Healthy ageing with Vaccination

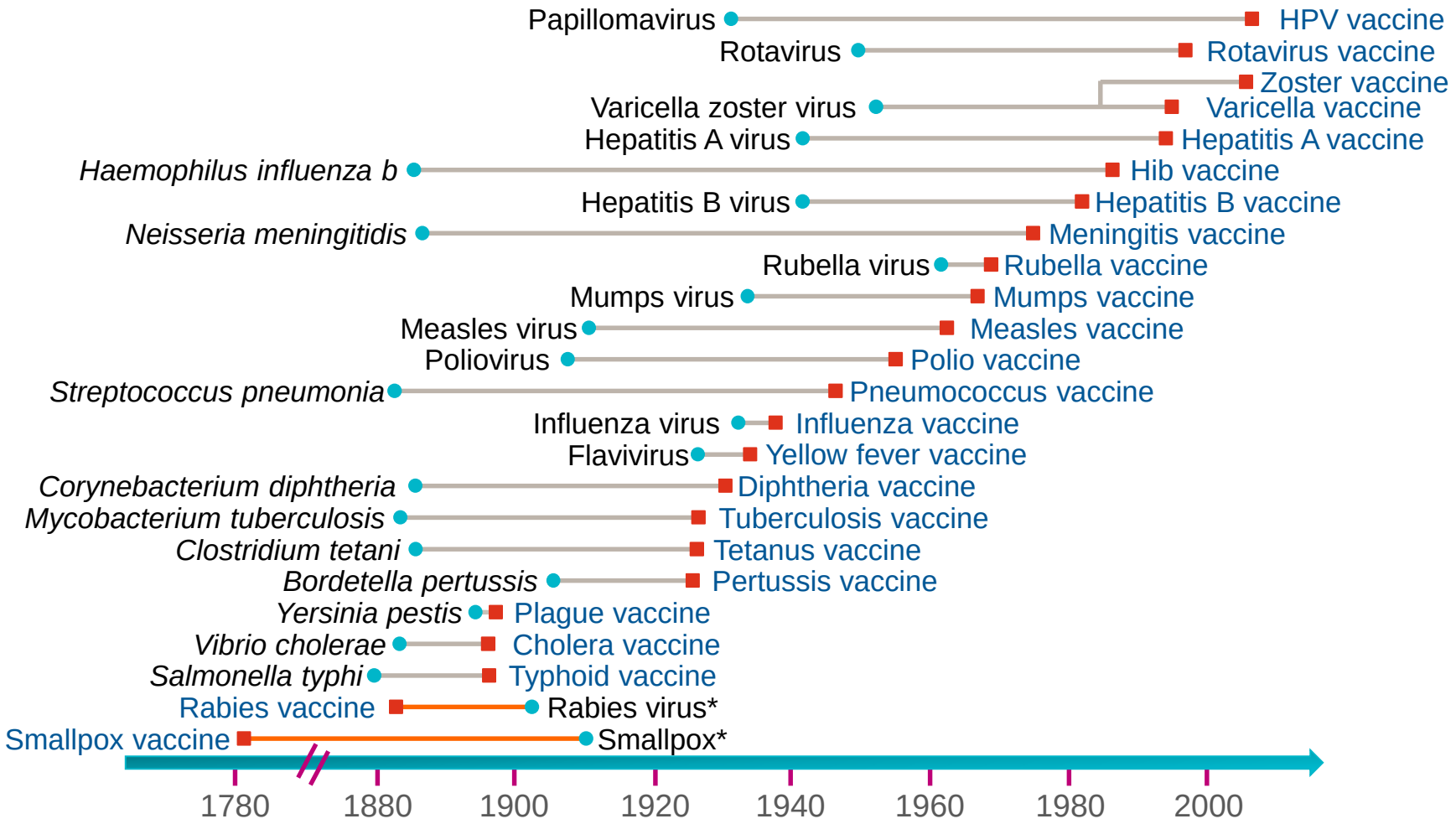
1808-VAB-16-0010-SSPH

Ageing population and vaccination

- The world's population is ageing in both economically advanced and developing countries
- WHO has defined the prevention of infectious diseases in the elderly as a global priority
- Infections are a major cause of morbidity and mortality in the elderly, and vaccination offers an ideal preventative tool
- There has been no focus on vaccinating the elderly in the less developed countries, but as the elderly population explosion continues this may well become an important way to maintain a healthy aging population worldwide.

Trans R Soc Trop Med Hyg 2016; 1–5

Pathogen isolation and vaccine availability



*During the development of the rabies and smallpox vaccines, it was discovered that the infectious agent was not a bacterium, although viruses would not be directly observed until the 1930s

Bonanni *et al.* Chapter 1 in: Garçon *et al.* Understanding Modern Vaccines, Perspectives in Vaccinology, Vol 1, Amsterdam, Elsevier, 2011, pp. 1–24

Ageing and noble approaches to vaccine design

Ageing and related physiologic changes

- Age-related disorders and conditions such as cancers, cardiovascular disease, diabetes, obesity and dementia are well-known risk factors for the occurrence of various Vaccine Preventable Diseases(VPD) e.g. influenza and invasive pneumococcal disease
- Many ageing people have polymorbidity
- Immunity conferred by childhood vaccines decreases with age and this phenomenon is called ‘immunosenescence’
- The burden of communicable diseases and mortality from VPDs are on the rise
- Improving vaccination strategies specifically aimed at elderly can reduce the burden of these chronic conditions

L. Ozisik et al. / European Journal of Internal Medicine 33 (2016) 14

ACIP's recommended Immunization Schedules for adults by age

Figure 1. Recommended Immunization schedule for adults aged 19 years or older, by vaccine and age group[1]

VACCINE ▼ / AGE GROUP ▶	19-21 years	22-26 years	27-49 years	50-59 years	60-64 years	≥ 65 years
Influenza*,2	1 dose annually					
Tetanus, diphtheria, pertussis (Td/Tdap)*,3	Substitute Tdap for Td once, then Td booster every 10 yrs					
Varicella*,4	2 doses					
Human papillomavirus (HPV) Female*,5	3 doses					
Human papillomavirus (HPV) Male*,5	3 doses					
Zoster6					1 dose	
Measles, mumps, rubella (MMR)*,7	1 or 2 doses depending on indication					
Pneumococcal 13-valent conjugate (PCV13)*,8	1 dose					
Pneumococcal 23-valent polysaccharide (PPSV23)8	1 or 2 doses depending on indication					1 dose
Hepatitis A*,9	2 or 3 doses depending on vaccine					
Hepatitis B*,10	3 doses					
Meningococcal 4-valent conjugate (MenACWY) or polysaccharide (MPSV4)*,11	1 or more doses depending on indication					
Meningococcal B (MenB)11	2 or 3 doses depending on vaccine					
Haemophilus influenzae type b (Hib)*,12	1 or 3 doses depending on indication					

*Covered by the Vaccine Injury Compensation Program

Recommended for all persons who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection; zoster vaccine is recommended regardless of past episode of zoster

Recommended for persons with a risk factor (medical, occupational, lifestyle, or other indication)

No recommendation

Report all clinically significant postvaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available at www.vaers.hhs.gov or by telephone, 800-822-7967.

