# Adjuvants Used in Vaccines

## National Adult and Influenza Immunization Summit

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This presentation on the Adjuvants Used in Vaccines and was created at the request of Bruce Gellin, MD, MPH, Deputy Assistant Secretary for Health, Director National Vaccine Program, Office US Department of Health and Human Services; Carolyn Bridges, MD, Associate Director for Adult Immunizations, Immunization Services Division, Centers for Disease Control and Prevention; and Litjen Tan, PhD, MS, Chief Strategy Officer, Immunization Action Coalition.

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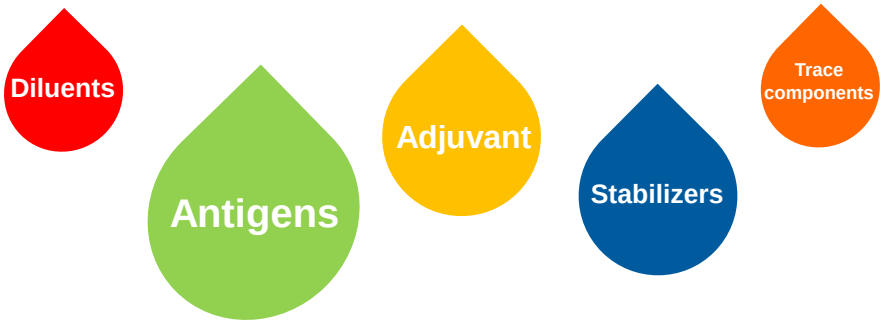
## Vaccines are Complex Biological Mixtures of Several Components

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CDC. Ingredients of vaccines – Fact sheet. http://www.cdc.gov/vaccines/vac-gen/additives.htm. Accessed Feb 5, 2016.

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## Adjuvant

From Latin, *adiuvare*: to aid

Pharmacological/immunological agent that modifies the effect of other agents

Compounds that enhance or shape the immune response

Immunological adjuvants added to vaccines stimulate the host immune system's response to target antigen, but do not themselves confer immunity

Old technology, made new

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Garçon N, et al. Understanding modern vaccines, Perspectives in vaccinology, Vol 1, Amsterdam: Elsevier; 2011; Chapter 4:89-113.

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# Antigens May Need Help: Role for Adjuvants

## CURRENT CHALLENGES FOR VACCINES[1]

**Challenging population** due to impaired immune system (e.g. elderly, children, immunocomprmised)

**Need for booster vaccinations**

**Recombinant antigen** Generally less immunogenic than live or attenuated organism vaccine[2]

**Pathogen** that requires broad and complex immune response

**Need for antigen sparing** Potential supply problems (e.g. pandemic flu)

**Increase** the level of the immune response

**Prolong** the duration of the immune response, improve immune memory, and protection

**Overcome** a weakened immunogenicity

**Induce** the generation of a high and broad immune response

**Reduce** the amount of antigen needed (dose-sparing)

1. Garçon N, et al. Understanding modern vaccines, Perspectives in vaccinology, Vol 1, Amsterdam: Elsevier; 2011; Chapter 4:89-113.
2. Petrovsky N, et al. Immunology and Cell Biology (2004) 82, 488–496; doi:10.1111/j.0818-9641.2004.01272.

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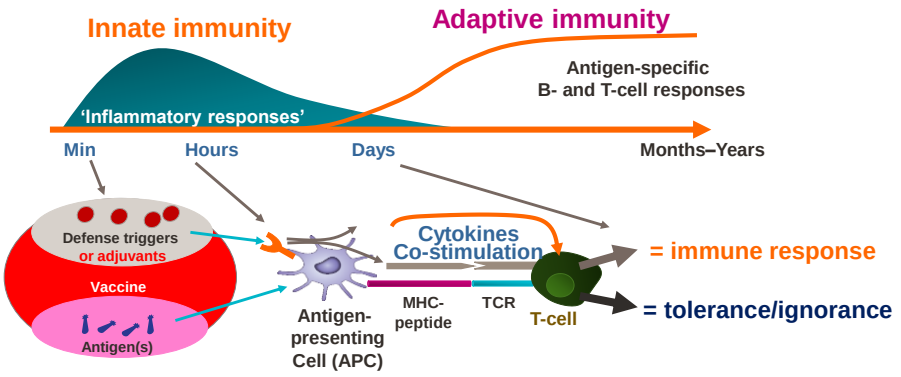
# Adjuvants Activate Innate Immunity[1]




An adjuvant can activate the innate immune system by acting like pathogen-associated molecular patterns and thus can enhance or restore the ability of the immune system to identify a vaccine antigen as a pathogen with subsequent activation/maturation of APCs and activation of the adaptive immune system.[2]

MHC = major histocompatibility complex; TCR = T-cell receptor.

