Adjuvanted Vaccines

Benefits and risks

Professor Paul Van Buynder

Griffith University

AIF June 14th

I acknowledge the Traditional Custodians of country throughout Australia and their connections to land, sea and community.

I pay my respect to their Elders past and present and extend that respect to all Aboriginal and Torres Strait Islander peoples present today.

Declarations of interest

o   I am a member of the Australian Influenza Vaccination Committee, a TGA body.

o   I am a past president of the Immunisation Coalition and a member of its Scientific Advisory Committee.

o   I am a member of the Asia Pacific Alliance for the control of influenza and a registered expert with the International Federation of Aging.

o   I have received support for education, travel, or research from GSK, MSD, CSL, Seqirus, Novartis, Pfizer, Moderna, Sanofi and Roche.

o   **The views expressed in these slides are my own.**

Agenda

Adjuvants
The journey

Adjuvants in current use

Benefits

Risks

Agenda
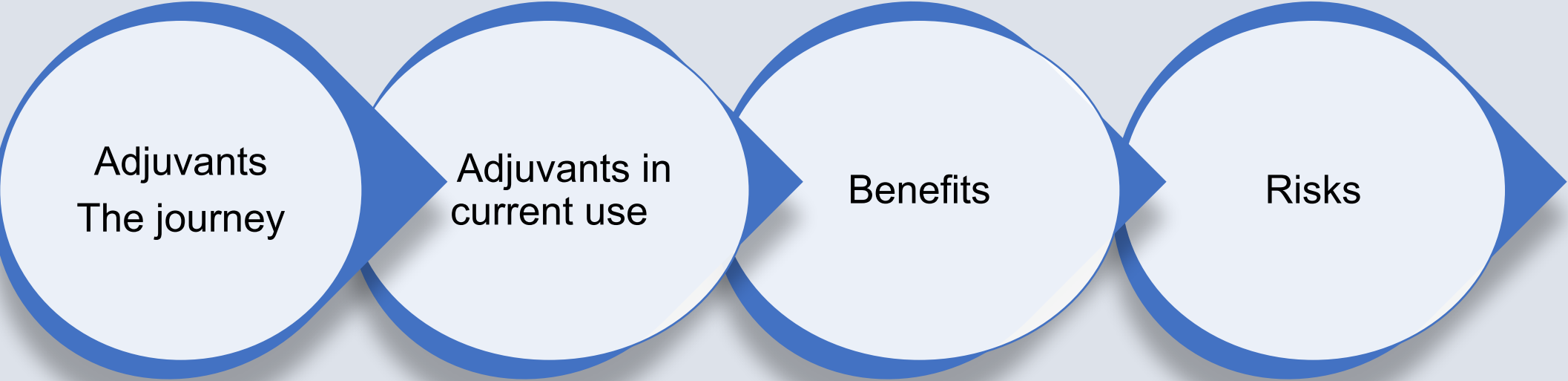
Adjuvants
The journey
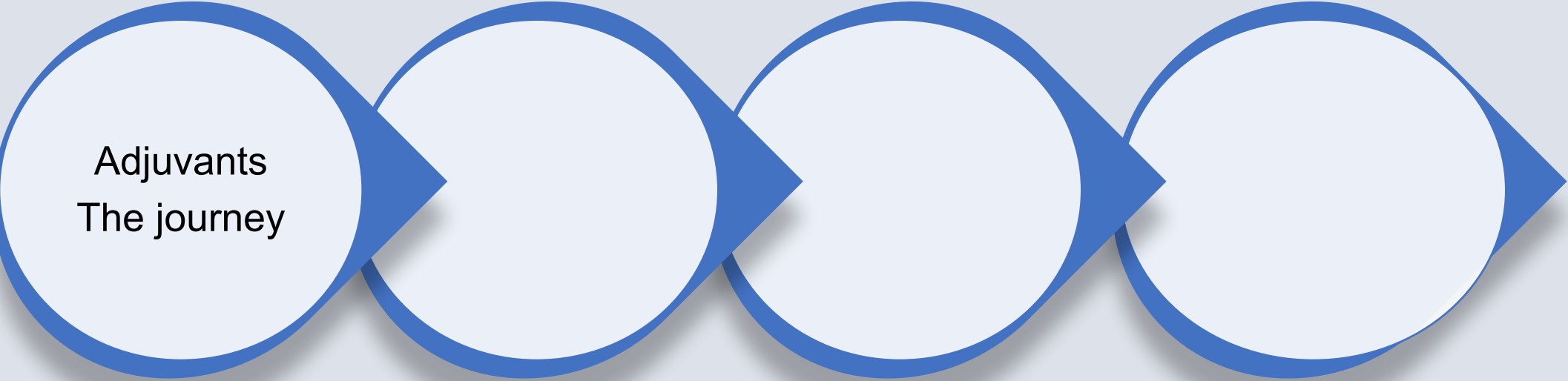
Adjuvants

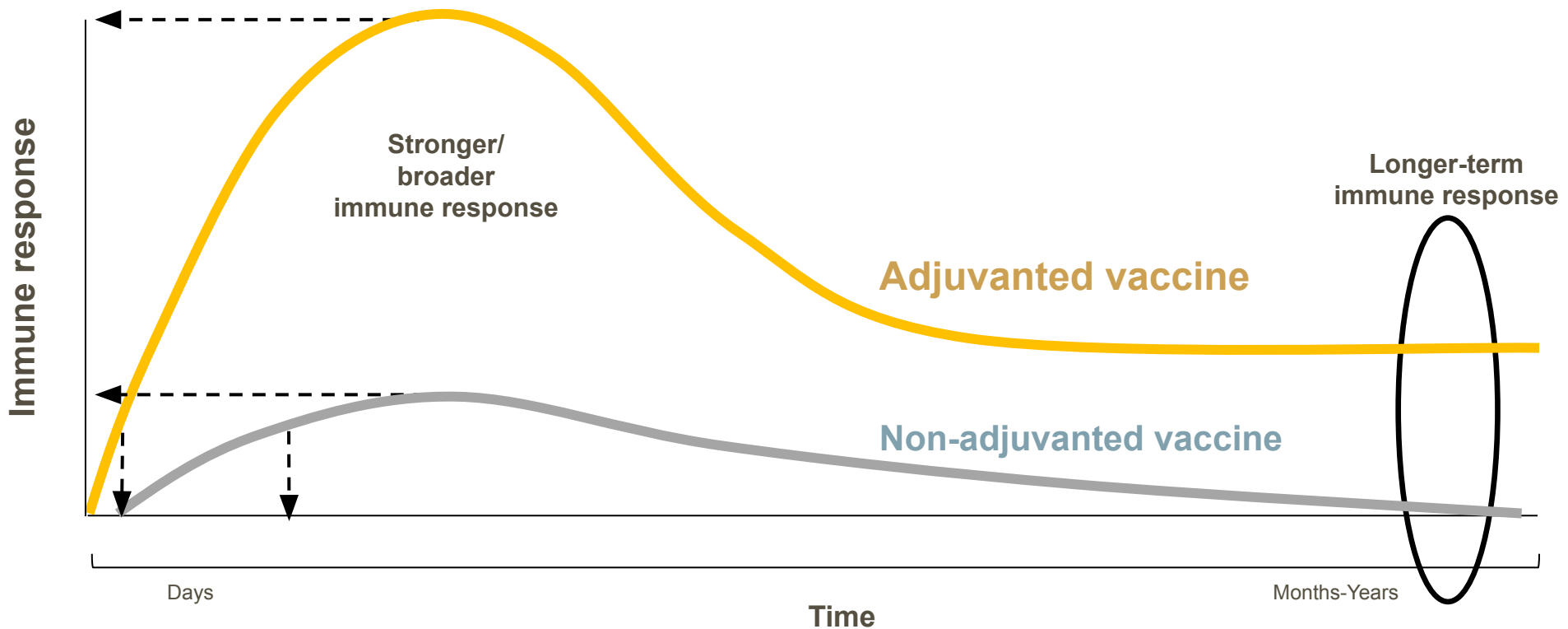- Constituents added to vaccines in order to improve immune responses towards an antigen.

- Adjuvant benefits:
  - Reduction in the antigen amount per vaccine dose and the number of vaccination sessions;
  - Increase the stability of the antigen component, extending its half-life and indirectly improving its immunogenic power

- Many different types of adjuvants are now available to use in vaccine manufacturing.

Adjuvants help generate a strong and long lasting immune response

Stronger/broader immune response

Adjuvanted vaccine

Non-adjuvanted vaccine

Longer-term immune response

Immune response

Days

Months-Years

Time

For conceptual purposes only, not a comparison between herpes zoster vaccines.
Illustrative figure independently created by GSK based on Garçon N, et al. Understanding modern vaccines. 2011[1]

1. Garçon N, et al. Understanding Modern Vaccines: Perspectives in Vaccinology. Vol 1. Amsterdam: Elsevier; 2011; Chapter 4: 89-113.