Information on how to file a Vaccine Injury Compensation Program claim is available at www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382. To file a claim for vaccine injury, contact the U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington, D.C. 20005; telephone, 202-357-6400.

Additional information about the vaccines in this schedule, extent of available data, and contraindications for vaccination is also available at www.cdc.gov/vaccines or from the CDC-INFO Contact Center at 800-CDC-INFO (800-232-4636) in English and Spanish, 8:00 a.m. - 8:00 p.m. Eastern Time, Monday - Friday, excluding holidays.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

The recommendations in this schedule were approved by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the America College of Physicians (ACP), the American College of Obstetricians and Gynecologists (ACOG) and the American College of Nurse-Midwives (ACNM).

Reference. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm Advisory Committee on Immunization Practice Guidelines may include information those are not indicated in GSK vaccines' local label

ACIP's recommended Immunization Schedules for adults by medical condition

Figure 2. Vaccines that might be indicated for adults aged 19 years or older based on medical and other indications[1]

VACCINE ▼ INDICATION ▶	Pregnancy	Immuno-compromising conditions (excluding HIV infection)[4,6,7,8,13]	HIV infection CD4+ count (cells/μL)[4,6,7,8,13]		Men who have sex with men (MSM)	Kidney failure, end-stage renal disease, on hemodialysis	Heart disease, chronic lung disease, chronic alcoholism	Asplenia and persistent complement component deficiencies[8,11,12]	Chronic liver disease	Diabetes	Healthcare personnel
			< 200	≥ 200							
Influenza*[2]	1 dose annually										
Tetanus, diphtheria, pertussis (Td/Tdap)*[3]	1 dose Tdap each pregnancy	Substitute Tdap for Td once, then Td booster every 10 yrs									
Varicella*[4]	Contraindicated			2 doses							
Human papillomavirus (HPV) Female*[5]		3 doses through age 26 yrs				3 doses through age 26 yrs					
Human papillomavirus (HPV) Male*[5]		3 doses through age 26 yrs				3 doses through age 21 yrs					
Zoster[6]	Contraindicated				1 dose						
Measles, mumps, rubella (MMR)*[7]	Contraindicated			1 or 2 doses depending on indication							
Pneumococcal 13-valent conjugate (PCV13)*[8]		1 dose									
Pneumococcal polysaccharide (PPSV23)[8]		1, 2, or 3 doses depending on indication									
Hepatitis A*[9]		2 or 3 doses depending on vaccine									
Hepatitis B*[10]		3 doses									
Meningococcal 4-valent conjugate (MenACWY) or polysaccharide (MPSV4)*[11]		1 or more doses depending on indication									
Meningococcal B (MenB)[11]		2 or 3 doses depending on vaccine									
Haemophilus influenzae type b (Hib)*[12]		3 doses post-HSCT recipients only		1 dose							

*Covered by the Vaccine Injury Compensation Program

Recommended for all persons who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection; zoster vaccine is recommended regardless of past episode of zoster

Recommended for persons with a risk factor (medical, occupational, lifestyle, or other indication)

No recommendation

Contraindicated

Reference. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm Advisory Committee on Immunization Practice Guidelines may include information those are not indicated in GSK vaccines' local label

KSID's recommended Immunization Schedules for adults by age

Recommended Adult Immunization Schedule, by vaccine and age group - KSID, 2012

Vaccine \ Age group	19~29 years	30~39 years	40~49 years	50~64 years	≥ 65 years
Tetanus-Pertussis-Diphtheria	1-time dose of Tdap for Td booster; then boost with Td every 10 years (Strength I)		1-time dose with Tdap; Td at 1 and 6 months; then Td booster every 10 years (strength I) (Tdap only for adults under 65 years old)		
Influenza	1 dose annually (strength III)			1 dose annually (strength I)	
Hepatitis A	2 doses (at 0 and 6 months) (strength II)	For seronegatives, 2 doses (at 0 and 6 months) (strength II)		For high-risk groups[a], check serology; 2 doses for seronegatives (at 0 and 6 months) (strength II)	
Hepatitis B	When 3-doses of immunization uncertain, vaccinate the seronegatives (strength III)			For high-risk groups[b] with uncertain immunization history of 3-doses, vaccinate seronegatives (strength III)	
Measles/mumps/ rubella	For high-risk groups[c], at least 1 dose; check rubella IgG for women planning a pregnancy (strength II)				
Varicella	For high-risk groups[d], check serology; 2 doses for seronegatives (strength II)				
Human Papillomavirus	Female (strength II)				
Meningococcal	For high-risk groups[e], 1 or 2 doses (strength II)				
Pneumococcal	For high-risk groups[f], 1 dose (strength I)				1 dose (strength I)
Zoster				1 dose (strength U)	1 dose (strength III)

For all persons in this category who meet the age requirements
Recommended for adults if other risk factor is present
No recommendation

- Tdap = Adult Tetanus-Pertussis-Diphtheria; Td = Adult Tetanus-Diphtheria
- For persons aged ≤15 years, follow the recommendations by the Korean Pediatric Society
- For persons aged 16-18 years, if no other recommendation, follow the recommendation of those aged 19-29 years

Strengths of recommendation

(I) Very strongly recommended: immunization may reduce mortality and be cost-effective. Most countries recommend the vaccination.
(II) Strongly recommended: immunization may reduce mortality but cost-effectiveness is unknown in Korea. Most developed countries recommend the vaccination.
(III) Recommended: immunization may reduce morbidity rather than mortality. Cost-effectiveness is unknown.
(U) Recommendation reserved: lack of evidence for recommendation.

Reference. http://www.ksid.or.kr/file/vaccine_eng.pdf Korea Society of Infectious Disease
Guidelines may include information those are not indicated in GSK vaccines' local label

KSID's recommended Immunization Schedules for adults by medical condition

Vaccines that might be indicated for adults, based on medical and other indications

	Chronic liver diseases	Chronic kidney disease	Chronic lung diseases	Chronic Cardio-vascular diseases	Diabetes	Solid organ Cancers receiving chemotherapy	Solid organ transplantation	Stem cell transplantation	Recipients of immunosuppressants other than transplantation	Asplenia	HIV infection		Pregnancy	Soldiers on duty
											CD4 <200/μℓ	CD4 ≥200/μℓ		
Influenza														
Pneumococcal														
Td/Tdap							Tdap	DTaP/ Tdap						
Hepatitis A							a)							
Hepatitis B														
Varicella								b)						
MMR								b)						
Meningococcal														
Zoster														
Hib														

Vaccinations indicated based on medical and other conditions
Vaccinations based on general recommended schedule
Contraindicated
No recommendation

a) Hepatitis A vaccination is indicated for adult patients for liver transplantation.
b) Vaccinations may be considered 24 months after transplantation provided there is no evidence of graft-versus-host reaction.