1. Adapted from Ishii et al. Curr Pharm Des 2006;12(32):4135–42.
2. Reed SG, et al. Nature Medicine. 2013:19;1597-1607.

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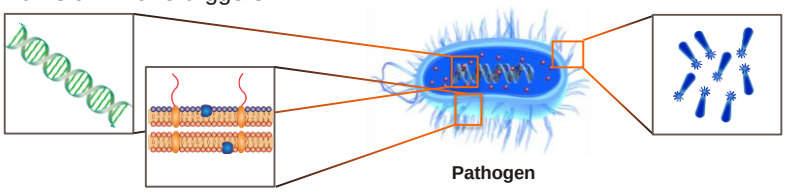
## Microbial Structures[1,2,3]

**Defense triggers**

(danger signals), e.g. PAMPs act as intrinsic immune-triggers

**Antigens**



Pathogen

**Alert immune system**

**Stimulate/direct immune response**

**Specific immune response**

PAMPs = pathogen-associated molecular patterns


1. Dougan G & Hormaeche C. Vaccine 2006;24(S2):S13–S19
2. O'Hagan DT & Valiente NM. Nat Rev Drug Discov 2003;2:727–35
3. Garçon N, et al. Understanding modern vaccines, Perspectives in vaccinology, Vol 1, Amsterdam: Elsevier; 2011; Chapter 4:89-113



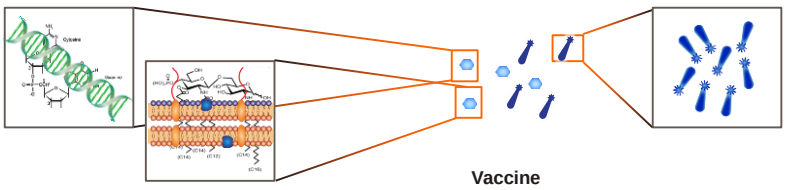



## Selecting From Nature: Right Antigens and Well Characterized Adjuvants[1,2]

- Vaccine antigens alone may exhibit insufficient immunogenicity
- Some selected adjuvants act as substitutes for natural immune-defense signals, enhancing and directing the immune response

**Defense triggers**

**Antigens**



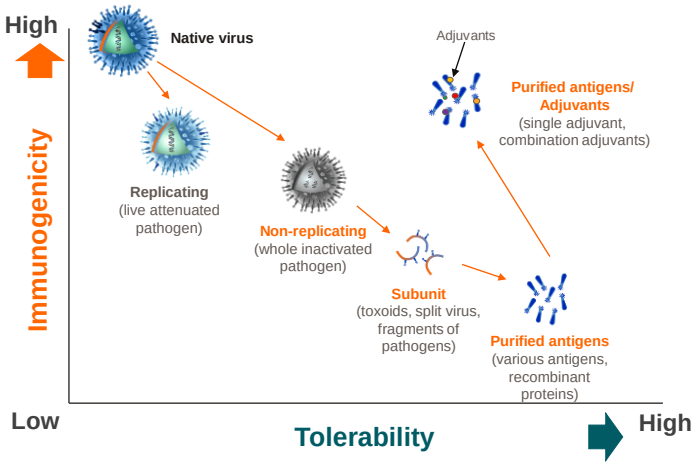
Vaccine

**Adjuvants act as substitutes for natural immune-defense triggers**

**Specific immune response**


1. Dougan G & Hormaeche C. *Vaccine* 2006;24(S2):S13–S19
2. O'Hagan DT & Valiente NM. *Nat Rev Drug Discov* 2003;2:727–35

## Antigens May Need Help: Why and When? The Role of Adjuvants[1,2]




Illustrative figure based on concepts from:

1. Pasquale AD, Preiss S, Da Silva FT et al. Vaccine adjuvants: from 1920-2015 and beyond. Vaccines . 2015. 3: 320-343.

2. Garçon N, *et al.* Understanding modern vaccines, Perspectives in vaccinology, Vol 1, Amsterdam: Elsevier; 2011; Chapter 4:89-1131.

