Medicine, Nursing and Health Sciences

Introduction to Immunisation

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Objective

• Overview of the immunisation schedules
• Basis of immunisation
• Infections
• Concerns of parents
• The cold chain
WHO: Major causes of death in children younger than age 5 years and in neonates

- Neonatal 37%
- Pneumonia 19%
- Diarrhoea 17%
- Malaria 8%
- Measles 4%
- Injuries 3%
- Other 10%
- HIV/AIDS 3%

Causes of neonatal deaths:
- Preterm 28%
- Asphyxia 23%
- Congenital 8%
- Sepsis or pneumonia 26%
- Tetanus 7%
- Diarrhoea 3%
- Other 7%

*Lancet 2005; 365: 1147–52*
Causes of deaths among children under 5 years, 2013

Postneonatal 1-59 months

- Pneumonia: 13%
- Injuries: 5%
- HIV/AIDS: 2%
- Malaria: 7%
- Measles: 2%

Neonatal 0-27 days

- Pneumonia: 2%
- Intrapartum-related complications, including birth asphyxia: 11%
- Neonatal sepsis: 7%
- Congenital anomalies: 4%
- Prematurity: 15%
- Other: 4%
- Neonatal tetanus: 1%

Other group 1 conditions: 10%

Congenital anomalies and other non-communicable diseases: 7%

Diarrhoea: 9%

Major Causes of Neonatal Deaths

1. Prematurity & low birth weight: 31%
2. Infections: 25%
3. Birth asphyxia & birth trauma: 23%
4. Congenital anomalies: 9%
5. Neonatal tetanus: 3%
6. Diarrheal diseases: 3%
7. Other neonatal: 8%

1-3 causes: ~80%
Global number of child deaths per year – by cause of death

Shown is the number of children younger than 5 years who died in a year. The height of the bar shows the total number of deaths with colored sections showing the number of children who died of diseases that are wholly or partially preventable by vaccines.

The number of child deaths for which there are vaccines available declined from 5.1 million deaths in 1990 to 1.5 million deaths 25 years later.

Data source: based on data from the Institute for Health Metrics and Evaluation (IHME)
The data visualization is available at OurWorldInData.org. There you find research and more visualizations on global development.

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Vaccination schedule

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<th>VACCINES</th>
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<td>Measles (Sabah Only)</td>
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<td>HPV (Girls Only)</td>
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<tr>
<td>JE (Sarawak Only)</td>
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**Primary Dose** | **Booster Dose**
## Optional Vaccines in Malaysia

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Month</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Pneumococcal Vaccine</td>
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<tr>
<td>Chickenpox Vaccine</td>
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<tr>
<td>Hepatitis A Vaccine</td>
<td></td>
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<tr>
<td>Rotavirus</td>
<td></td>
</tr>
</tbody>
</table>
VACCINATION SCHEDULE
BY THE HEALTH MINISTRY

Age: Newborn
Vaccine: Bacillus Calmette-Guérin (BCG)
• 1st dose: Hepatitis B

Age: 6 weeks old
Vaccine: Rotavirus

Age: 1 month old
Vaccine: 2nd dose: Hepatitis B

Age: 2 months old
Vaccine: 1st dose:
• Diphtheria, tetanus, acellular pertussis (DtaP)
• Haemophilus influenzae b (Hib)
• Inactivated poliovirus (IPV)

Age: 3 months old
Vaccine: 2nd dose: DtaP

Age: 5 months old
Vaccine: 3rd dose: DtaP

Age: 6 months old
Vaccine: Rotavirus

Age: 6 months old
Vaccine: 1st dose:
• Measles, mumps and rubella (MMR)

Age: 6 months old
Vaccine: 2nd dose: JE (Sarawak only)

Age: 6 months old
Vaccine: 3rd dose: Hib

Age: 6 months old
Vaccine: IPV

Age: 10 months old
Vaccine: 1st dose:
• Japanese Encephalitis (JE) (Sarawak only)

Age: 10 months old
Vaccine: 2nd dose: Measles (Sabah only)

Age: 10 months old
Vaccine: 3rd dose: DtaP

Age: 10 months old
Vaccine: Hib

Age: 10 months old
Vaccine: IPV

Age: 12 months old
Vaccine: MMR

Age: 12 months old
Vaccine: 4th dose: JE (Sarawak only)

Age: 18 months old
Vaccine: 4th dose:
• Diphtheria, tetanus (DT booster)

Age: 7 years old
Vaccine: BCG (optional — only if no scar found)