Reference. http://www.ksid.or.kr/file/vaccine_eng.pdf Korea Society of Infectious Disease
Guidelines may include information those are not indicated in GSK vaccines' local label

Unmet needs in immunisation: challenging populations

Reduced immune competence[1]

Very young/ naïve[2]

Elderly/ Immunosenescence[3]

Chronic conditions/ Immunodeficiencies[4]

- Need to tailor vaccines to suboptimally responsive populations[5]
- Need to consider the issues of naïve populations versus pre-exposed populations

1. Zepp. *Vaccine* 2010;28S:C14–24; 2. Garcia A *et al. Immunologic Res* 2000;22:177–90; 3. Targonski PV *et al. Vaccine* 2007;25:3066–9;
4. Boasso A *et al. J Intern Med* 2008;265:78–96; 5. Jacques P *et al. Vaccine* 2002;20:3644–9

New strategies are required for the development of efficacious vaccines to protect against more complex pathogens

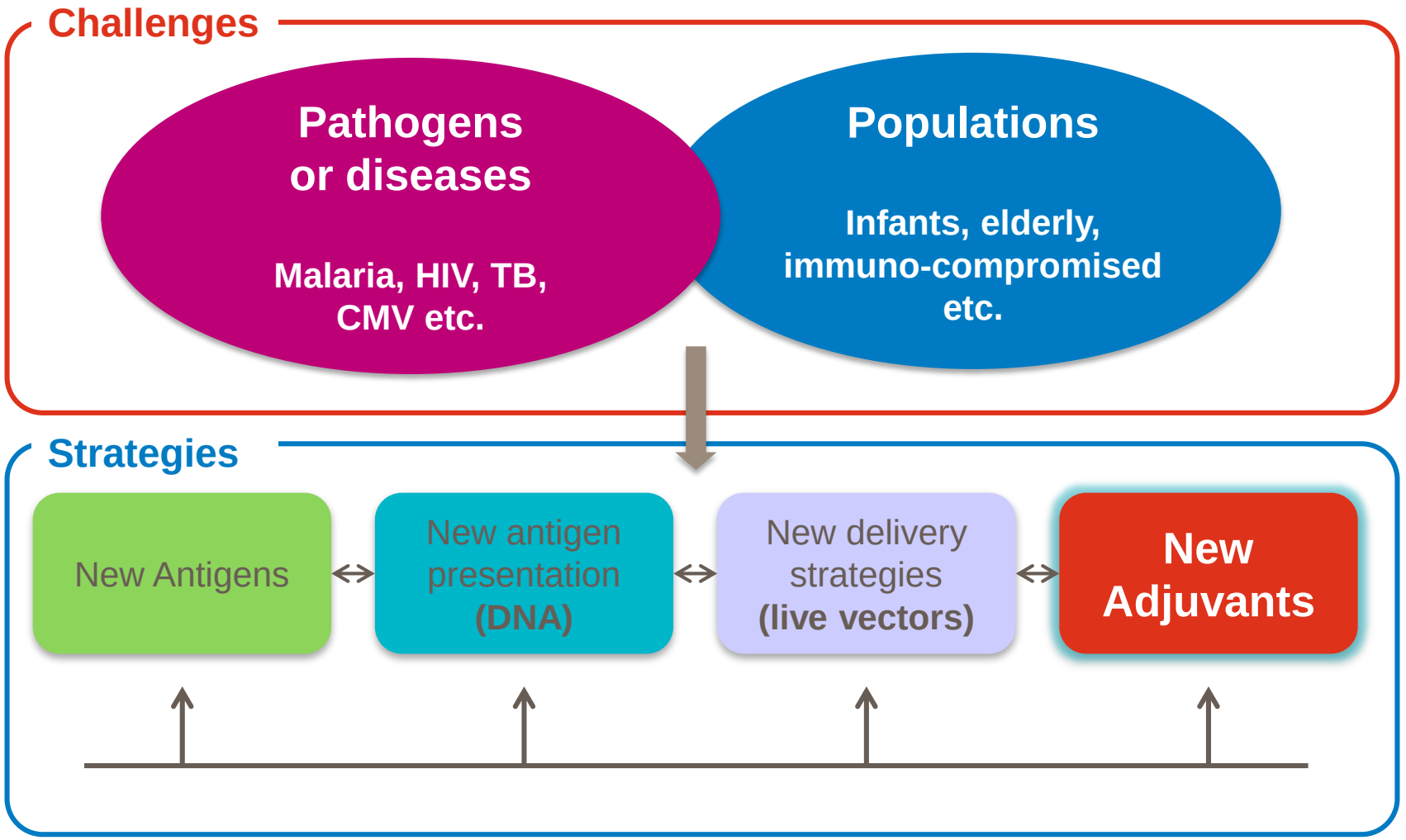
To enhance and guide the immune response

Induction of long-term persistence of the immune response: reducing the needs for boosters[1]

Better targeting of effector responses (cellular and humoral):
e.g. induction of Th1 response, T-cytotoxic response and antibody response[2]

1. Banatvala J. *Vaccine* 2001;19:877–85; 2. Pichyangkul S *et al. Vaccine* 2004;22:3831–40

Strategies to address challenges in vaccine development

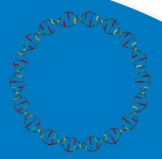


CMV = Cytomegalovirus; HIV = human immunodeficiency virus; TB = tuberculosis

Garçon N *et al.* Understanding Modern Vaccines: Perspectives in Vaccinology, Vol 1. Amsterdam: Elsevier; 2011 (chapter 6: p151–99)

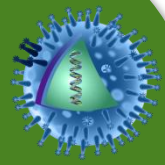
Novel approaches to vaccine design

DNA



- Pathogen-derived genetic material coding for the antigens contained in a non-replicating DNA plasmid
- Antigen is expressed by the cells of the vaccine recipient

Live vectors



- Targeted antigens encoded by gene(s) incorporated into the vector's genetic material
- Antigens expressed by a vector (like virus or bacterium) that is non-pathogenic

Novel adjuvants and adjuvant combinations

- Substances included in a vaccine formulation to enhance the quality and strength of the immune response induced by the vaccine antigen(s)

Garçon N *et al.* Understanding Modern Vaccines: Perspectives in Vaccinology, Vol 1. Amsterdam: Elsevier; 2011 (Chapter 3: p61–88);
Garçon N *et al.* Understanding Modern Vaccines: Perspectives in Vaccinology, Vol 1. Amsterdam: Elsevier; 2011 (Glossary: pXI- XXII)

