VACCINE AND PHARMACEUTICAL TECHNOLOGIES GROUP

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# ADVANCING VACCINE FORMULATIONS OF IMPORTANCE TO DEVELOPING COUNTRIES USING NEW AND EXISTING ADJUVANT TECHNOLOGIES

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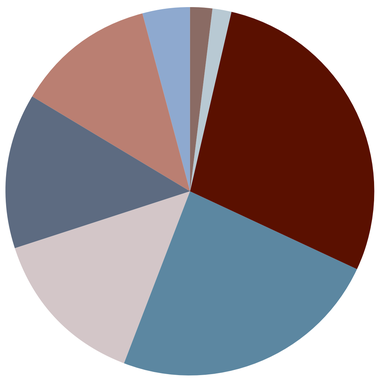
## Health Need

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] Yet, millions of children remain at risk in developing countries, where the infectious disease burden is highest (Figure 1), because vaccines that protect against specific diseases are either too expensive or not yet available.

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




For other 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 delivery could potentially address these gaps.

## Benefits of Adjuvants

Depending on the profile of the antigen and adjuvant, the positive impact of adjuvants on vaccination can be functional (e.g., increase the magnitude/efficacy of the immune response) and practical (e.g., improve the immunization schedule). A handful of adjuvants are currently licensed for human vaccination, and a number of new adjuvants have reached advanced development stages (Table 2). These adjuvants have the potential to address previous development barriers by enhancing 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, but broad effects on affordability have yet to be confirmed.

## Ongoing Challenges

To address gaps, PATH collaborates with numerous 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 (IP) restrictions:** Most adjuvant IP is held by a small concentration of pharmaceutical and biotech companies. As a result, many developing-country vaccine manufacturers, vaccine development programs, and 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.

**Lack of relevant data, limited access to existing 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 non-proprietary 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 the effectiveness of existing adjuvanted formulations.
- Identifying and engaging with relevant 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.
- 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.

## Contact Information

Numerous opportunities exist to support and engage in this effort. For more information on potential partnerships and collaboration, please email the poster authors at **vxpharmatech@path.org.**

## References

1. World Health Organization (WHO), UNICEF, World Bank. *State of the world's vaccines and immunization, 3rd ed.* Geneva, WHO, 2009.
2. WHO. *The global burden of disease: 2004 update*. Geneva, Switzerland: WHO; 2008. Available at: www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf.
3. Schijns VE, Lavelle EC. Trends in vaccine adjuvants. *Expert Review of Vaccines*. 2011;10(4):539–550.
4. Matthias DM, Robertson J, Garrison MM, Newland S, Nelson C. Freezing temperatures in the vaccine cold chain: a systematic literature review. *Vaccine*. 2007;25(20):3980–3986.
5. Braun LJ, Tyagi A, Perkins S, et al. Development of a freeze-stable formulation for vaccines containing aluminum salt adjuvants. *Vaccine*. 2009;27(1):72–79.

### 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 from freeze damage. By adding low-cost excipients (e.g., propylene glycol or glycerin) 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). And the adjuvant proved stable against agglomeration or sedimentation upon thawing. PATH has also applied this freeze-protection method to diphtheria-tetanus-pertussis (DTP), and DTP-Hep B-*Haemophilus influenzae* type B vaccines. To facilitate widespread adoption, all relevant IP is within the public domain.

Figure 2: Propylene glycol protects Hep B vaccine from freeze damage.[5]

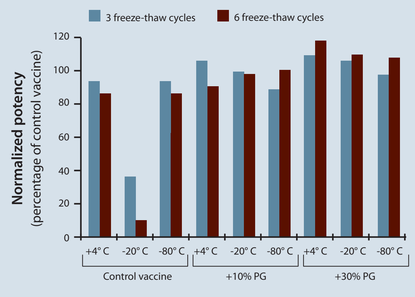




Table 1: Vaccines in development.

| Disease | Product Development Partnership (PDP) | Lead Vaccine Candidates | Desired Immunity |
|---|---|---|---|
| Tuberculosis (TB) | Aeras | • Heparin-binding hemagglutinin (HBHA).<br>• *Mtb*39a *Mtb*32a fusion protein (M72).<br>• Ag85 TB10.4 fusion protein (H4).<br>• Ag85, ESAT6, and rv2660 fusion protein (H56). | • CMI.<br>• Broadly neutralizing antibodies. |
| HIV | International AIDS Vaccine Initiative | • HIV envelope immunogens. | • Broadly neutralizing antibodies.<br>• Antibody affinity maturation. |
| Malaria | PATH Malaria Vaccine Initiative | • Modified circumsporozoite protein (RTS, S).<br>• *Pfs*25, *Pfv*25.<br>• *Pv*DBPII. | • CMI.<br>• Broadly neutralizing antibodies. |
| Diarrheal diseases<br>• Enterotoxigenic *E. coli* (ETEC)<br>• *Shigella* | PATH Enteric Vaccine Initiative | • ETEC inactivated whole-cell vaccines.<br>• Purified ETEC colonization-factor antigens.<br>• *Shigella* conserved, surface-expressed proteins. | • Mucosal antibodies. |
| Diarrheal diseases<br>• Rotavirus | PATH Rotavirus Vaccine Program* | • VP8-subunit.<br>• VP8-VLP.<br>• Inactivated whole virion. | • Broadly neutralizing antibodies. |

*Non-replicating rotavirus vaccine.


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Table 2: 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.<br>• Improves humoral response and CMI. |
| ISS | Oligonucleotide | HBV *Phase III* | Dynavax | • Immunostimulant.<br>• Improves humoral response and CMI. |
| QS-21 Stimulon® | Saponin | Various *Phase III* | Agenus | • Ag processing.<br>• Improves humoral response and CMI. |
| AS02 | MPL + oil-in-water emulsion + QS21 | Malaria *Phase II* | GSK | • Immunostimulant, Ag processing, and Ag delivery.<br>• Improves humoral response and CMI. |
| IC31® | Peptide + oligonucleotide | TB *Phase II* | Intercell | • Immunostimulant.<br>• Improves humoral response and CMI. |
| CAF01 | Liposome | TB *Phase I* | Statens Serum Institut | • Ag delivery.<br>• Improves humoral response and CMI. |
| dmLT | Detoxified protein | Enteric *Phase I* | Tulane University | • Immunostimulant.<br>• Improves mucosal antibody response. |
| Flagellin | Flagellin linked to antigen | Flu *Phase I* | VaxInnate | • Immunostimulant.<br>• Improves humoral response and CMI. |
| ISCOMATRIX® | ISCOM (Saponins + cholesterol + phospholipids) | Various *Phase I* | CSL | • Ag delivery.<br>• Improves humoral response and CMI. |
| Matrix-M™ | ISCOM (Saponins + cholesterol + phospholipids) | Flu *Phase I* | Isconova | • Ag delivery.<br>• Improves humoral response and CMI. |
| MPL-SE | MPL + Oil-in-water emulsion | Leishmaniasis *Phase I* | Infectious Disease Research Institute | • Ag delivery.<br>• Improves humoral response and CMI. |
| PCPP | Synthetic polyelectrolyte | Flu *Phase I* | Parallel Solutions, Inc. | • Ag delivery.<br>• Improves humoral response and CMI. |
| PLG | Polymeric microparticles | *DNA vaccine (HIV) Phase I* | Novartis | • Ag delivery.<br>• Improves CMI. |