OPTIONAL VACCINES IN MALAYSIA
Most paediatricians will recommend additional or optional vaccinations in addition to the ones mandated by the Health Ministry. Parents can choose to administer them to their children based on their doctor’s advice.
### National Childhood and Adolescent Immunisation Schedule, Singapore
For persons aged 0 to <18 years

<table>
<thead>
<tr>
<th>Vaccination against</th>
<th>Birth</th>
<th>1 month</th>
<th>3 months</th>
<th>4 months</th>
<th>5 months</th>
<th>6 months</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
<th>6-7 years</th>
<th>10-11 years</th>
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<tr>
<td>Tuberculosis</td>
<td>BCG</td>
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<tr>
<td>Hepatitis B*</td>
<td>HepB (D1)</td>
<td>HepB (D2)</td>
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<td>HepB (D3)*</td>
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<tr>
<td>Diphtheria, Tetanus, Pertussis</td>
<td>DTaP (D1)</td>
<td>DTaP (D2)</td>
<td>DTaP (D3)</td>
<td></td>
<td>DTaP (B1)</td>
<td></td>
<td>Tdap (B2)</td>
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<tr>
<td>Poliovirus</td>
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<td>OPV (D2)</td>
<td>OPV (D3)</td>
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<td>OPV (B1)</td>
<td>OPV (B2)</td>
<td>OPV (B3)</td>
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<tr>
<td>Measles, Mumps, Rubella</td>
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<td>MMR (D1)</td>
<td>MMR (D2)*</td>
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<tr>
<td>Pneumococcal Disease**</td>
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<td>PCV (B1)</td>
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</table>

### Human Papillomavirus
Recommended for females 9 to 26 years; three doses are required at intervals of 0, 2, 6 months

| Influenza |       |          |          |          |          |          |          |          |          |            |             |

*Recommended annually for all children aged 6 months to <5 years and children aged 6 months to <18 years in high-risk groups**

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National Immunisation Registry, Health promotion Board, Singapore, update 23/06/2011
### Australian Government Department of Health and Ageing National Immunisation Program Schedule (1 Feb 2013-30 June 2013)

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccines and Immunizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>Hepatitis B (hepB)</td>
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<tr>
<td>2 months</td>
<td>• Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), <em>Haemophilus influenzae</em> type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV)</td>
</tr>
<tr>
<td></td>
<td>• Pneumococcal conjugate (13vPCV)</td>
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<td></td>
<td>• Rotavirus</td>
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<tr>
<td>4 months</td>
<td>• Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), <em>Haemophilus influenzae</em> type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV)</td>
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<tr>
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<td>• Pneumococcal conjugate (13vPCV)</td>
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<td>• Rotavirus</td>
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<td>6 months</td>
<td>• Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), <em>Haemophilus influenzae</em> type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV)</td>
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<td>• Pneumococcal conjugate (13vPCV)</td>
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<td>• Rotavirus</td>
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<tr>
<td>12 months</td>
<td>• <em>Haemophilus influenzae</em> type b (Hib)</td>
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<td></td>
<td>• Meningococcal C (MenCCV)</td>
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<td></td>
<td>• Measles, mumps and rubella (MMR)</td>
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<tr>
<td>18 months</td>
<td>• Varicella (chickenpox)</td>
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<tr>
<td>4 years</td>
<td>• Diphtheria, tetanus, acellular pertussis (whooping cough) and inactivated poliomyelitis (polio) (DTPa-IPV)</td>
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<td></td>
<td>• Measles, mumps and rubella (MMR)</td>
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</table>

www.immunise.health.gov.au
# Australian Government Department of Health and Ageing National Immunisation Program Schedule (From July 2013)

<table>
<thead>
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<th>Age</th>
<th>Immunisations</th>
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<tbody>
<tr>
<td>Birth</td>
<td>Hepatitis B (hepB)</td>
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</tbody>
</table>
| 2 months | • Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV)  
• Pneumococcal conjugate (13vPCV)  
• Rotavirus |
| 4 months | • Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV)  
• Pneumococcal conjugate (13vPCV)  
• Rotavirus |
| 6 months | • Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV)  
• Pneumococcal conjugate (13vPCV)  
• Rotavirus |
| 12 months | • *Haemophilus influenzae* type b (Hib)  
• Meningococcal C (MenCCV)  
• Measles, mumps and rubella (MMR) |
| 18 months | • Measles, mumps, rubella and varicella (chickenpox) (MMRV) |
| 4 years | • Diphtheria, tetanus, acellular pertussis (whooping cough) and inactivated poliomyelitis (polio) (DTPa-IPV)  
• Measles, mumps and rubella (MMR) |
2016 Recommended Immunizations for Children from Birth Through 6 Years Old

<table>
<thead>
<tr>
<th>Birth</th>
<th>1 month</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
<th>12 months</th>
<th>15 months</th>
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<th>19–23 months</th>
<th>2–3 years</th>
<th>4–6 years</th>
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Is your family growing? To protect your new baby and yourself against whooping cough, get a Tdap vaccine in the third trimester of each pregnancy. Talk to your doctor for more details.