Adjuvant

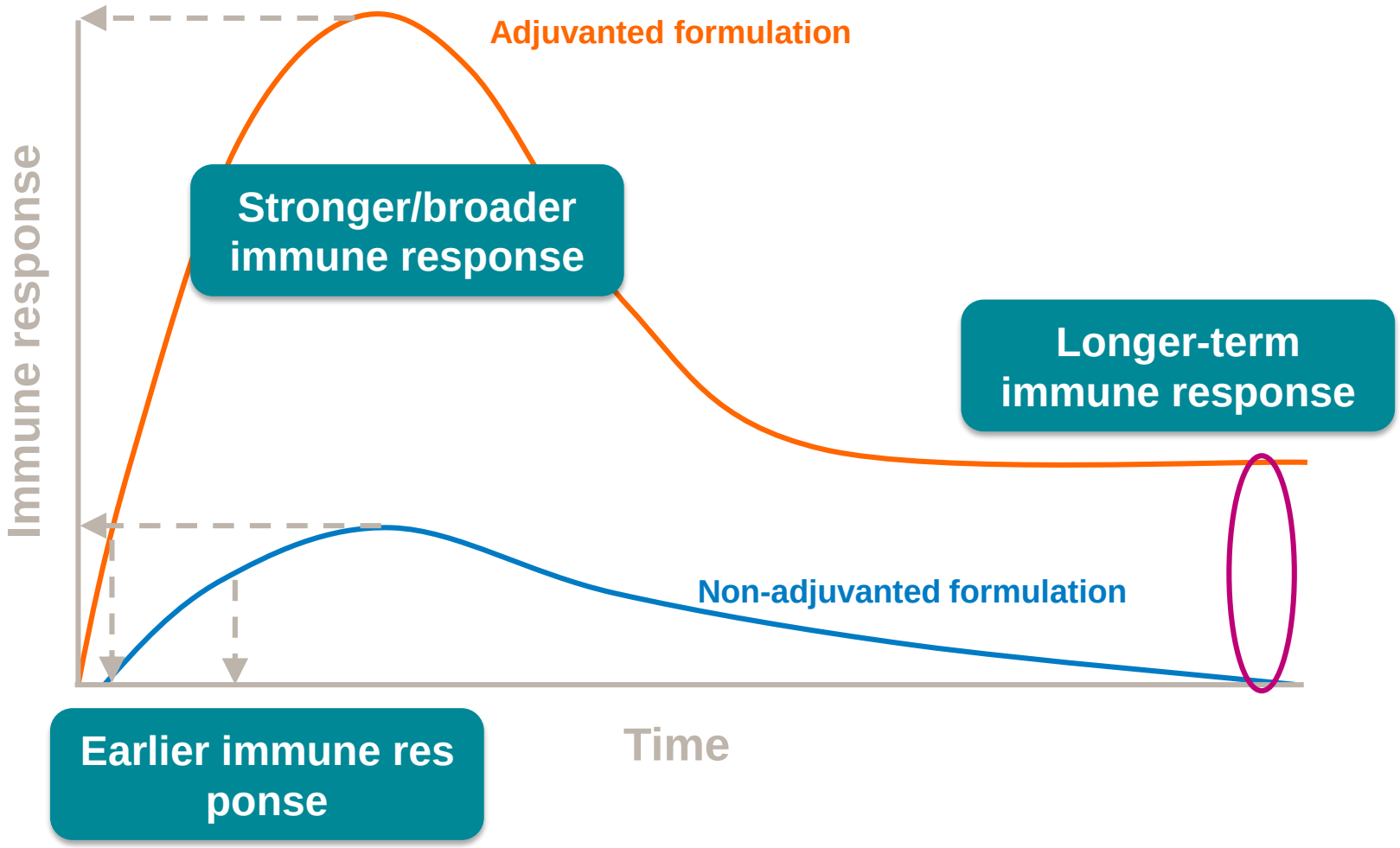
What is an adjuvant?

- Adjuvants are substances that are intended to enhance relevant immune responses and subsequent clinical efficacy of vaccines[1]

- A vaccine adjuvant is a component that potentiates the immune responses to an antigen and/or modulates it towards the desired immune responses[2]

1. WHO. Technical Report No. 927, 2005. Available at: www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf (Accessed November 2014);
2. EMA. Guideline on adjuvants in vaccines for human use. 2005. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003809.pdf (Accessed November 2014)

Adjuvant: expected impact on vaccine response



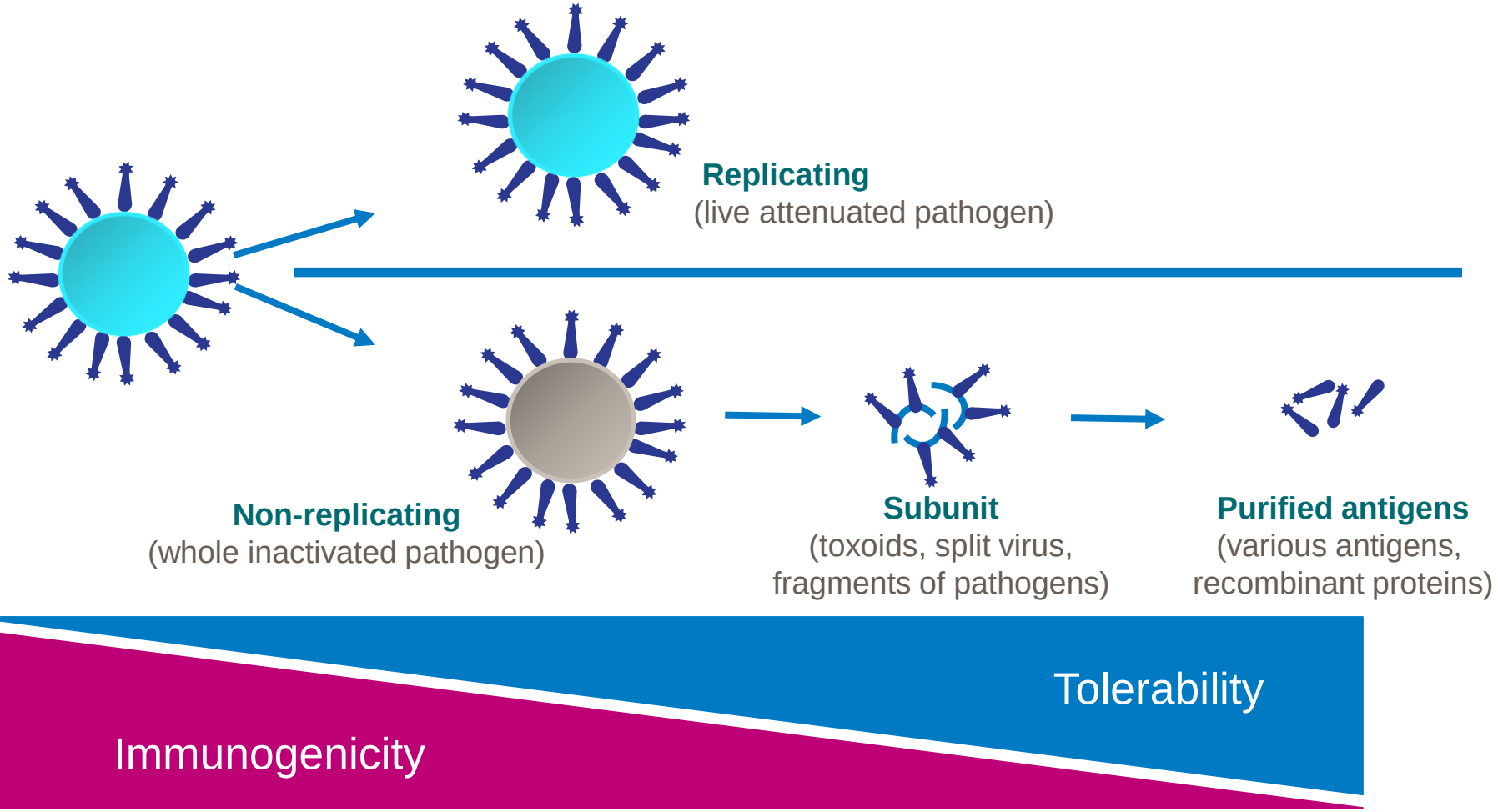
Adapted from Garçon *et al.* Chapter 4 in: Garçon *et al.* Understanding Modern Vaccines, Perspectives in Vaccinology, Vol 1, Amsterdam. Elsevier 2011;p89-113