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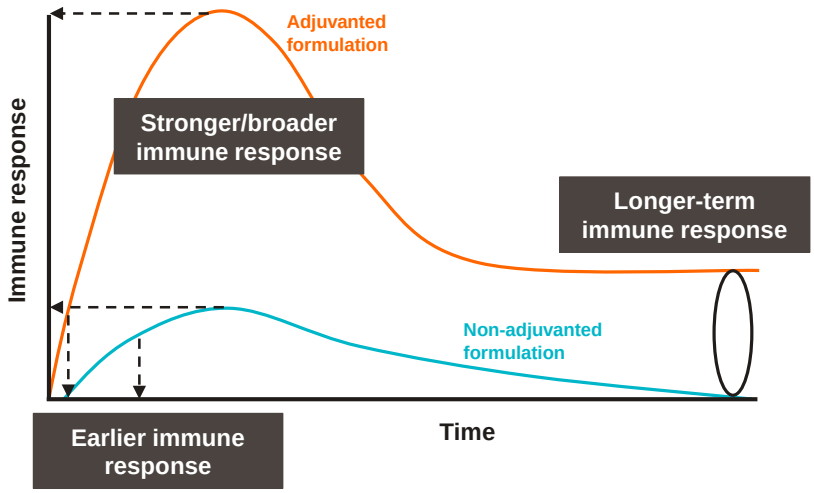
## Adjuvant: Expected Impact on Vaccine Immune Response




Illustrative figure based on concepts from:

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## Adjuvants in Clinical Trials/Licensed Vaccines

| Adjuvant name | Mechanism or receptor | Clinical phase or licensed product |
|---|---|---|
| dsRNA analogues (for example, poly(I:C)) | TLR3 | Phase 1 |
| Lipid A analogues (for example, MPL, RC529, GLA, E6020) | TLR4 | Cervarix® |
| Flagellin | TLR5 | Phase 1 |
| Imidazoquinolines (for example, Imiquimod, R848) | TLR7 and TLR8 | Aldara |
| CpG ODN | TLR9 | Phase 3 |
| Saponins (for example, QS21) | Immunostimulatory | Phase 3 |
| C-type lectin ligands (for example, TDB ) | Mincle, Nalp3 | Phase 1 |
| CD1d ligands (for example, α- galactosylceramide) | CD1d | Phase 1 |
| Aluminum salts (for example, aluminum oxyhydroxide, aluminum phosphate) | Nalp3, ITAM, Ag delivery | Numerous license products |
| Emulsions (for example, MF59, AS03) | Immune cell recruitment, ASC, Ag uptake | Fluad®, Pandemrix ® |
| AS01 (MPL,QS21, liposomes) | TLR4, immunostimulatory | Phase 3 |
| AS04 (MPL, aluminum salt) | TLR4 | Cervarix |
| AS15 (MPL, QS21, CpG, liposomes) | TLR4 ,TLR9, immunostimulatory | Phase 3 |
| GLA-SE (GLA, emulsion) | TLR4 | Phase 1 |
| IC31 (CpG, cationic peptide) | TLR9 | Phase 1 |
| CAF01 (TDB, cationic liposomes) | Mincle, Ag delivery | Phase 1 |
| ISCOMs (saponin, phospholipid) | Immunostimulatory | Phase 2 |

Ag = antigen; ASC= apoptosis-associated speck-like protein containing caspase recruitment domain; dsRNA = double-stranded RNA; ITAM = immunoreceptor tyrosine-based activation motif; TDB = trehalose dibehenate. Some particulate formulations (such as aluminum salts and emulsions) also generate immunomodulatory activity.



Adapted from Reed SG et al, Nature Med 19: 1597-1608, 2014





## Pearl Of Wisdom

Adjuvants,

acting as substitutes for natural immune defense signals, enhancing and directing the immune response,

have the potential to help antigens overcome challenges including:[1,2]

- challenging populations
- need for booster vaccination
- poorly immunogenic recombinant antigens
- complex pathogens
- antigen sparing



1. Garçon N, *et al.* Understanding modern vaccines, Perspectives in vaccinology, Vol 1, Amsterdam: Elsevier; 2011; Chapter 4:89-113.
2. Petrovsky N, et al. Immunology and Cell Biology (2004) 82, 488–496; doi:10.1111/j.0818-9641.2004.01272.