NOTE: If your child misses a shot, you don’t need to start over, just go back to your child’s doctor for the next shot. Talk with your child’s doctor if you have questions about vaccines.

FOOTNOTES:

1. Two doses given at least four weeks apart are recommended for children aged 6 months through 8 years of age who are getting an influenza (flu) vaccine for the first time and for some other children in this age group.

2. Two doses of HepA vaccine are needed for lasting protection. The first dose of HepA vaccine should be given between 12 months and 23 months of age. The second dose should be given 6 to 18 months later. HepA vaccination may be given to any child 12 months and older to protect against HepA. Children and adolescents who did not receive the HepA vaccine and are at high risk should be vaccinated against HepA.

If your child has any medical conditions that put him at risk for infection or is traveling outside the United States, talk to your child’s doctor about additional vaccines that he may need.

For more information, call toll free 1-800-CDC-INFO (1-800-232-4636) or visit http://www.cdc.gov/vaccines U.S. Department of Health and Human Services Centers for Disease Control and Prevention AMERICAN ACADEMY OF FAMILY PHYSICIANS STRONG MEDICINE FOR AMERICA American Academy of Pediatrics DEDICATED TO THE HEALTH OF ALL CHILDREN
2015 Recommended Immunizations for Children from 7 Through 18 Years Old

### FOOTNOTES

1. Tdap vaccine is recommended at age 11 or 12 to protect against tetanus, diphtheria, and pertussis. If your child has not received any or all of the DTaP vaccine series, or if you don’t know if your child has received all shots, your child needs a single dose of Tdap when they are 7-18 years old. Talk to your child’s health care provider to find out if they need additional catch-up vaccines.

2. All 11 or 12 year olds — both girls and boys — should receive 3 doses of HPV vaccine to protect against HPV-related disease. The full HPV vaccine series should be given as recommended for best protection.

3. Meningococcal conjugate vaccine (MCV) is recommended at age 11 or 12. A booster shot is recommended at age 16. Teens who received MCV for the first time at age 13 through 15 years will need a one-time booster dose between the ages of 16 and 18 years. If your teenager missed getting the vaccine altogether, ask their health care provider about getting it now, especially if your teenager is about to move into a college dorm or military barracks.

4. Everyone, 6 months of age and older—including preteens and teens—should get a flu vaccine every year. Children under the age of 9 years may require more than one dose. Talk to your child’s health care provider to find out if they need more than one dose.

5. Pneumococcal Conjugate Vaccine (PCV13) and Pneumococcal Polysaccharide Vaccine (PPSV23) are recommended for some children 6 through 18 years old with certain medical conditions that place them at high risk. Talk to your healthcare provider about pneumococcal vaccines and what factors may place your child at high risk for pneumococcal disease.

6. Hepatitis A vaccination is recommended for older children with certain medical conditions that place them at high risk. HepA vaccine is licensed, safe, and effective for all children of all ages. Even if your child is not at high risk, you may decide you want your child protected against HepA. Talk to your healthcare provider about HepA vaccine and what factors may place your child at high risk for HepA.

For more information, call toll free 1-800-CDC-INFO (1-800-232-4636) or visit http://www.cdc.gov/vaccines/teens
Recommended Immunisation Schedule