Elderly and vaccine immune response

- Decline in innate immunity and concomitant inflammaging in the elderly
- Declining adaptive immunity in the elderly
- Poorer vaccine responses and vaccine efficacy in the elderly
- We are only just beginning to understand how the human immune system ages, and to identify molecular pathways that might be targeted by vaccination.
- Strategies to improve vaccine efficacy have included the use of new adjuvants, different routes of immunization (e.g., intradermal), higher vaccine doses and boosters with limited benefits.

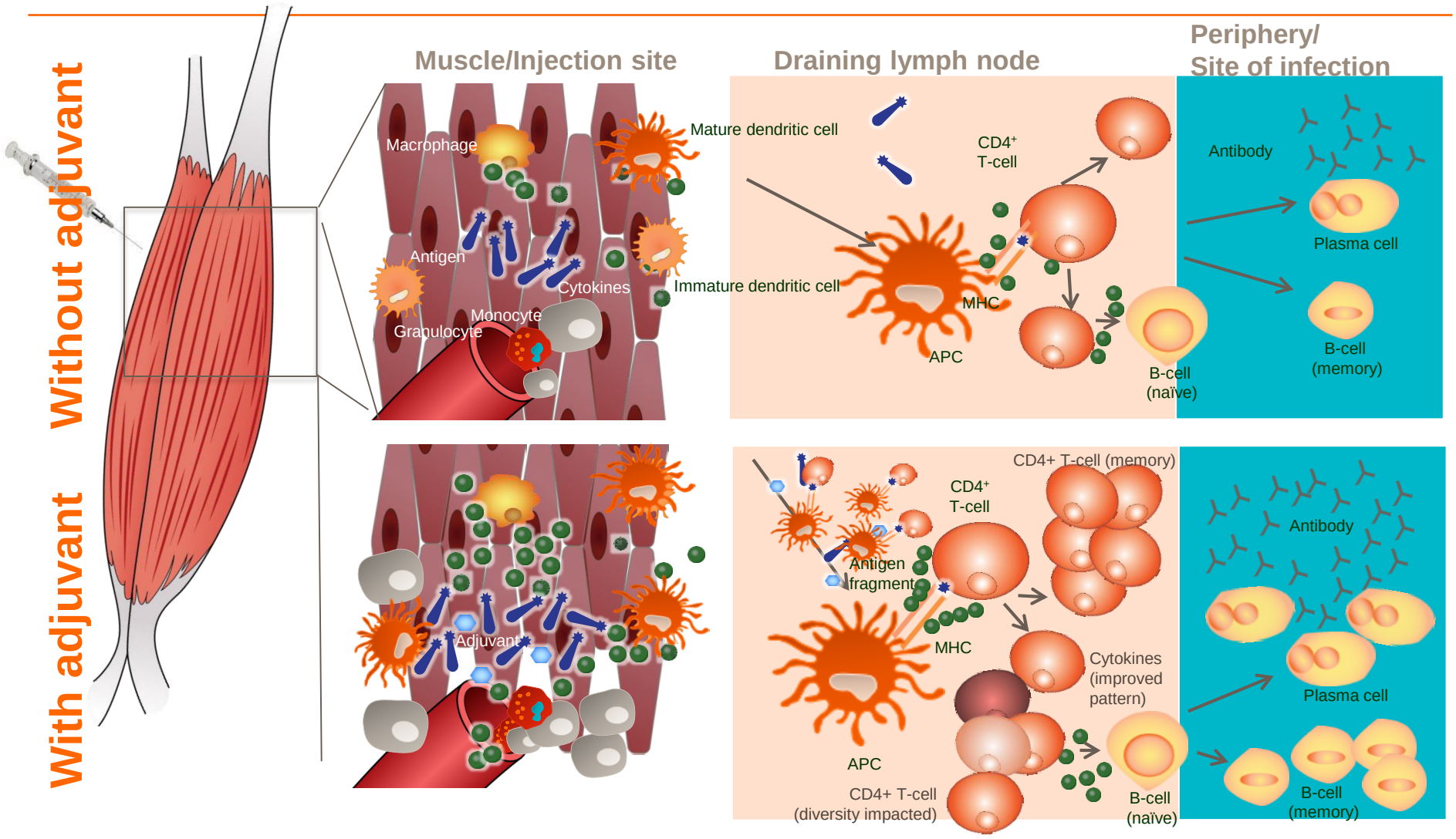
Trans R Soc Trop Med Hyg 2016; 1–5

Why do we need new approaches?



Dougan G & Hormaeche C. *Vaccine* 2006;24S2:S2/13–9; Garçon N & Van Mechelen M. *Expert Rev Vaccines* 2011;10:471–86