Adjuvants

- Adjuvants, through molecular mimicry, act as ligand for TLRs, which in turn, once activated, start producing type I INF and proinflammatory cytokines.

- Moreover, adjuvants lead to the recruitment of dendritic cells via chemotaxis and activation of antigen presenting cells, which in turn results in more portent B-cell and T-cell responses.

- This ultimately results in a stronger adaptive immune response to antigens. (but also important in reactogenicity issues)

Why we need adjuvants

Figure 5. Challenges for modern vaccine development.

Pathogen-related challenges

- Immune evasion, intracellular infection
- Multiple serotypes
- Complex life cycle, latent disease
- Short duration of protection
- Antigenic drift
- Moderate/limited efficacy
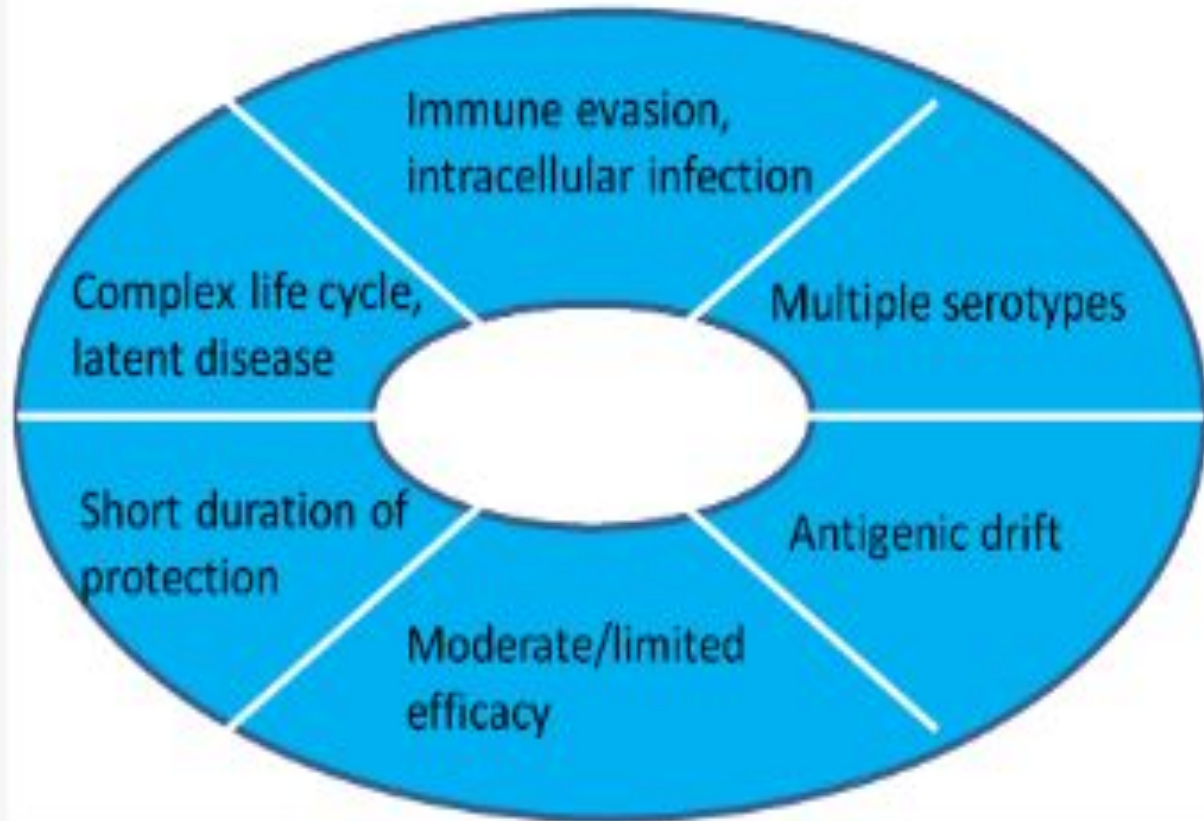
Population-related challenges

- Elderly: immune senescence
- Immunosuppressed: reduced responses/live vaccines contraindicated
- Chronic disease: reduced responses
- Infants: immature immune system
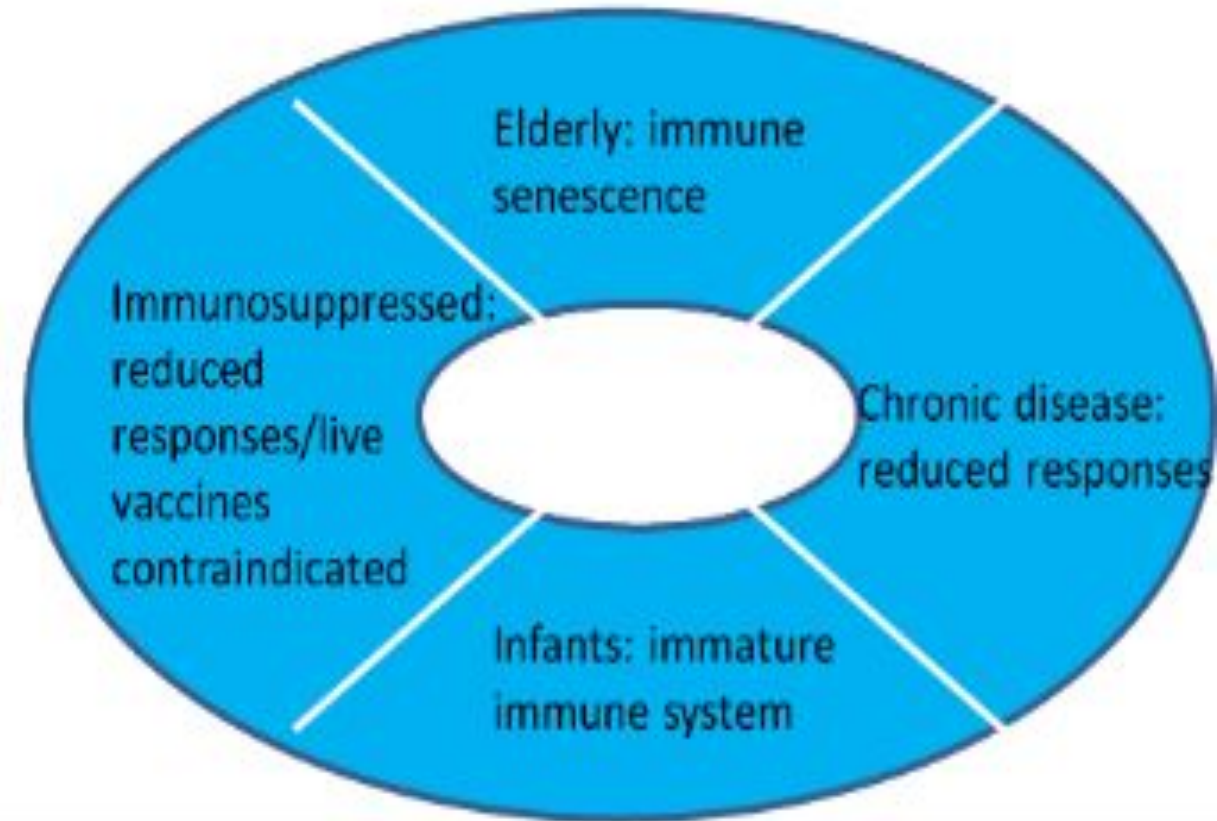
a. Vaccines without adjuvants

Immature APCs accumulation · APCs maturation · Lymph nodes · Adaptive immune response

B cell (Naïve) · Antibodies · B cell (memory)
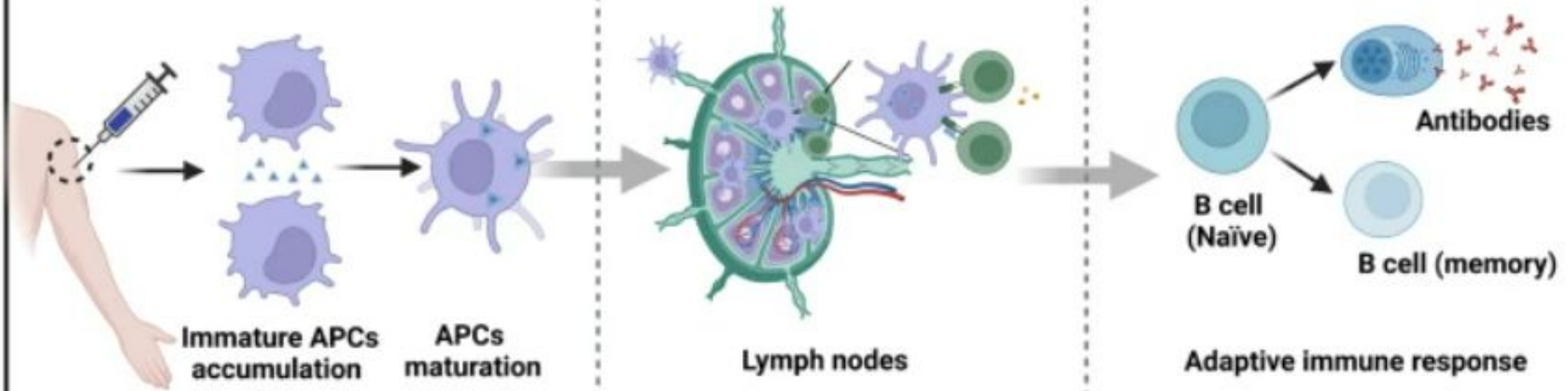
b. Vaccines with adjuvants