<table>
<thead>
<tr>
<th>Age (month)</th>
<th>Immunisation</th>
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<tbody>
<tr>
<td>1</td>
<td>• General checkup. No injection 考查, 无注射</td>
</tr>
<tr>
<td>2</td>
<td>• Triple antigen+polio+Hep B+ Hib (6 in 1) 三种并合针, 小儿麻痹症, 乙型肝炎及脑膜炎疫苗（六合一）</td>
</tr>
<tr>
<td></td>
<td>• Rotavirus 轮状病毒口服疫苗</td>
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<tr>
<td>3</td>
<td>• Pneumococcal (PncV) 肺炎链球菌疫苗</td>
</tr>
<tr>
<td>4</td>
<td>• Triple antigen+polio+Hep B+ Hib (6 in 1) 三种并合针, 小儿麻痹症, 乙型肝炎及脑膜炎疫苗（六合一）</td>
</tr>
<tr>
<td></td>
<td>• Rotavirus 轮状病毒口服疫苗</td>
</tr>
<tr>
<td>5</td>
<td>• Pneumococcal (PncV) 肺炎链球菌疫苗</td>
</tr>
<tr>
<td>6</td>
<td>• Triple antigen+polio+Hep B+ Hib (6 in 1) 三种并合针, 小儿麻痹症, 乙型肝炎及脑膜炎疫苗（六合一）</td>
</tr>
<tr>
<td></td>
<td>• Rotavirus 轮状病毒口服疫苗</td>
</tr>
<tr>
<td>7</td>
<td>• ±Pneumococcal (PncV) 肺炎链球菌疫苗</td>
</tr>
<tr>
<td>9</td>
<td>• MMR 麻疹,腮腺炎及风疹</td>
</tr>
<tr>
<td>12</td>
<td>• MMR-Chickenpox/MMR 麻疹, 腮腺炎及风疹 /水痘</td>
</tr>
<tr>
<td>13</td>
<td>• ±Chickenpox 水痘 (see above)</td>
</tr>
<tr>
<td>15</td>
<td>• Booster Pneumococcal (PncV) 肺炎链球菌疫苗</td>
</tr>
<tr>
<td>18</td>
<td>• Booster Double antigen+polio+ Hib 二种并合针, 小儿麻痹症及脑膜炎疫苗</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years</th>
<th>Immunisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>• Booster Double antigen+polio 二种并合针及小儿麻痹症</td>
</tr>
<tr>
<td></td>
<td>• MMR 麻疹,腮腺炎及风疹</td>
</tr>
<tr>
<td>9-13</td>
<td>• HPV (for girls) 人类乳头状瘤病毒疫苗</td>
</tr>
<tr>
<td>15</td>
<td>• Tetanus 破伤风</td>
</tr>
</tbody>
</table>

(updated Jan 2016)
# Types of vaccines

<table>
<thead>
<tr>
<th>Live vaccines</th>
<th>Live Attenuated vaccines</th>
<th>Killed Inactivated vaccines</th>
<th>Toxoids</th>
<th>Cellular fraction vaccines</th>
<th>Recombinant vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smallpox variola vaccine</strong></td>
<td><strong>BCG</strong>&lt;br&gt;<strong>Typhoid oral</strong>&lt;br&gt;<strong>Plague</strong>&lt;br&gt;<strong>Oral polio</strong>&lt;br&gt;<strong>Yellow fever</strong>&lt;br&gt;<strong>Measles</strong>&lt;br&gt;<strong>Mumps</strong>&lt;br&gt;<strong>Rubella</strong>&lt;br&gt;<strong>Intranasal Influenza</strong>&lt;br&gt;<strong>Typhus</strong></td>
<td><strong>Typhoid</strong>&lt;br&gt;<strong>Cholera</strong>&lt;br&gt;<strong>Pertussis</strong>&lt;br&gt;<strong>Plague</strong>&lt;br&gt;<strong>Rabies</strong>&lt;br&gt;<strong>Salk polio</strong>&lt;br&gt;<strong>Intramuscular influenza</strong>&lt;br&gt;<strong>Japanese encephalitis</strong></td>
<td><strong>Diphtheria</strong>&lt;br&gt;<strong>Tetanus</strong></td>
<td><strong>Meningococcal polysaccharide vaccine</strong>&lt;br&gt;<strong>Pneumococcal polysaccharide vaccine</strong>&lt;br&gt;<strong>Hepatitis B polypeptide vaccine</strong></td>
<td><strong>Hepatitis B vaccine</strong></td>
</tr>
</tbody>
</table>
Vaccination successes

• Vaccination has:
  – Eradicated smallpox\textsuperscript{5}
  – Nearly eradicated polio\textsuperscript{8}
  – Controlled many major diseases\textsuperscript{3}
Immunological Memory

Vaccine stimulates an immune response to an antigen

Humoral immunity = actions of B-lymphocytes to produce antibodies

Cellular immunity = specialized T-lymphocytes to combat the antigen

Long-term acquired immunity = “Immunological Memory”

Secondary immune response = reestablish protection
The Main Cell Types in the Immune Response

Phagocytes
- Monocytes
- Macrophages
- Polymorphonuclear neutrophils (PMNs)

Lymphocytes
- B cells
- T cells
  - Helper
  - Killer
- Natural Killer cells
Indirect Effect of Vaccination

Vaccines help to reduce the spread of disease through indirect effect, sometimes called “herd immunity” or “community immunity.”

