 4: Adjuvant examples in the development of new vaccines.

Adjuvant	Composition	Vaccine Target	Developer	Rationale
AS01	MPL + liposome + QS21	Malaria *Phase III*	GlaxoSmithKline (GSK)	• Immunostimulant, Ag processing, and Ag delivery. • Improves humoral response and CMI.
ISS	Oligonucleotide	HBV *Phase III*	Dynavax	• Immunostimulant. • Improves humoral response and CMI.
QS-21 Stimulon®	Saponin	Various *Phase III*	Agenus	• Ag processing. • Improves humoral response and CMI.
AS02	MPL + oil-in-water emulsion + QS21	Malaria *Phase II*	GSK	• Immunostimulant, Ag processing, and Ag delivery. • Improves humoral response and CMI.
IC31®	Peptide + oligonucleotide	Tuberculosis *Phase II*	Intercell	• Immunostimulant. • Improves humoral response and CMI.
CAF01	Liposome	Tuberculosis *Phase I*	Statens Serum Institut	• Ag delivery. • Improves humoral response and CMI.
dmLT	Detoxified protein	Enteric *Phase I*	Tulane University	• Immunostimulant. • Improves mucosal antibody response.
Flagellin	Flagellin linked to antigen	Flu *Phase I*	VaxInnate	• Immunostimulant. • Improves humoral response and CMI.
ISCOMATRIX®	ISCOM (Saponins + cholesterol + phospholipids)	Various *Phase I*	CSL	• Ag delivery. • Improves humoral response and CMI.
Matrix-M™	ISCOM (Saponins + cholesterol + phospholipids)	Flu *Phase I*	Isconova	• Ag delivery. • Improves humoral response and CMI.
MPL-SE	MPL + oil-in-water emulsion	Leishmaniasis *Phase I*	Infectious Disease Research Institute	• Ag delivery. • Improves humoral response and CMI.
PCPP	Synthetic polyelectrolyte	Flu *Phase I*	Parallel Solutions, Inc.	• Ag delivery. • Improves humoral response and CMI.
PLG	Polymeric microparticles	DNA vaccine (HIV) *Phase I*	Novartis	• Ag delivery. • Improves CMI.

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