Cytotoxic T cells · Antibodies · B cell (Naïve) · B cell (memory)
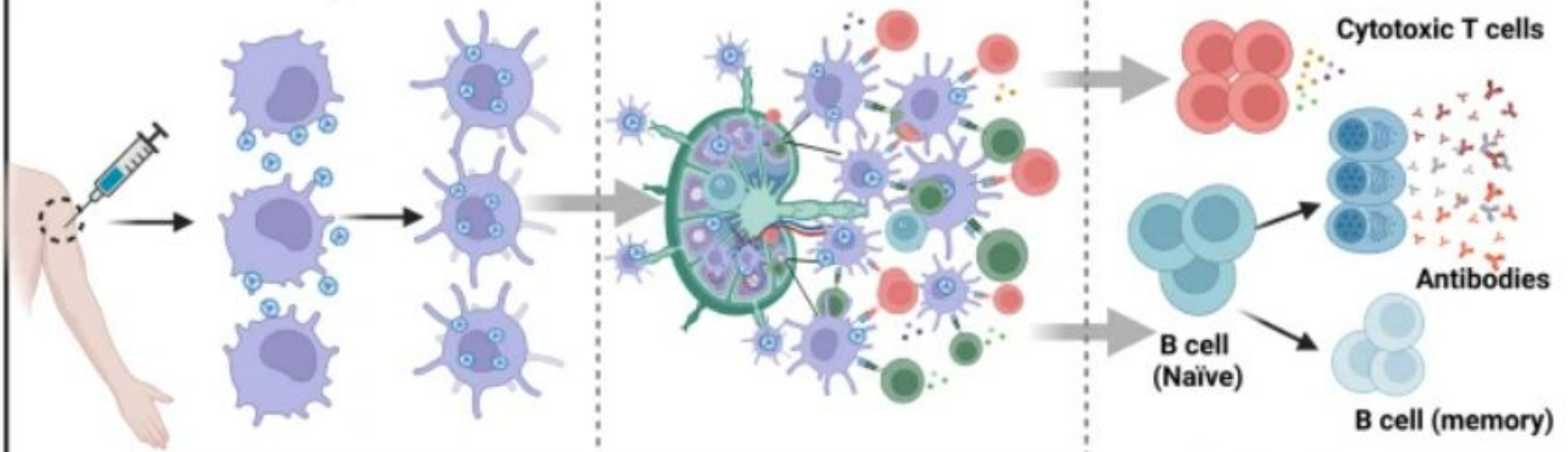
Adjuvant · Antigen-presenting cell (APC) · CD8+ T cell · B cell

Antigen · Cytokine · CD4+ T cell · Plasma cell

Mechanism of action of Adjuvants.

Fig. 2

Timeline of major events in the research history of vaccine adjuvants. This figure was created with BioRender (https://biorender.com/)

Agenda

Adjuvants in current use

Table 1 | The 'known knowns' and 'known unknowns' of adjuvants used in licensed vaccines