- Once a person is vaccinated against a disease, they are less likely to develop it as well as pass it on to someone who is not immunized.
<table>
<thead>
<tr>
<th>Disease</th>
<th>R0</th>
<th>Threshold (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mumps</td>
<td>4-7</td>
<td>75–86</td>
</tr>
<tr>
<td>Polio</td>
<td>5-7</td>
<td>80–86</td>
</tr>
<tr>
<td>Smallpox</td>
<td>5-7</td>
<td>80–85</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>6-7</td>
<td>85</td>
</tr>
<tr>
<td>Rubella</td>
<td>6-7</td>
<td>83–85</td>
</tr>
<tr>
<td>Pertussis</td>
<td>12-17</td>
<td>92–94</td>
</tr>
<tr>
<td>Measles</td>
<td>12-18</td>
<td>83–94</td>
</tr>
</tbody>
</table>
# Vaccine-Preventable Diseases and the Vaccines that Prevent Them

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccine</th>
<th>Disease spread by</th>
<th>Disease symptoms</th>
<th>Disease complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chickenpox</td>
<td>Varicella vaccine protects against chickenpox</td>
<td>Air, direct contact</td>
<td>Rash, tiredness, headache, fever</td>
<td>Infected blisters, bleeding disorders, encephalitis (brain swelling), pneumonia (infection in the lungs)</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>DTaP* vaccine protects against diphtheria.</td>
<td>Air, direct contact</td>
<td>Sore throat, mild fever, weakness, swollen glands in neck</td>
<td>Swelling of the heart muscle, heart failure, coma, paralysis, death</td>
</tr>
<tr>
<td>Hib</td>
<td>Hib vaccine protects against <em>Haemophilus influenzae</em> type b.</td>
<td>Air, direct contact</td>
<td>May be no symptoms unless bacteria enter the blood</td>
<td>Meningitis (infection of the covering around the brain and spinal cord), intellectual disability, epiglottitis (life-threatening infection that can block the windpipe and lead to serious breathing problems), pneumonia (infection in the lungs), death</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>HepA vaccine protects against hepatitis A.</td>
<td>Direct contact, contaminated food or water</td>
<td>May be no symptoms, fever, stomach pain, loss of appetite, fatigue, vomiting, jaundice (yellowing of skin and eyes), dark urine</td>
<td>Liver failure, arthralgia (joint pain), kidney, pancreatic, and blood disorders</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>HepB vaccine protects against hepatitis B.</td>
<td>Contact with blood or body fluids</td>
<td>May be no symptoms, fever, headache, weakness, vomiting, jaundice (yellowing of skin and eyes), joint pain</td>
<td>Chronic liver infection, liver failure, liver cancer</td>
</tr>
<tr>
<td>Influenza (Flu)</td>
<td>Flu vaccine protects against influenza.</td>
<td>Air, direct contact</td>
<td>Fever, muscle pain, sore throat, cough, extreme fatigue</td>
<td>Pneumonia (infection in the lungs)</td>
</tr>
<tr>
<td>Measles</td>
<td>MMR** vaccine protects against measles.</td>
<td>Air, direct contact</td>
<td>Rash, fever, cough, runny nose, pinkeye</td>
<td>Encephalitis (brain swelling), pneumonia (infection in the lungs), death</td>
</tr>
<tr>
<td>Mumps</td>
<td>MMR** vaccine protects against mumps.</td>
<td>Air, direct contact</td>
<td>Swollen salivary glands (under the jaw), fever, headache, tiredness, muscle pain</td>
<td>Meningitis (infection of the covering around the brain and spinal cord), encephalitis (brain swelling), inflammation of testicles or ovaries, deafness</td>
</tr>
<tr>
<td>Pertussis</td>
<td>DTaP* vaccine protects against pertussis (whooping cough).</td>
<td>Air, direct contact</td>
<td>Severe cough, runny nose, apnea (a pause in breathing in infants)</td>
<td>Pneumonia (infection in the lungs), death</td>
</tr>
<tr>
<td>Polio</td>
<td>IPV vaccine protects against polio.</td>
<td>Air, direct contact, through the mouth</td>
<td>May be no symptoms, sore throat, fever, nausea, headache</td>
<td>Paralysis, death</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>PCV vaccine protects against pneumococcal.</td>
<td>Air, direct contact</td>
<td>May be no symptoms, pneumonia (infection in the lungs)</td>
<td>Bacteremia (blood infection), meningitis (infection of the covering around the brain and spinal cord), death</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>RV vaccine protects against rotavirus.</td>
<td>Through the mouth</td>
<td>Diarrhea, fever, vomiting</td>
<td>Severe diarrhea, dehydration</td>
</tr>
<tr>
<td>Rubella</td>
<td>MMR** vaccine protects against rubella.</td>
<td>Air, direct contact</td>
<td>Children infected with rubella virus sometimes have a rash, fever, swollen lymph nodes</td>
<td>Very serious in pregnant women—can lead to miscarriage, stillbirth, premature delivery, birth defects</td>
</tr>
<tr>
<td>Tetanus</td>
<td>DTaP* vaccine protects against tetanus.</td>
<td>Exposure through cuts in skin</td>
<td>Stiffness in neck and abdominal muscles, difficulty swallowing, muscle spasms, fever</td>
<td>Broken bones, breathing difficulty, death</td>
</tr>
</tbody>
</table>