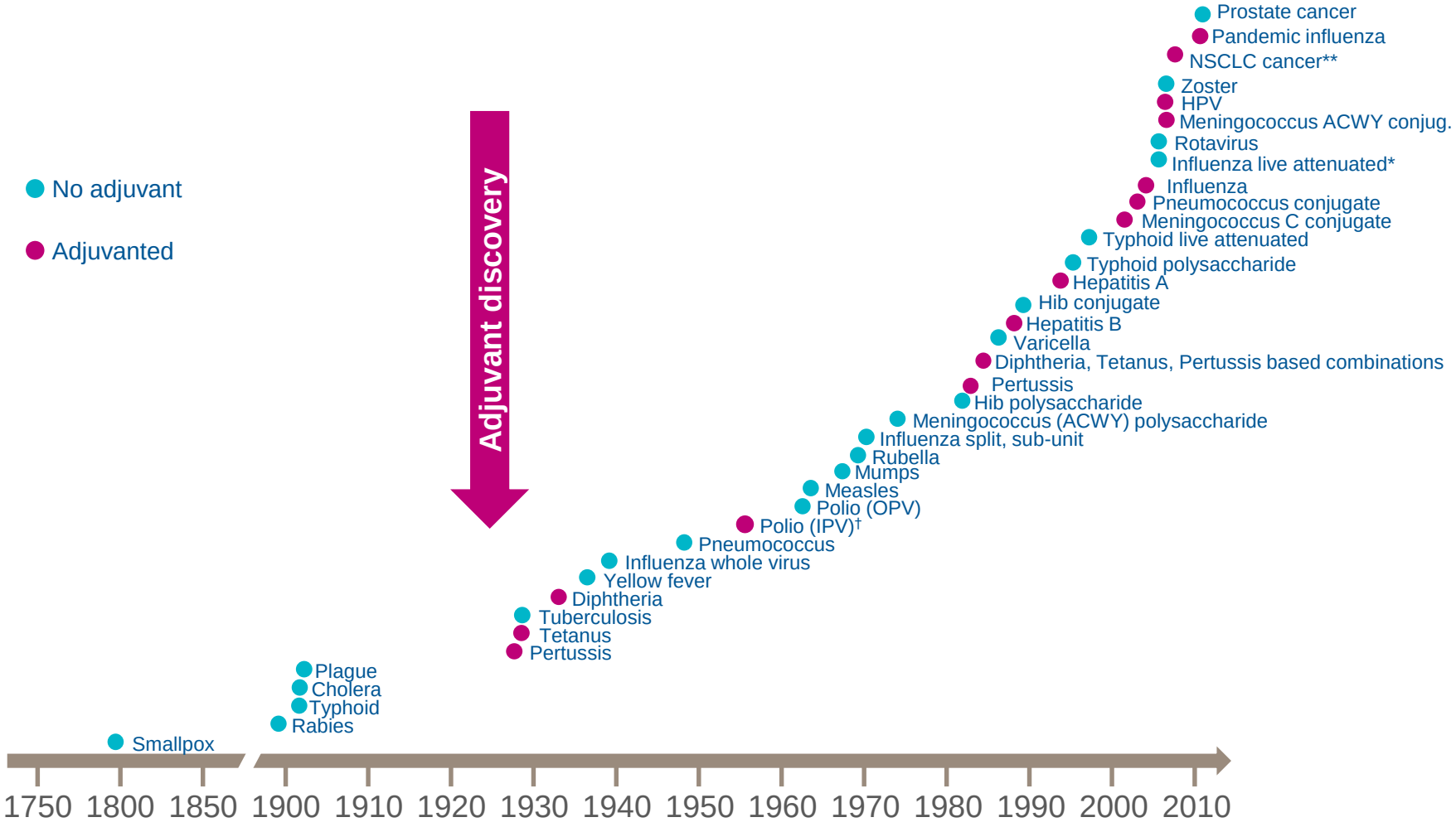
With or Without Adjuvant



APC = antigen-presenting cell; MHC = major histocompatibility complex

Garçon N *et al.* Understanding Modern Vaccines: Perspectives in Vaccinology, Vol 1. Amsterdam: Elsevier; 2011 (Chapter 4: p89–113)

Vaccines with or without adjuvants



*Reassortant, **Registered in Cuba and Chile, †IPV is adjuvanted when formulated in combination with diphtheria, tetanus, pertussis-based vaccines, but is not adjuvanted when formulated as a standalone vaccine. NSCLC = non-small cell lung cancer; HPV = human papilloma virus; Hib = Haemophilus influenzae type b; IPV = inactivated polio vaccine; OPV = oral polio vaccine (live).

Adapted from *Understanding Modern Vaccines: Perspectives in Vaccinology*, Vol. 1, Strugnell *et al.* in: Garçon N *et al.* (ed), Chapter 3: p61–88, copyright Elsevier, 2011

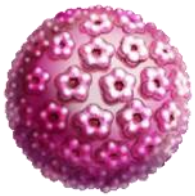
AS04 and HPV vaccine

The adjuvanted vaccine design principle

Vaccine

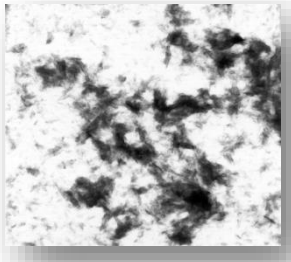
Antigen
HPV L1 16/18 VLPs

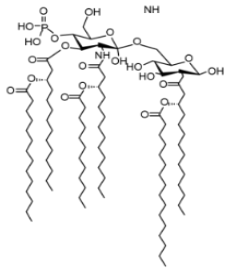
Specificity of the immune response



Adjuvant System
AS04

Designed to enhance the immune response to vaccine antigen





Courtesy of GSK

HPV = human papilloma virus; VLP, virus-like particle

Garçon N *et al. Expert Rev Vaccines* 2011;10:471–86;
Garçon N *et al.* Understanding Modern Vaccines: Perspectives in Vaccinology, Vol 1. Amsterdam: Elsevier; 2011 (Chapter 4: p89–113)

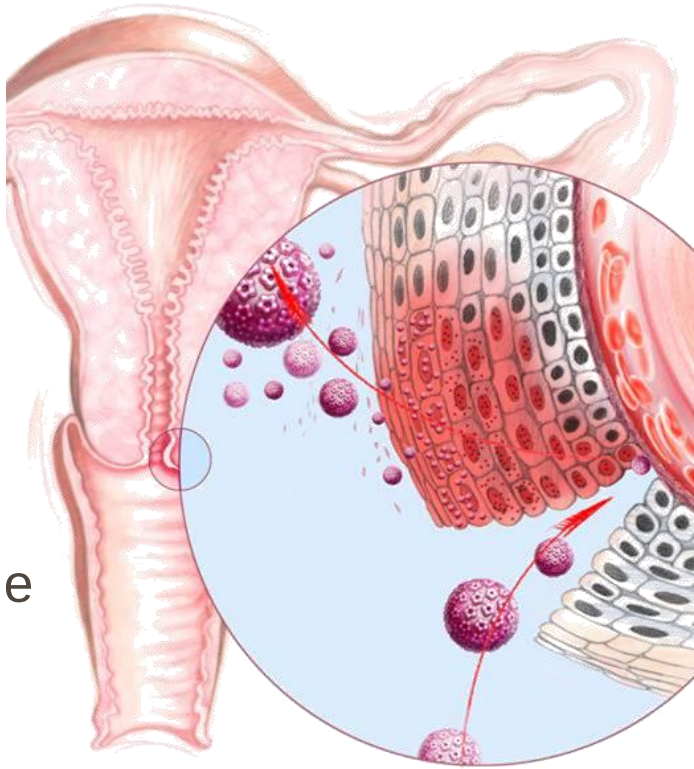
HPV vaccine: development rationale

- Girls and women are at risk of HPV infection throughout their life from sexual debut
- Natural immune responses following infection with oncogenic HPV types may not always protect against subsequent HPV infection or eliminate the risk of persistent infection
- It is important to protect women