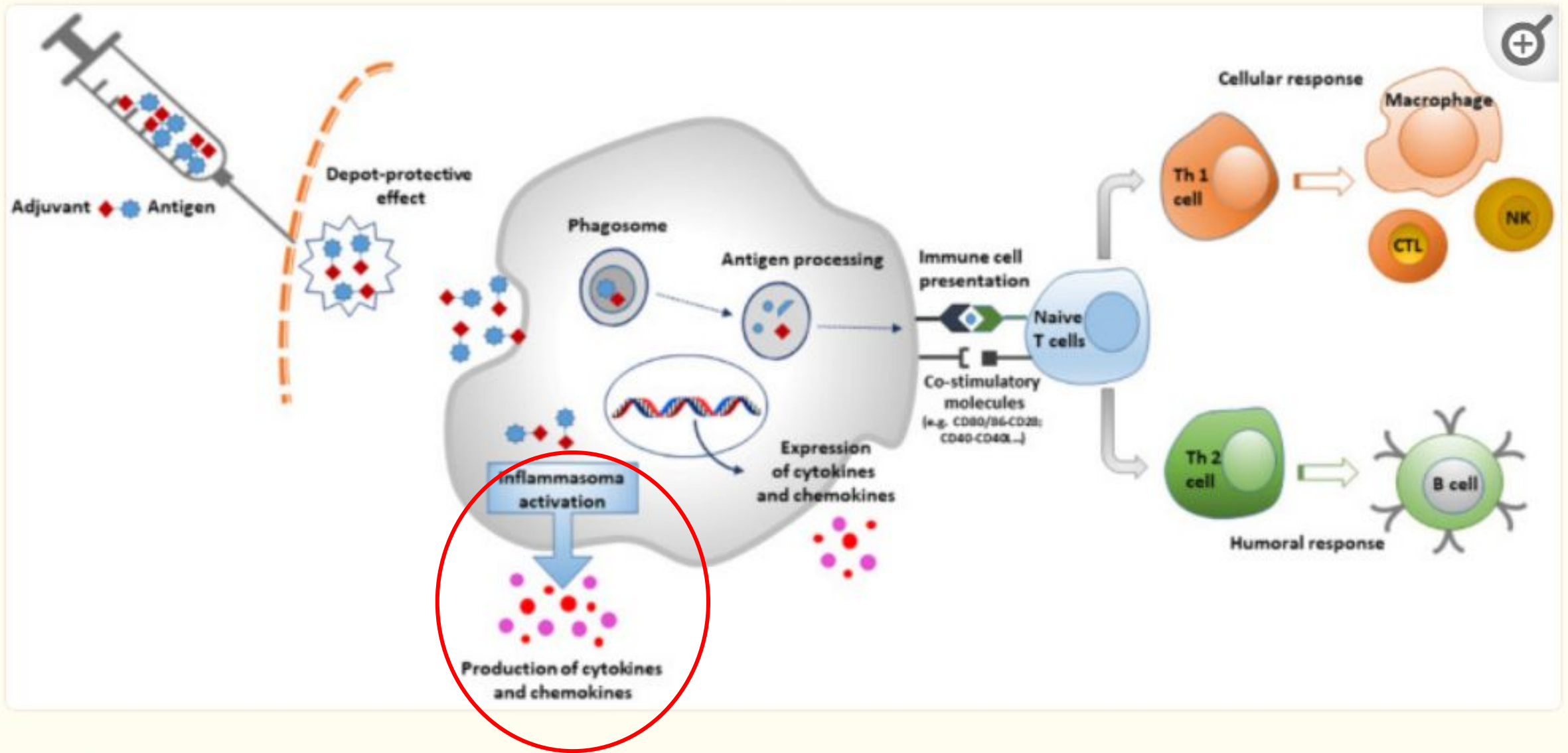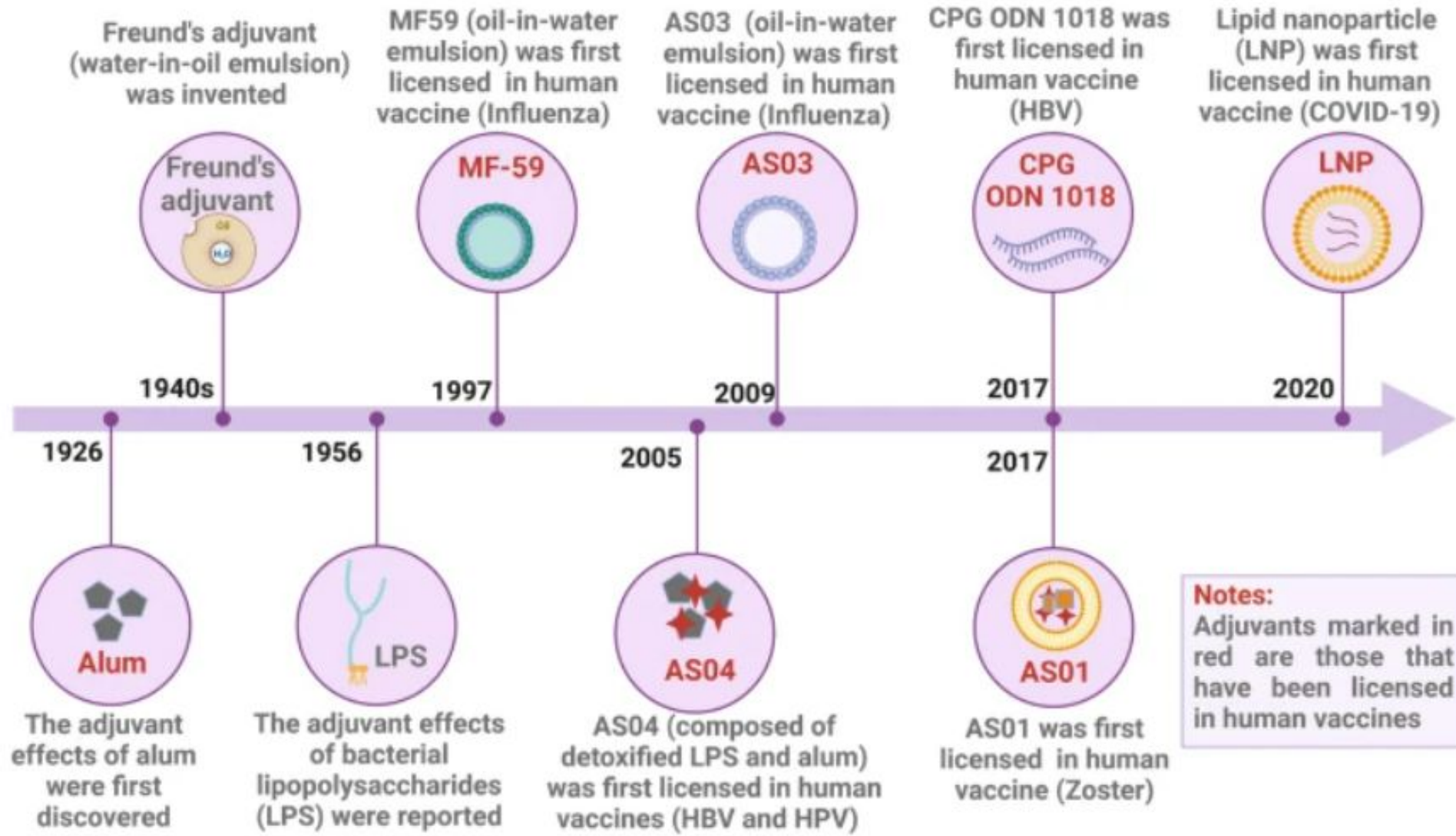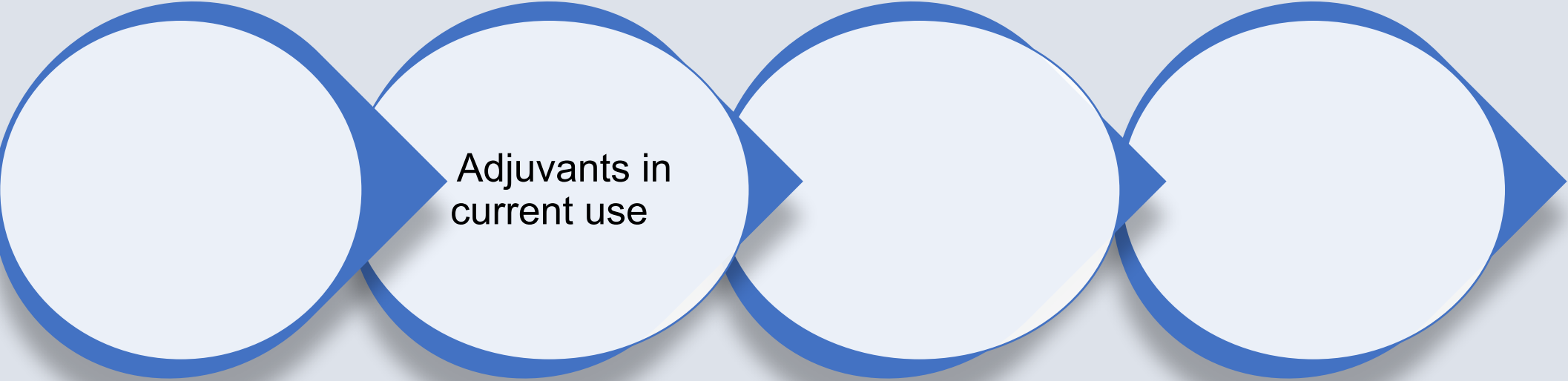| Adjuvant	Known knowns	Known unknowns
Alum Aluminium hydroxide Aluminium phosphate	Antibody response independent of TLR signalling[52] Activation of NLRP3 inflammasome in macrophages and DCs[53,54] Activation of DCs is mediated by uric acid[59] Rapid recruitment of neutrophils and formation of NETs[62] Induces cell death that releases DNA, which triggers STING–IRF3 activation, necessary for IgE antibody and T_H2 cell responsed[62]	Innate receptors and signalling that result in antibody and T helper cell responses are poorly understood The relevance of stress response signals, tissue damage, and metabolic and nutrient sensing pathways is poorly understood There is conflicting evidence for a role of NLRP3 inflammasome in mediating adjuvant activity[53,54,57]
MF59 Squalene Tween (polysorbate) 80 Span 85	Activates macrophages and DCs at injection site[68] Induces chemokine secretion[71] Antibody and $CD4^+$ T cell responses depend on transient release of ATP by muscle cells[71] TLR-independent MyD88 activation and NLRP3-independent ASC activation[74,75] Stimulation of antigen-specific $CD8^+$ T cells in tissues is via RIPK3-dependent pathway[76]	Innate receptors and signalling that result in antibody and T helper cell responses are poorly understood The relevance of stress response signals, tissue damage, and metabolic and nutrient sensing pathways is poorly understood
AS04 Alum MPL	Enhanced antigen presentation by AS04-activated DCs in comparison with alum[78] TLR4 activation by MPL is critical and alum prolongs TLR4-induced responses[78]	Innate receptors and signalling that sense alum and result in antibody and T helper cell responses poorly understood
AS03 Squalence and α-tocopherol Tween (polysorbate) 80	Induction of NF-κB activity and chemokine response locally and in draining lymph nodes in mouse between 6 and 48 h (REF.[88]) α-Tocopherol activates human monocytes and macrophages[87]	Innate receptors and signalling that result in antibody and T helper cell responses are poorly understood The relevance of stress response signals tissue damage, and metabolic and nutrient sensing pathways is poorly understood
AS01 MPL QS-21 Liposomes	Local secretion of chemokines, and IFNγ by NK cells and $CD8^+$ T cells in draining LNs within hours[101] QS-21 activates caspase 1 in SSMs[98] Induces differentiation of monocytes to DCs[211] Heterogeneous DC populations responsible for T cell activation in draining LNs[213]	Innate receptors and signalling that sense QS-21 and result in antibody and T helper cell responses are poorly understood The relevance of stress response signals, tissue damage, and metabolic and nutrient sensing pathways is poorly understood

Aluminum (D, T, pertussis, IPV, hepatitis A & B, HPV, meningococcal and pneumococcal) — Aluminum as salts mixed with antigen (adsorption)

MF59® (Influenza-seasonal and pandemic) — Squalene

AS04 (Hepatitis B, HPV) — (3-deacyl-monophosphoryl lipid A) derived from LPS from *Salmonella Minnesota*, *Aluminum salts*

AS03 (Influenza-pandemic)
- Vitamin E (α-Tocopherol)
- Surfactant polysorbate 80
- Squalene

Agenda

Benefits
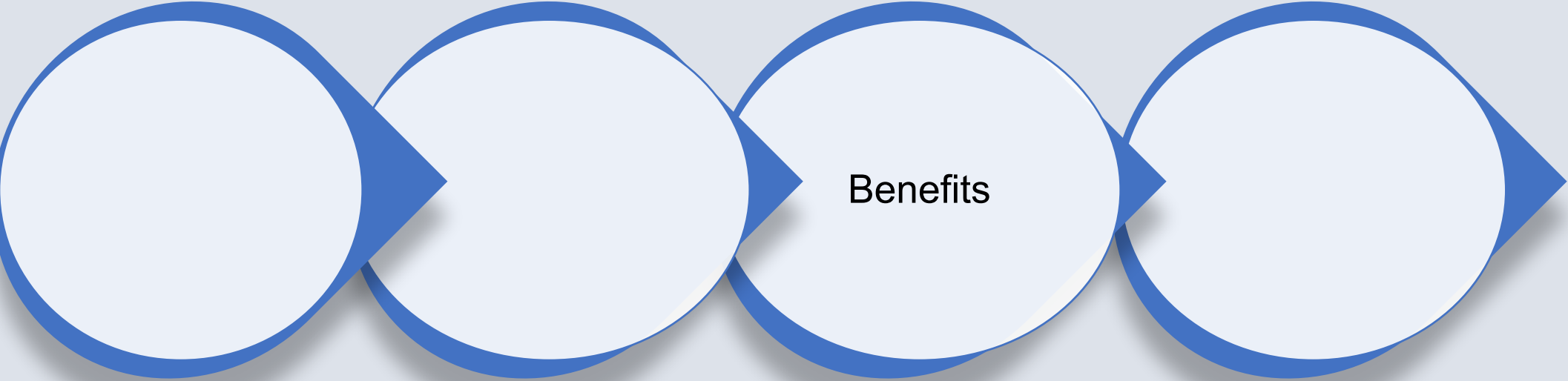
Current examples

- MF 59
- ASO1
- LNP

MF59®: OIL-IN-WATER ADJUVANT

MF59
Approximately 160 nm

Span 85 (0.5%)
Tween 80 (0.5%)