* DTaP combines protection against diphtheria, tetanus, and pertussis.
** MMR combines protection against measles, mumps, and rubella.
Polio

- Affects the nervous system and spinal cord, causing paralysis
- ≈1/200 infections lead to paralysis
- Two types of vaccine
- In 1994, wild polio transmission was interrupted in the Americas
For polio, even at 80% coverage we can see the impact – reduced number of cases.
MMR – THE FACTS

- Measles, Mumps & Rubella
- Short memories of deadly Measles epidemic
- 1990 – 45 million Measles; 1 million dead
- 32.8/100,000 (1987) – 2.6/100,000 (1997)
- National epidemic 1999-2000; 10 deaths
- 2004 – PI 270 cases in 6 mths.
- 2 deaths, 45 pneumonia, 8 bro. obliterans
Measles Vaccine in Malaysia

- Measles life attenuated vaccine was first introduced to Malaysia on 1982.
- Malaysia registered 8727 cases of measles in 1980 and this number dropped to 483 in 1998. Most of the cases occurred before the eligible age of immunisation.
- In 2002, measles, mumps and rubella (MMR) was introduced \(^{(3)}\).
• Malaysia managed to have a coverage rate of 95% for the MMR on 2009.
• In recent years, parent’s refusal to vaccination has increased measles in Malaysia from 68 cases in 2010 to 1378 cases in 2011.
• MMR vaccine was thought to be associated with autism or other neurological disorders but it was proven wrong (1)
Confirmed measles cases by month of onset, Malaysia, 2008–2012

Number of measles cases:

2008 (N=332) Lab & Epi=110 Clinically=222
2009 (N=56) Lab & Epi=55 Clinically=1
2010 (N=74) Lab & Epi=70 Clinically=4
2011 (N=1573) Lab & Epi=1530 Clinically=43
2012 (N=2112) Lab & Epi=1720 Clinically=392

Source: National measles and rubella monthly country reports

1 Reports received for January to December 2012
Smallpox

- Caused by variola virus
- A deadly disease
- Most survivors scarred with residual facial marks, some left blind
Last Person Infected with Naturally Occurring Smallpox in Somalia in 1977
Tetanus

- Known as lockjaw
- Caused by *Clostridium tetani*
  - Releases a toxin causing muscle spasms
  - May lead to death by suffocation
- Neonatal tetanus occurs most often in developing countries
Diphtheria

- Caused by *Corynebacterium diphtheriae*
- Affects upper respiratory tract, also other organs
- Mortality rate 5-10 percent
  - If early treatment, < 1 percent

Kuala Lumpur, Nov 2015
Pertussis
(“Whooping Cough”)

- Caused by *Bordetella pertussis*
-Characteristic cough
- Three phases
  - Catartrhal phase
  - Paroxysmal phase
  - Convalescent phase
- Greatest risk in infants and young children
Rubella
(“German Measles”)

- A generally mild childhood disease caused by a virus
- Infection during pregnancy may result in fetal infection (congenital rubella syndrome)
  - Multiple defects in infants
    - Brain, Heart, Hearing, Liver
Incidence Diphtheria, Measles and Pertussis Malaysia 1980-2016

<table>
<thead>
<tr>
<th>Year</th>
<th>Diphtheria</th>
<th>Measles</th>
<th>Pertussis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>131</td>
<td>8'727</td>
<td>97</td>
</tr>
<tr>
<td>1990</td>
<td>9</td>
<td>563</td>
<td>24</td>
</tr>
<tr>
<td>2000</td>
<td>1</td>
<td>6'187</td>
<td>42</td>
</tr>
<tr>
<td>2012</td>
<td>0</td>
<td>1'868</td>
<td>217</td>
</tr>
<tr>
<td>2013</td>
<td>4</td>
<td>195</td>
<td>222</td>
</tr>
<tr>
<td>2014</td>
<td>2</td>
<td>221</td>
<td>500</td>
</tr>
<tr>
<td>2015</td>
<td>4</td>
<td>1'318</td>
<td>939</td>
</tr>
<tr>
<td>2016</td>
<td>31</td>
<td>1'569</td>
<td>298</td>
</tr>
</tbody>
</table>
Hepatitis B