  throughout their lifetime
- Long-term protection will require

  high quality and sustained immune response
- Vaccine should have

  an acceptable safety and reactogenicity profile

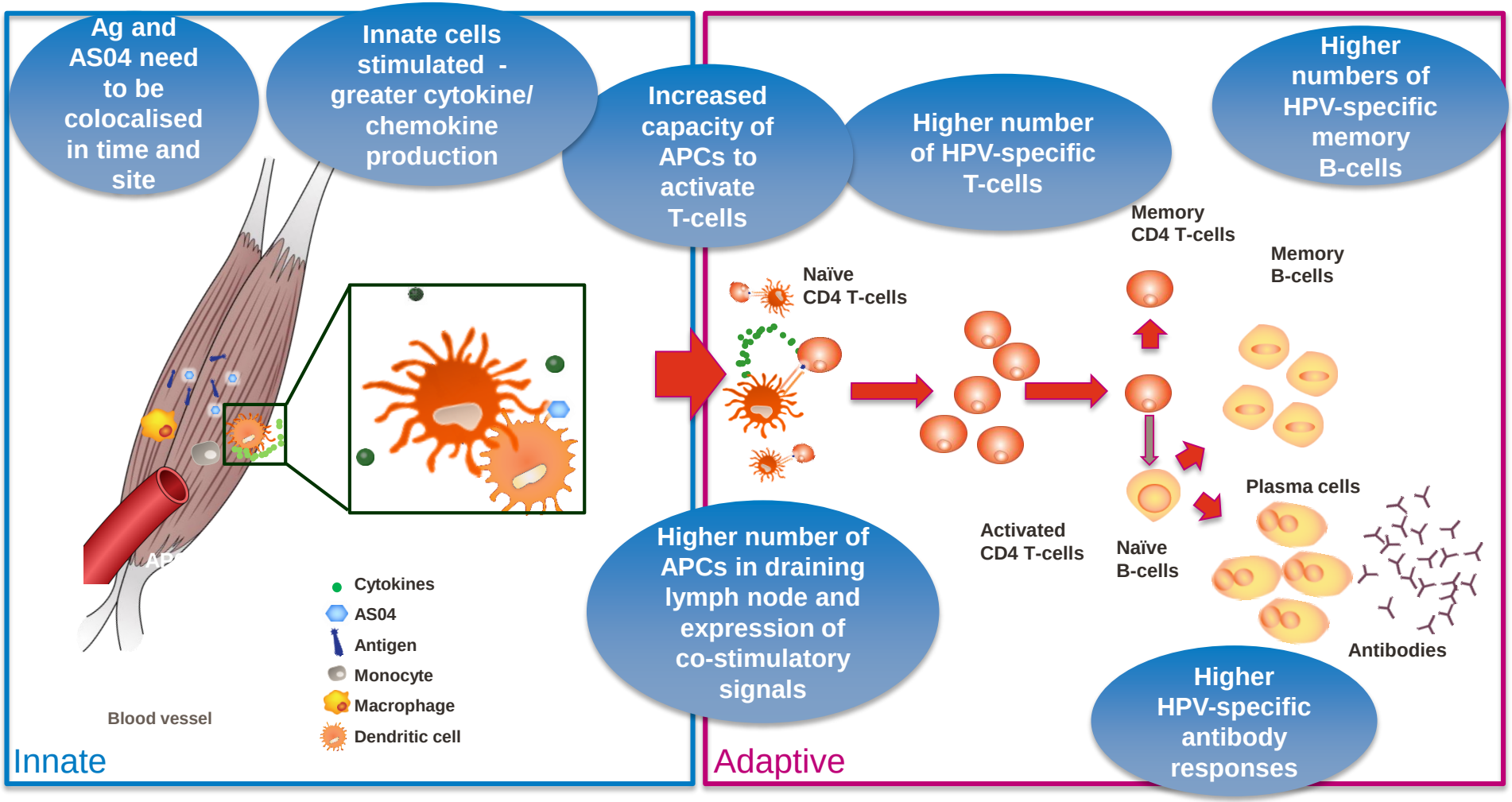


HPV = human papilloma virus

Garçon N *et al. BioDrugs* 2011;25:217–26

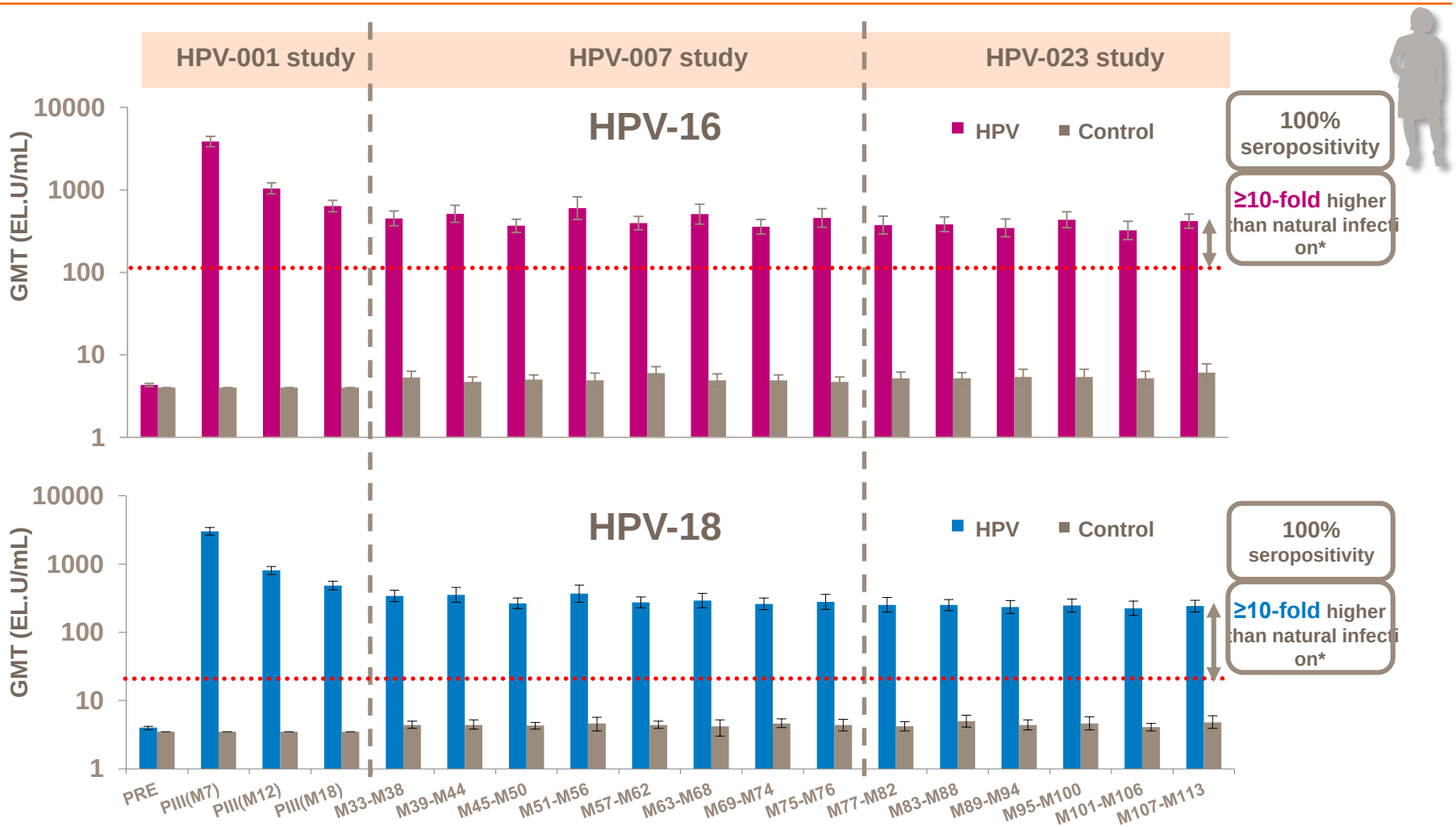
Stern PL, Einstein MH. *Curr Cancer Ther Rev* 2010; 6: 110–6. Illustration from Florence Gendre©