H_2O

Squalene oil

H_2O

H_2O
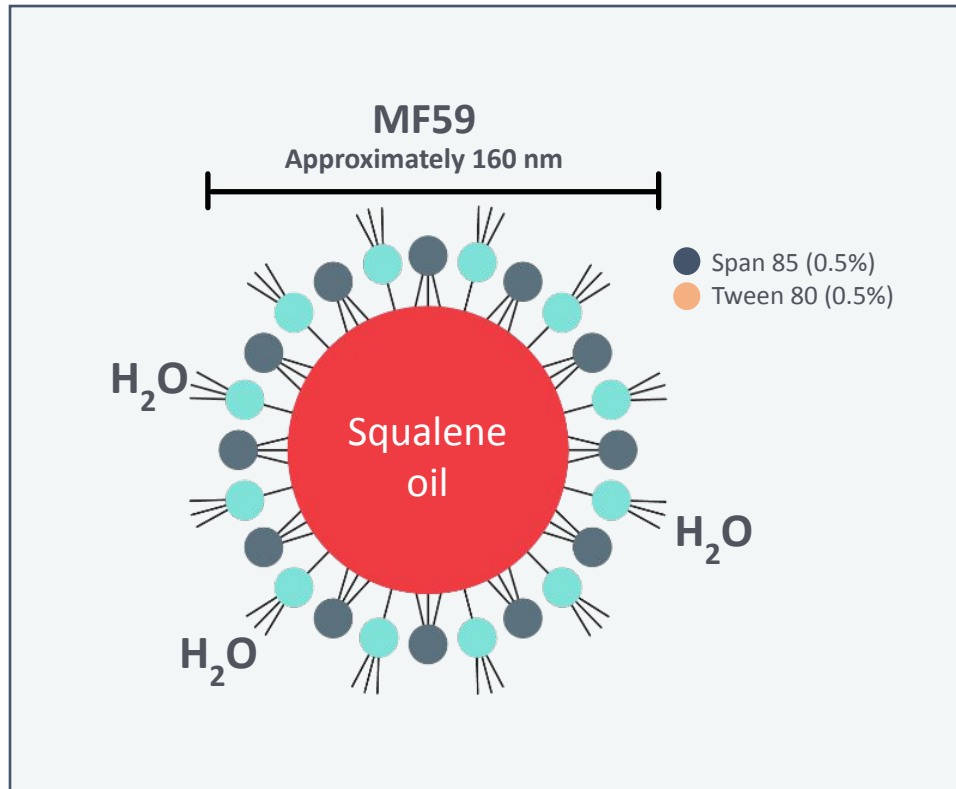
MF59 mechanism of action (Adapted from O'Hagan DT et al., 2013)

Injection site

1. MF59 promotes recruitment of immune cells[1,2]

Macrophages

MF59

Antigen

Chemo attractants

Release   Recruit

Monocytes and neutrophils

Increased antigen reuptake

APCs

Increased APC migration

Lymph node

3. T-cell activation and B-cell expansion[1,2,4,5]

Vaccine-specific responses

T-cell activation   B-cell activation   Antibody release

Neutralizing influenza-specific antibodies

2. MF59 enhances differentiation of immune cells into APCs[1,3]

First approved for use as an adjuvant in 1997, as part of aTIV (FLUAD®)[1]
MF59 is an oil-in-water emulsion composed of squalene, which is stabilised by Tween 80 and Span 85[2]

FLUAD® and MF59® are registered trademarks of Seqirus UK Limited or its affiliates.
APC, antigen-presenting cell; aTIV, adjuvanted trivalent influenza vaccine.
1. O'Hagan DT, et al. *Expert Rev Vaccines*. 2013;12(1):13–30; 2. Fluad [package insert]. Summit, NJ: Seqirus Inc; 2020.

BODY OF EVIDENCE – SEASONALITY
RELATIVE VACCINE EFFECTIVENESS aTIV VS QIVe OVER 3 US SEASONS

	Boikos C *et al*	Pelton S *et al*	Izurieta H *et al*
	Influenza related Medical encounters (65+ years)	Influenza related hospitalisations/ ER visits (65+ years)	Influenza related hospitalisations/ ER visits (65+ years)
2017/18	rVE= 18.2% (95%CI 15.8, 20.5)[#1]	rVE= 8.6% (95%CI 1.2, 15.6)[2]	rVE= 3.9% (95%CI 1.4, 6.3)[3]
2018/19	rVE= 27.8% (95%CI 25.7, 29.9)[#1]	HD-TIV only comparator[6]	rVE= 7.7% (95%CI 3.9, 11.4)[4]
2019/20	rVE= 27.5% (95%CI 24.4, 30.5)[7]	HD-TIV only comparator[8]	rVE= 8.2% (95%CI 4.2, 12.0)[5]

aTIV = MF59® Adjuvanted Trivalent Influenza Vaccine; QIVe = Standard-dose Egg-based Quadrivalent Influenza Vaccine.
[#]Primary results shown. *Post hoc* doubly robust analysis akin to 2019/20 season found rVE= 20.8% [18.4 to 23.2%] and 26% [23.4 to 28.6%] respectively

1. Boikos C et al. *Clinical Infectious Disease* [Epub ahead of print]. doi:10.1093/cid/ciaa1944/6064642. 2. Pelton SI et al. *Vaccines.* 2020; 8: 446. 3. Izurieta HS et al. *J Infect Dis.* 2018; 220: 1255–1264. 4. Izurieta HS et al. *J Infect Dis.* 2020; 222: 278–287. 5. Izurieta HS et al. *Clin Infect Dis.* 2020; ciaa1727. 6. Pelton SI et al. *Vaccine.* 2021. doi:10.1016/j.vaccine.2021.03.054. 7. Imran M et al. Relative effectiveness of MF-59-adjuvanted, trivalent influenza vaccine vs quadrivalent influenza vaccine and high-dose trivalent influenza vaccine in preventing influenza-related medical encounters in adults ≥65 years of age during the 2019-2020 influenza season in the United States. ISIRV-WHO Virtual Conference. 2021. 8. Levin M *et al.* Relative Effectiveness of Adjuvanted Trivalent Influenza Vaccine Compared to Egg-Based High-Dose Trivalent Influenza Vaccine Among Older Adults in the US During the 2019-20 Influenza Season. ISIRV-WHO Virtual Conference. 2021.

aTIV Is Effective in reducing Medical Encounters

a. Outpatient visit

Analysis	Season		VE, % (95% CI)	Pooling weight
Van Buynder (2013a)	2011/12		58.1 (4.9, 81.5)	11.3
Van Buynder (2013b)	2012/13		39.3 (13.8, 57.3)	61.4
Pebody (2020b)	2018/19		62 (3.4, 85)	8.7
PHE (2020)	2019/20		16.2 (−58.7, 55.7)	18.6
Pooled effect size (I sq=0%, *P*=0.44)			40.7 (21.9, 54.9)	

−60 −40 −20 0 20 40 60 80 100

Favors no vaccine ← **Favors aTIV** →

b. Hospital

Analysis	Season		VE, % (95% CI)	Pooling weight
Van Buynder (2013b)	2012/13		75.6 (55.3, 86.7)	22.3
Bella (2019)	2017/18		48.3 (18.7, 67.2)	31.1
Pebody (2020a)	2018/19		53.8 (39.8, 64.5)	46.6
Pooled effect size (I sq=52.9%, *P*=0.12)			58.5 (40.7, 70.9)	

−20 0 20 40 60 80 100

Favors no vaccine ← **Favors aTIV** →

aTIV, adjuvanted trivalent influenza vaccine; CI, confidence interval; I sq, I^2; VE, vaccine effectiveness.
Coleman BL, et al. *Influenza Other Respir Viruses*. 2021. doi: 10.1111/irv.12871.

aTIV Outcome in Australia in 2019

- 2017 and 2019 were both big years with very high notifications in over 65 year group in a largely H3N2 year

- Qld data showed that in 2019 hospitalisations were down 60% cf 2017

- aTIV in elderly in 2019, non-adjuvanted in 2017

Age	Vaccine	VE (H3N2)	95% CI
All	QIV	37%	(24 - 59)
Under 18	QIV	34%	(-2 – 58)
18-64	QIV	39%	(23 – 53)
65 years +	aTIV	50%	(16 – 70)

Sullivan S et al Euro Surveill 2019

SUMMARY

Systematic review of 21 studies comparing aTIV with either no vaccination or egg-based vaccines in adults aged ≥65 years

Real-world evidence from North America or Europe during 2006–07 and 2019–20 influenza seasons

The MF59-adjuvanted trivalent influenza vaccine was effective in preventing influenza in adults aged ≥65 years

Compared with standard-dose egg-based QIV and TIV, aTIV was significantly more effective in preventing influenza-related medical encounters

The effectiveness of aTIV was comparable to high-dose TIV in preventing influenza-related medical encounters

ASO1

- AS01 is a liposome-based adjuvant that contains two immunostimulants (MPL and QS-21). A series of experiments in mice determined that AS01 induces a rapid and transient innate immune response at injected site and the draining lymph node.
- AS01 induces an innate-immune response that leads to the activation of a broad range of APCs that are efficient at presenting antigen to activate T cells leading to modulation and enhancement of protective immune response.
- AS01 activity depends on the synergistic contributions of MPL and QS-21.
- The common pattern to emerge from the clinical experience with AS01-adjuvanted vaccines is that AS01 promotes both antigen-specific antibodies and CD4$^+$ T cells, which can be detected in the peripheral blood.
- AS01 directs the response toward a predominantly IFN-driven pathway which may reinforce the cellular immune response.