Countries using HepB vaccine in their national infant immunization system, as of December 2003

Date of slide: 20 September 2004
Incidence of acute Hepatitis B, by year
United States, 1980-2010

Number of cases

Year

Hepatitis B Immune Response Level Through 5 Years Post-Vaccination

- Protection against hepatitis B virus (HBV) is based on the presence of specific antibodies against anti-HBs antigen.²
  - Anti-HBs levels disappear in 10-50% of vaccinees after a few years.²
  - No booster has been recommended to date.³

---

Anti-HBs After Immune Challenge

- Immune memory persists beyond the time at which anti-HBs levels may no longer be detectable.
- Immune memory leads to a rapid anamnestic response after exposure to HBV, which prevents acute infection (and disease).

Haemophilus influenzae type b (Hib)

- Causes severe infection in many organs
- Before routine use of effective vaccines, Hib was the leading cause of bacterial meningitis in young children
Typical rash of meningococcal septicemia

In this picture, confluent purpuric areas have formed with blistering and necrosis
N. meningitidis

Custom Medical Stock Photo, 2003
Streptococcus pneumoniae

- Gram-positive, facultative, encapsulated
- Capsular polysaccharides form the basis of serogroup and serotype classifications
- 90 serotypes
- Leading cause of vaccine-preventable bacterial disease in children
- The most common bacterial cause of
  - Community-acquired pneumonia (17-28%)
  - AOM (25 - 50%)
  - Sinusitis

Pediatr Infect Dis J 1992;11:S7--11
**S. pneumoniae** Disease Classification

<table>
<thead>
<tr>
<th>Mucosal Disease</th>
<th>Invasive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Pneumonia*</td>
</tr>
<tr>
<td>Acute otitis media (AOM)</td>
<td>Bacteremia/sepsis</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Other focal, sterile-site infections from hematogenous dissemination</td>
</tr>
</tbody>
</table>

*S. pneumoniae* disease may be classified as mucosal or invasive

*Pneumonia may be classified as mucosal or invasive disease. It is invasive if accompanied by bacteremia, pleural effusion, or other invasive complication.*

Impact of Pneumococcal Disease on Children

- Pneumococcal disease can result in:
  - Death
  - Paralysis
  - Mental retardation
  - Seizures
  - Learning disabilities
  - Hearing loss
  - Other sequelae

## Risk Factors for IPD

<table>
<thead>
<tr>
<th>Age¹</th>
<th>Underlying Medical Conditions²,³</th>
<th>Demographic Features³,⁴</th>
</tr>
</thead>
</table>
| • Children ≤2 years of age  
• Adults ≥65 years of age | • Congenital or acquired immunodeficiency  
• Sickle cell disease, asplenia, HIV  
• Pulmonary disease  
• Chronic heart disease  
• Chronic renal insufficiency, nephrotic syndrome  
• Diabetes  
• Cerebrospinal fistula  
• Existing or cochlear implants | • Day care attendance  
• Ethnicity |

• Age is the most important risk factor for pneumococcal disease¹

---

Nasopharyngeal Colonization

- *S. pneumoniae* can be a normal inhabitant of the nasopharynx\(^1\)
- Global nasopharyngeal (NP) colonization/carriage ranges:
  - 10% to 85% in children <5 years of age\(^2,3\)
  - 4% to 45% in adults\(^2\)-\(^4\)

NP colonization is generally a prerequisite for mucosal and invasive pneumococcal disease\(^2,4\)


Infection Pathogenesis

Nose

Sinus

Tympanic membrane

Blood vessel

Meninges

Lung

Bone
Invasive Pneumococcal Diseases among Malaysian Children

Tan Kah Kee MD
Pediatric Infectious Disease Consultant
Hospital Tuanku Ja’afar
70300 Seremban

Presented at National Pneumococcal workshop 28 March 2015
Pneumococcal Infections

• Burden of disease highest in youngest & oldest sections of population
• Annual deaths : 1 million < 5 years old
• High case fatality rates in meningitis (20-50%)
• 30-60 % of survivors with long-term sequelae
• Treatment complicated by worldwide emergence of penicillin-resistance (IMR 2011: 36.9% penicillin-nonsusceptible)
**Streptococcus Pneumoniae**

- Common inhabitants of respiratory tract
- > 90 known serotypes
- 6-11 most common serotypes account for >70% of invasive disease worldwide.
- Polysaccharide capsule important virulence factor
- Type-specific antibody is protective