AS04 Mode of Action: key points



Didierlaurent AM *et al. J Immunol* 2009;183(10):6186–97; Garçon N *et al. Biodrugs* 2011;25:217–26

Immunogenicity up to 9.4 years (ELISA) (HPV-023 ATP immuno cohort)



Red line indicates natural infection levels; HPV = human papilloma virus

*Antibody levels in women (seropositive and DNA-negative) from a phase III study who cleared a natural infection before enrolment

Adapted from Roteli-Martins *et al. Hum Vaccin Immunother* 2012;8:390–397; CTRS (Adapted from GSK Clinical Study Register); EMA. Cervarix® European Summary of Product Characteristics, 2015. Available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf (Accessed April 2015)

Overall vaccine efficacy results against CIN2+ and CIN3+

Approximate to young women before sexual debut: ≥ 1 dose

End-of-study analysis;[1] TVC-naïve cohort*

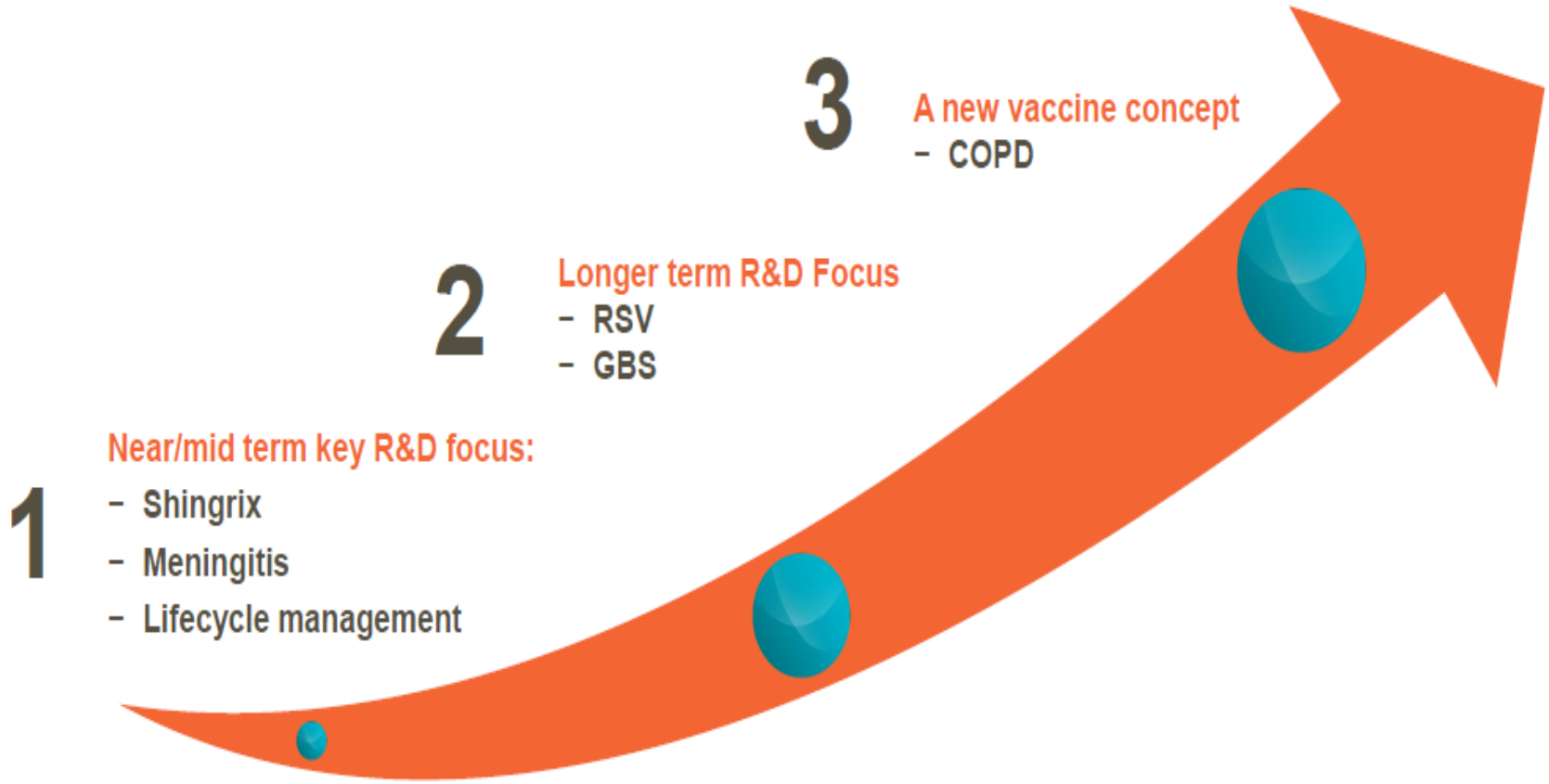
Endpoint	Vaccine cases (N = 5,466)	Control cases (N = 5,452)	Efficacy %	95% CI
HPV 16/18 CIN2+ (TAA)	1	97	99.0	94.2–100
CIN2+ irrespective of DNA in the lesion	61	172	64.9	52.7–74.2
CIN3+ irrespective of DNA in the lesion	3	44	93.2	78.9–98.7

Estimated worldwide prevalence of HPV 16/18 in high-grade lesions (CIN2/3) is 52%[2]

* DNA-negative for 14 oncogenic HPV types and normal cytology at baseline; seronegative for HPV 16/18
CIN = cervical intraepithelial neoplasia; TVC = Total Vaccinated Cohort; TAA = type assignment analysis

1. Lehtinen M *et al. Lancet Oncol* 2012;13(1):89–99; 2. ICO Information Centre on Human Papilloma Virus (HPV) and Cancer 2013. Available at: http://www.hpvcentre.net/statistics.php (Accessed November 2014)

R & D programmes to deliver near-term growth with significant future opportunities and novel immunization platforms



GSK data on file.

Conclusion

- The worldwide population >60 years old is predicted to reach 2 billion by 2050.
- Vaccines prevent infectious diseases and adult vaccination rate is still low
- Vaccines are one of the most successful and cost-effective health investments in history.
- Strategies to improve the prevention and treatment of diseases for the elderly through the use of vaccination are multifaceted
- Vaccine efficacy needs to be improved to protect this vulnerable age group.
- GSK has developed innovative adjuvanted vaccines as one solution.

Thank you