ASO1

A liposome-based vaccine adjuvant system containing two immunostimulants: 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and the saponin QS-21.

Shingrix
Arexvy

T = 0

IM injection

Inflammation

Steady state

Day 7

Co-injection of antigen with AS01

AS01 increases release of chemokines attracting circulating granulocytes and monocytes

Activated APCs

Draining lymph node

AS01 induces IFN-pathway related pro-inflammatory cytokines

Cellular and cytokine responses peak at day 1 and has fully resolved by day 7
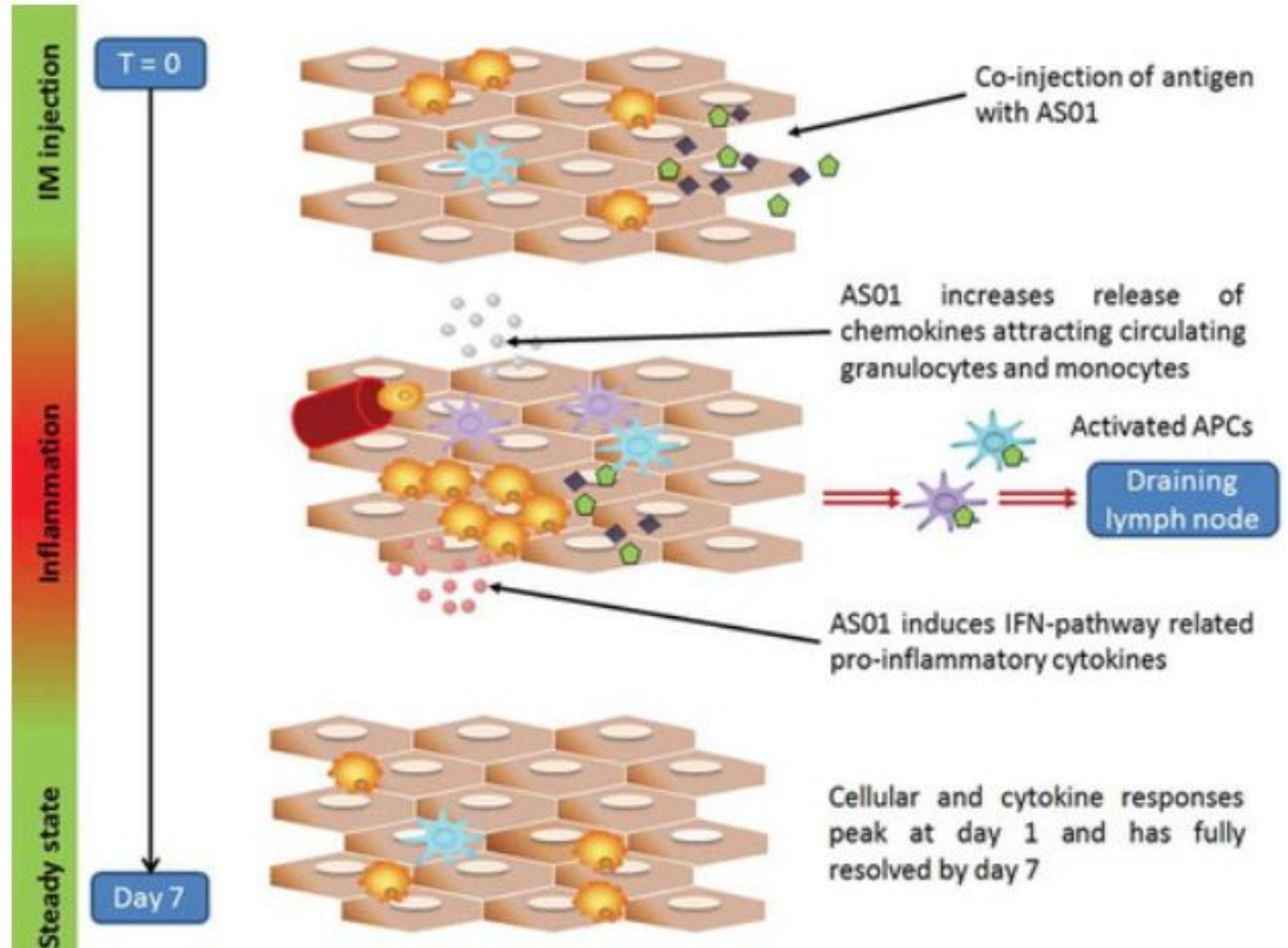
Shingrix was designed to help address age-related decline in immunity and immunocompromise[1-5]

ANTIGEN
Glycoprotein E
(gE)

SHINGRIX
Recombinant Varicella Zoster Virus glycoprotein E antigen (AS01$_B$ adjuvanted vaccine)

ADJUVANT SYSTEM
AS01$_B$

Elicits a specific immune response against VZV[6]
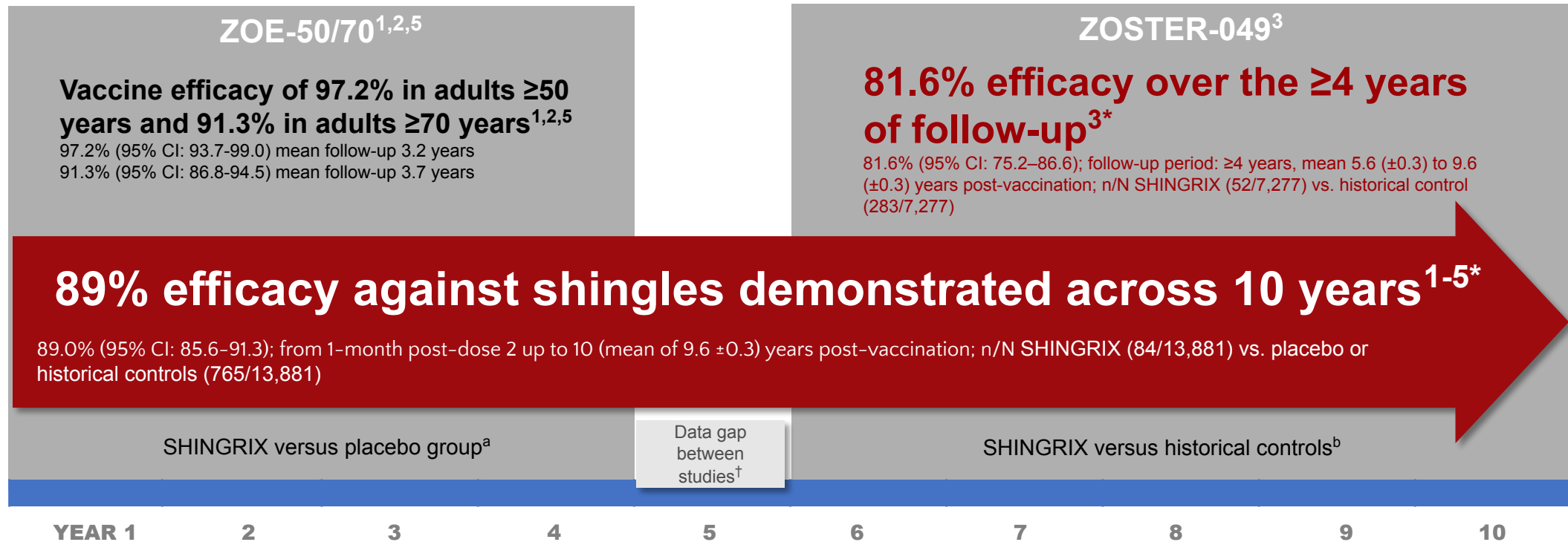
- Primary target for VZV-specific immune response[8]
- Expressed on the surface of VZV-infected cells[8]
- Key to viral replication[8]

Enhances the immune response to the vaccine antigen[6,7]

- Designed to induce strong and sustained anti-gE immune response[8]
- The combination of MPL and QS-21 enhances both antibody and cellular immune response against gE[8]

MPL=monophosphoryl lipid A; QS-21=*Quillaja saponaria* Molina fraction 21; VZV=varicella zoster virus

1. Chlibek R, et al. Vaccine. 2014 Mar;32(15):1745-53. **2.** Lal H, et al. N Engl J Med. 2015 May;372(22):2087-96. **3.** Bharucha T, et al. Hum Vaccin Immunother. 2017 Aug;13(8):1789-97. **4.** Garçon N, et al. Vaccine adjuvants. Amsterdam: Elsevier; 2011. **5.** SHINGRIX Approved Product Information. **6.** Dendouga N, et al. Vaccine. 2012 Apr;30(20):3126-35. **7.** Leroux-Roels G, et al. Clin Immunol. 2016 Aug;169:16-27. **8.** Lecrenier N, et al. Exp Rev Vaccine. 2018 Jun;17(7):619-634.

