Healthy ageing with Vaccination
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.
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.

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 ‘immunosenesence’.
- 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.
ACIP’s recommended Immunization Schedules for adults by age

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

*Covered by the Vaccine Injury Compensation Program

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 American 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 that are not indicated in GSK vaccines’ local label.
ACIP’s recommended Immunization Schedules for adults by medical condition

Reference. [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm](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.
### Recommended Adult Immunization Schedule, by vaccine and age group - KSID, 2012

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>19~29 years</th>
<th>30~39 years</th>
<th>40~49 years</th>
<th>50~64 years</th>
<th>≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus-Pertussis-Diphtheria</td>
<td>1-time dose of Tdap for Td booster; then boost with Td every 10 years (Strength I)</td>
<td>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)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>1 dose annually (strength III)</td>
<td>1 dose annually (strength I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>2 doses (at 0 and 6 months) (strength II)</td>
<td>For seronegatives, 2 doses (at 0 and 6 months) (strength II)</td>
<td>For high-risk groups(^9), check serology; 2 doses for seronegatives (at 0 and 6 months) (strength II)</td>
<td>For high-risk groups(^9) with uncertain immunization history of 3-doses, vaccinate seronegatives (strength III)</td>
<td>For high-risk groups(^9) with uncertain immunization history of 3-doses, vaccinate seronegatives (strength III)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>When 3-doses of immunization uncertain, vaccinate the seronegatives (strength III)</td>
<td></td>
<td></td>
<td>For high-risk groups(^9), check serology; 2 doses for seronegatives (strength II)</td>
<td>For high-risk groups(^9) with uncertain immunization history of 3-doses, vaccinate seronegatives (strength III)</td>
</tr>
<tr>
<td>Measles/mumps/rubella</td>
<td>For high-risk groups(^9), at least 1 dose; check rubella IgG for women planning a pregnancy (strength II)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>For high-risk groups(^9), check serology; 2 doses for seronegatives (strength II)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human Papillomavirus</td>
<td>Female (strength II)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal</td>
<td>For high-risk groups(^9), 1 or 2 doses (strength II)</td>
<td></td>
<td>1 dose (strength I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>For high-risk groups(^9), 1 dose (strength I)</td>
<td></td>
<td>1 dose (strength I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoster</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 dose (strength III)</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th></th>
<th>Chronic liver diseases</th>
<th>Chronic kidney disease</th>
<th>Chronic lung diseases</th>
<th>Chronic Cardiovascular diseases</th>
<th>Diabetes</th>
<th>Solid organ Cancers receiving chemotherapy</th>
<th>Solid organ transplantation</th>
<th>Stem cell transplantation</th>
<th>Recipients of immunosuppressants other than transplantation</th>
<th>Asplenia</th>
<th>HIV infection</th>
<th>Pregnancy</th>
<th>Soldiers on duty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Td/Tdap</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tdap</td>
<td></td>
<td></td>
<td>DTaP/Tdap</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Varicella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoster</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Zoster</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

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

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

Strategies to address challenges in vaccine development

Challenges

Pathogens or diseases
- Malaria, HIV, TB, CMV etc.

Populations
- Infants, elderly, immuno-compromised etc.

Strategies

- New Antigens
- New antigen presentation (DNA)
- New delivery strategies (live vectors)
- New Adjuvants

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

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)
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\(^2\)

---

Adjuvant: expected impact on vaccine response

Adjuvanted formulation

Stronger/broader immune response

Earlier immune response

Time

Longer-term immune response

Non-adjuvanted formulation

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.
Why do we need new approaches?

- Replicating (live attenuated pathogen)
- Non-replicating (whole inactivated pathogen)
- Subunit (toxoids, split virus, fragments of pathogens)
- Purified antigens (various antigens, recombinant proteins)

With or Without Adjuvant

**Without adjuvant**

**With adjuvant**

**Muscle/Injection site**
- Macrophage
- Monocyte
- Granulocyte
- Antigen
- Cytokines

**Draining lymph node**
- Immature dendritic cell
- Mature dendritic cell
- APC
- MHC
- CD4+ T-cell

**Periphery/Site of infection**
- B-cell (naive)
- Plasma cell
- B-cell (memory)
- Antibody

**Antigen**
- CD4+ T-cell
- CD4+ T-cell (memory)
- CD4+ T-cell (diversity impacted)
- Cytokines (improved pattern)

**Adjuvant**
- With adjuvant
- Without adjuvant

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

Vaccines with or without adjuvants

- No adjuvant
- Adjuvanted

Adjuvant discovery

- Prostate cancer
- Pandemic influenza
- NSCLC cancer**
- Zoster
- HPV
- Meningococcus ACWY conjug.
- Rotavirus
- Influenza live attenuated*
- Influenza
- Pneumococcus conjugate
- Meningococcus C conjugate
- Typhoid live attenuated
- Typhoid polysaccharide
- Hib conjugate
- Hepatitis A
- Hepatitis B
- Varicella
- Diphtheria, Tetanus, Pertussis based combinations
- Pertussis
- Hib polysaccharide
- Meningococcus (ACWY) polysaccharide
- Influenza split, sub-unit
- Mumps
- Measles
- Hib polysaccharide
- Polio (OPV)
- Polio (IPV)*
- Influenza whole virus
- Yellow fever
- Diphtheria
- Tuberculosis
- Pertussis
- Smallpox
- cholera
- Typhoid
- Rabies


*Reassortant, **Registered in Cuba and Chile, tIPV 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).

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


HPV = human papilloma virus; VLP, virus-like particle
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
AS04 Mode of Action: key points

- Higher number of APCs in draining lymph node and expression of co-stimulatory signals
- Higher number of HPV-specific T-cells
- Increased capacity of APCs to activate T-cells
- Higher HPV-specific antibody responses
- Naomi CD4 T-cells
- Activated CD4 T-cells
- Naïve B-cells
- Memory CD4 T-cells
- Memory B-cells
- Plasma cells
- Antibodies

Ag and AS04 need to be colocalised in time and site

Innate cells stimulated - greater cytokine/chemokine production

Increased number of HPV-specific T-cells

Higher HPV-specific antibody responses

Naïve CD4 T-cells

Activated CD4 T-cells

Naïve B-cells

Memory CD4 T-cells

Memory B-cells

Plasma cells

Antibodies

Cytokines

AS04

Antigen

Monocyte

Macrophage

Dendritic cell

Blood vessel

Innate

Adaptive

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

Overall vaccine efficacy results against CIN2+ and CIN3+

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

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

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

¹ DNA-negative for 14 oncogenic HPV types and normal cytology at baseline; seronegative for HPV 16/18
² CIN = cervical intraepithelial neoplasia; TVC = Total Vaccinated Cohort; TAA = type assignment analysis

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

1. Near/mid term key R&D focus:
   - Shingrix
   - Meningitis
   - Lifecycle management

2. Longer term R&D Focus
   - RSV
   - GBS

3. A new vaccine concept
   - COPD

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