HIGH EFFICACY AGAINST SHINGLES SUSTAINED ACROSS 10 YEARS AND CONTINUES TO BE MONITORED[1-5]

ZOE-50/70[1,2,5]

Vaccine efficacy of 97.2% in adults ≥50 years and 91.3% in adults ≥70 years[1,2,5]

97.2% (95% CI: 93.7–99.0) mean follow-up 3.2 years
91.3% (95% CI: 86.8–94.5) mean follow-up 3.7 years

ZOSTER-049[3]

81.6% efficacy over the ≥4 years of follow-up[3]*

81.6% (95% CI: 75.2–86.6); follow-up period: ≥4 years, mean 5.6 (±0.3) to 9.6 (±0.3) years post-vaccination; n/N SHINGRIX (52/7,277) vs. historical control (283/7,277)

89% efficacy against shingles demonstrated across 10 years[1-5]*

89.0% (95% CI: 85.6–91.3); from 1-month post–dose 2 up to 10 (mean of 9.6 ±0.3) years post-vaccination; n/N SHINGRIX (84/13,881) vs. placebo or historical controls (765/13,881)

SHINGRIX versus placebo group[a]

Data gap between studies[†]

SHINGRIX versus historical controls[b]

YEAR 1   2   3   4   5   6   7   8   9   10

The image has been independently created by GSK from the original data. The same results were first published in Lal et al.[1], Cunningham et al.[2], Strezova A, et al.[3]

*Of the 14,648 ZOE-50/70 participants who received at least 1 SHINGRIX dose, 7,413 (50.6%) were enrolled in ZOSTER-049. Of these, 7,277 had previously received both SHINGRIX doses and were included in the modified total vaccinated cohort for the efficacy assessments. In the absence of an unvaccinated placebo group for the long-term follow-up study, the efficacy analyses in ZOSTER-049 used historical control estimates from the ZOE-50/70 placebo groups recorded during the trials. At this data lock point, data accrual was complete through Year 9. Results for Year 10 are also included although still incomplete, precision of estimates for this time point will increase at the final analysis.[3]

[a]SHINGRIX versus placebo recipients from the ZOE-50/70 trials, adjusted for age and region.[1,2,5] [b]SHINGRIX versus matched historical controls from the placebo group in the ZOE-50/70 trials, adjusted for age and region.[3,4] [†]No data are available for year 5 because that period corresponds to the gap between ZOE-50/70 and the ZOSTER-049 follow-up study[1-4]

CI, confidence interval; N, number of individuals included in each group; n, number of individuals having at least one confirmed herpes zoster episode.
1. Lal H, et al. N Engl J Med 2015;372:2087–96. **2.** Cunningham AL, et al. N Engl J Med 2016;75:1019–32. **3.** Strezova A. et al. Open Forum Infec Dis 2022; ofac485, https://doi.org/10.1093/ofid/ofac485. **4.** Boutry C, et al. Clin Infect Dis. 2022;74(8):1459-1467. **5.** SHINGRIX Approved Product Information GSK Australia

AREXVY includes both an antigen component and an adjuvant system[1]

- Immunity after natural RSV infection wanes.[2] People can experience reinfection throughout their lives[2-4]

- Older adults have higher rates of serious complications with RSV infection,*[5-7] partly due to age-related decline in immunity reducing an effective immune response[8-10]

- By combining the RSVPreF3 antigen with an adjuvant system (AS01$_E$), AREXVY induces an **antigen-specific cellular immune response and neutralising antibodies** that help protect against lower respiratory tract disease (LRTD) caused by RSV in adults aged 60 years and older.[1]

RSVpreF3 antigen
(120 µg)

+

AS01$_E$ Adjuvant System

=

AREXVY
(RESPIRATORY SYNCYTIAL VIRUS VACCINE RECOMBINANT ADJUVANTED)

Indicated efficacy against severe RSV-LRTD for your patients aged 60 years and older over 17.8 months (2 RSV seasons)[*][1-3]

1 RSV Season

Indicated efficacy against severe RSV-LRTD[1,2]

94.1%

Secondary descriptive endpoint, vs. placebo (95% CI, 62.4, 99.9); no adjustment for multiplicity, p value not reported.[‡]

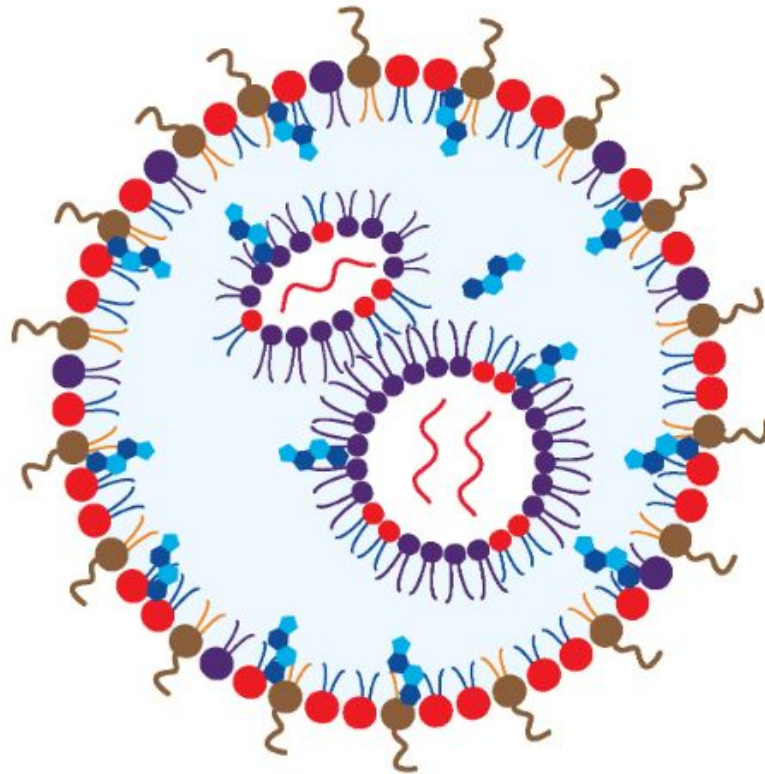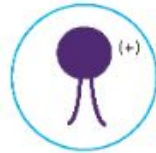RSV-LRTD events: AREXVY 1/12,466; placebo 17/12,494.[1,2]

2 RSV Seasons

Indicated efficacy against severe RSV-LRTD[3]

78.8%

Secondary descriptive endpoint, vs. placebo (95% CI, 52.6, 92.0); no adjustment for multiplicity, p value not reported.[‡]

RSV-LRTD events: AREXVY 7/12,469; placebo 48/12,498.[3]

Lipid nanoparticles

Ionizable cationic lipids (40-60%)

Possess transient cationic charge at low pH, form reverse micelles in complex with oligonucleotide cargos. Circumvent toxicity of cationic lipids. Critical LNP component for *in vivo* delivery.

Phospholipids (8-12%)

Contribute to particle structure and efficacy of membrane fusion, neutral/zwitterionic phospholipids commonly used.

PEGylated lipids (1-2%)

'Stealth lipid', prevent serum protein adsorption, nanoparticle aggregation, increase *in vivo* circulation time, can be functionalized for targeted delivery.

Sterol lipids (30-50%)

Provide structural integrity, aid in membrane fusion to target cell.

Cargo

Ionizable cationic lipids are ideal for encapsulating negatively charged oligonucleotides such as siRNA, mRNA, and pDNA.

Nanoparticle diameter 50-100 nm

Lipid nanoparticles

- Not just a carrier

- mRNA vaccines rely on the delivery of mRNA into the cytoplasm of host cells, where it can be transcribed into antigenic proteins to trigger the production of neutralizing antibodies.

- However, mRNA is three to four orders of magnitude larger than molecules that readily diffuse into cells;

- In addition, the dense negative charge of mRNA electrostatically repulses the anionic cell membrane, preventing its uptake.

- Therefore, mRNA vaccines require a delivery vehicle that not only protects the nucleic acid from degradation but allows the mRNA to get into cells. = various LNPs

Lipid nanoparticles

o Lipid nanoparticles are known to have their own adjuvant activity.

o Various studies, largely in mice have shown
  - o Increased recruitment of T follicular helper cells leading to increased long-term b cell memory and plasma cells
  - o Elicited potent antigen specific CD4$^+$ and CD8$^+$ T cell responses

Zhang L, More KR, Ojha A, Jackson CB, Quinlan BD, Li H, He W, Farzan M, Pardi N, Choe H. Effect of mRNA-LNP components of two globally-marketed COVID-19 vaccines on efficacy and stability. NPJ Vaccines. 2023 Oct 11;8(1):156. doi: 10.1038/s41541-023-00751-6. PMID: 37821446; PMCID: PMC10567765.

Buschmann MD, Carrasco MJ, Alishetty S, Paige M, Alameh MG, Weissman D. Nanomaterial Delivery Systems for mRNA Vaccines. *Vaccines*. 2021; 9(1):65. https://doi.org/10.3390/vaccines9010065
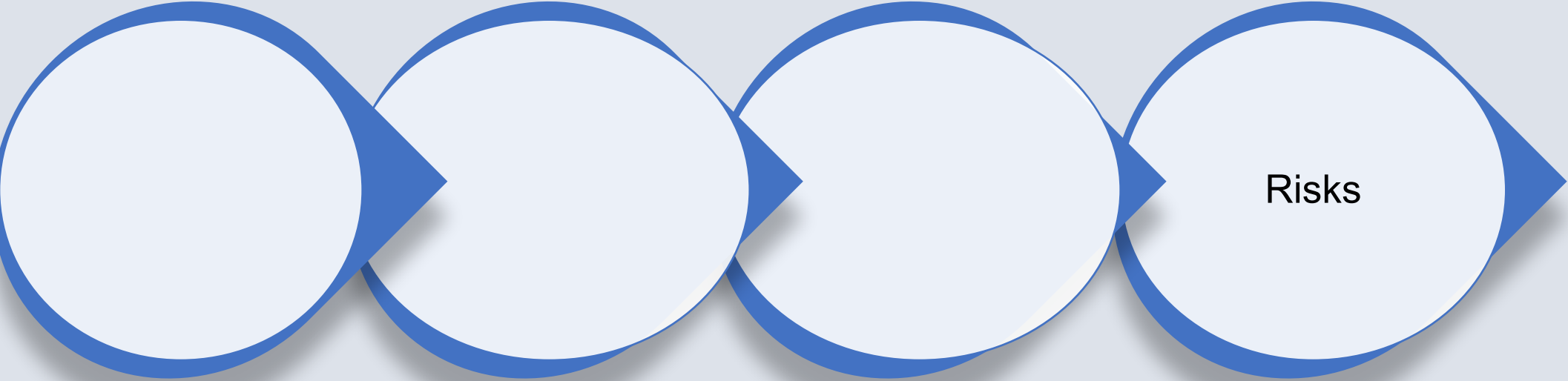
Works better = more reactogenicity
Does it matter?

- Examples: (ASO1)
  - Shingrix:
    - Solicited reports of injection-site and systemic reactions within 7 days after vaccination were more frequent in the vaccine group. There were solicited or unsolicited reports of grade 3 symptoms in 17.0% of vaccine recipients and 3.2% of placebo recipients.
    - The proportions of participants who had serious adverse events or potential immune-mediated diseases or who died were similar in the two groups.
  - Arexvy
    - Up to an order of magnitude more local reactions than placebo and 2-3 times systemic
    - In the solicited safety set, the local administration site adverse reactions reported with AREXVY had a median duration of 2 days. The systemic adverse reactions reported with AREXVY had a median duration ranging between 1 and 2 days.
    - Similar rates of SAEs (4.2% vs 4.0%), deaths (0.4% vs 0.5%), and pIMDs (0.3% vs 0.3%) were reported between participants who received AREXVY (n=12,467) and placebo (n=12,499), respectively.[1]

Works better = more reactogenicity
Does it matter?

- Examples: MF59
  - Compared with traditional trivalent influenza vaccines, MF59® adjuvanted trivalent influenza vaccines were associated with a greater number of local adverse events (RR = 1.90, 95% CI 1.50-2.39) and systemic reactions (RR = 1.18, 95% CI 1.02-1.38).
  - BC study. Pain at site 38% cf 29% ID and 20% TIV
 - 96% would have aTIV again

Benefits of mRNA COVID vaccines for Omicron outweigh risks

Benefit risk difference = incremental QALYs gained by vaccination − decremental QALYs lost by vaccination.

BENEFITS
Prevention of

- symptomatic nonhospitalized infection
- hospitalization
- admission to intensive care unit (ICU)
- death
- multisystem inflammatory syndrome in children (MIS-C)

RISKS
Adverse events following immunization (AEFI):

- anaphylaxis
- myocarditis
- others (eg, fever, headache, local pain)

Kitano T, et al. *Am J Epidemiol* 2023

Summary

- Recent years have brought on a range of new adjuvants leading to improved vaccines providing better protection for vulnerable groups

- While reactogenicity increases with improved protection the risk-benefit heavily favours vaccination

- Newer vaccines should be preferentially used
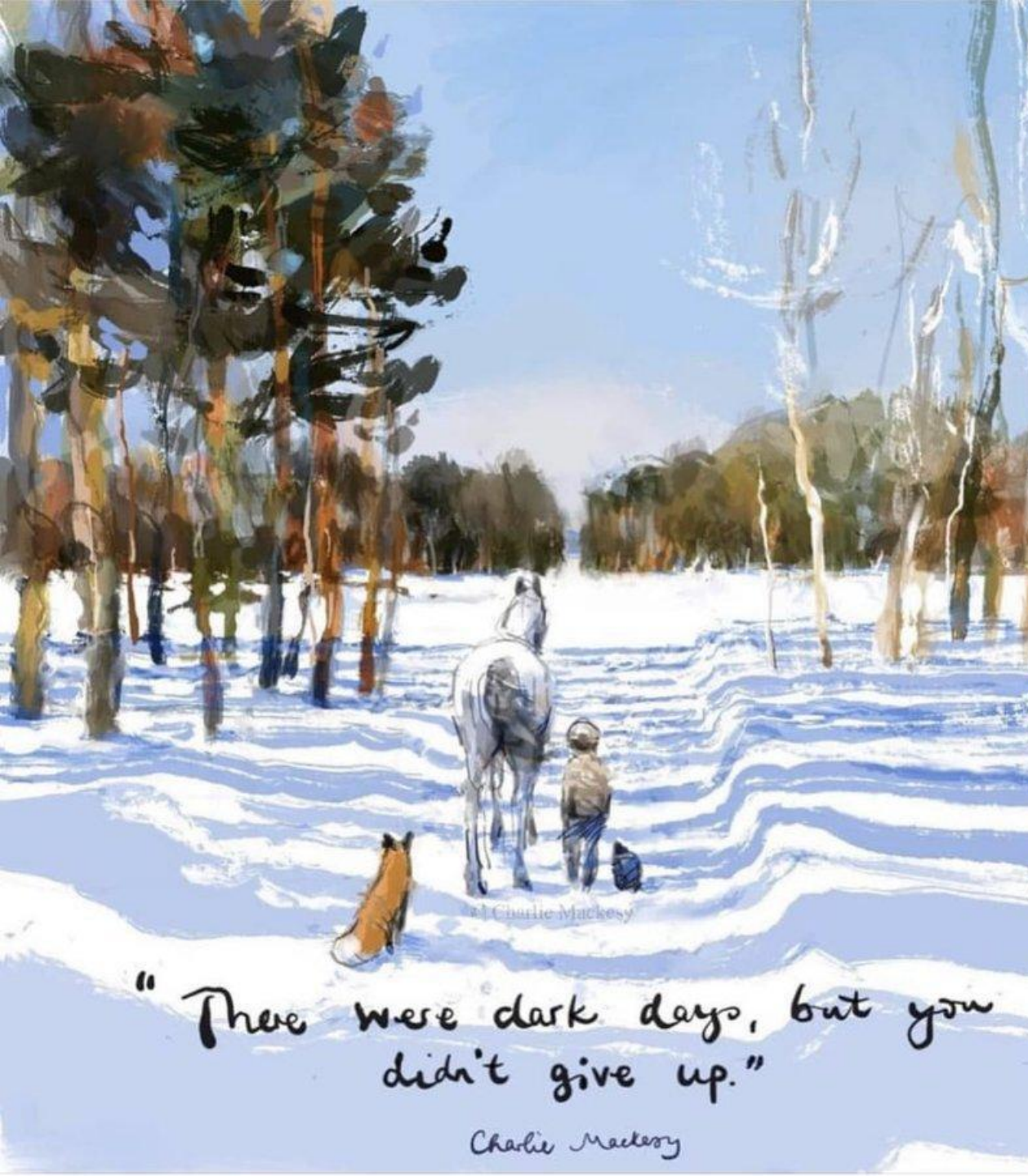
"There were dark days, but you didn't give up."
Charlie Mackesy

Questions?