*Weekly Epidemiol Record 2012; 87:129-144*
*Johnson HL et al; PLoS Med 2010*
S. pneumoniae Disease Burden in Children

For each case of pneumococcal meningitis in a year

Incidence

Annual incidence of invasive pneumococcal disease in <2 year olds
~150/100,00, United States

Invasive Pneumococcal Disease Syndromes

- Bacteremia
- Meningitis
- Pneumonia
- Septic arthritis
- Hemolytic uremic syndrome

Copelovitch L et al; Pediatrics 2010 ; 125
Pneumococcal serotypes in Malaysia
N=433 strains, 33.5% < 5 years

Serotype

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.80%</td>
</tr>
<tr>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>18C</td>
<td>3.90%</td>
</tr>
<tr>
<td>23F</td>
<td>4.80%</td>
</tr>
<tr>
<td>6A</td>
<td>5%</td>
</tr>
<tr>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>14</td>
<td>6.70%</td>
</tr>
<tr>
<td>19A</td>
<td>6.90%</td>
</tr>
<tr>
<td>6B</td>
<td>10.60%</td>
</tr>
<tr>
<td>19F</td>
<td>15.00%</td>
</tr>
</tbody>
</table>

PCV 7 : 44% covered
PCV 10 : 56% covered
PCV 13 : 78% covered

Yasin MR et al; Vaccine 2011;34
Invasive Pneumococcal Disease in Hospitalised Malaysian Children

• Children with IPD & isolation of Strept. Pneumo. in sterile sites recruited (blood, CSF, pleural fluid, joint, peritoneal & pericardial) between 1 Jan 2007-31 Dec 2009
• 13 participating hospitals nationwide
• Pneumococcal isolates send to IMR for serotyping.
• Quellung reaction for serotyping.

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)
Participating Hospitals (N=13)

- HKL
- HIP
- HPP
- HKB
- HTJ
- UMMC
- HKT
- HTAA
- HTAR
- HSB Alor Setar
- HSelayang
- HUS Kuching
- HLikas KK

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)
Results (1) - Demographics

- Total patients with IPD = 164 (2008:88 ; 2009:76)
- Gender distribution: Males 56.7%(N=93) ; Females 43.3%(N=71)(M:F = 1.3 : 1)
- Racial distribution: Malays 66.7% , Chinese 7.3% , Indians 1.8% , Ibans 1.8% , Bidayuh(0.6%) , Kadazan 0.6% , Others 21.2%

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)
Results(2) - Demographics

- Mean age = 25.7 mths
- Median age = 15.0 months
- Range = 0-144 months
- Age < 2 yrs = 68.3% (N=112)
- Age < 5 yrs = 86.6% (N=142)
Results(3) – Blood, CSF, Pleural fluid

• Blood culture +ve = 85.6% (N=160)
• CSF culture +ve = 39.6% (N=56)
• CSF antigen +ve (latex) = 55.6% (N=20)
• Pleural fluid culture +ve = 64.3% (N=28)
Results(4)- Pneumococcal Serotypes (N=79)

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)
Serotypic Coverage

- 7-valent = 37.9% (30/79)
- 10-valent = 43.0% (34/79)
- 13-valent = 51.8% (41/79)

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)
13% (N=21) has neurological sequelae at discharge

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)
Ventilatory Support

- 44%(N=72) required ventilatory support
- Median duration = 4 days
- Range = 1-43 days

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)
Penicillin Susceptibility

- Blood isolates: S 84.5% I 2.3% R 13.2%
- CSF isolates: S 89.5% I 10.5% R 0%

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)
Study Limitations

• Mild cases may not be captured
• Private hospital cases not included
• Culture method limited by prior antibiotics
• Molecular methods during study not available

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)
Summary of findings

• IPD is severe in Malaysian children
• Significant mortality
• Serotypic coverage moderate
• Penicillin resistance moderate
Conclusions

• Invasive pneumococcal disease is a serious cause of morbidity & mortality in Malaysian children
• Different spectrum of pneumococcal infection seen
• Mortality does occur in spite of appropriate therapy
• Penicillin resistance moderate
• Preventive measure by vaccination needs urgent consideration

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)
Pneumococcal
Rotavirus
Chickenpox
Meningococcal

### Jadual Lama:

<table>
<thead>
<tr>
<th>IMUNISASI</th>
<th>Umur (Bulan)</th>
<th>(Tahun)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>BCG</td>
<td>Dos 1</td>
<td>Dos 2</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Dos 1</td>
<td>Dos 2</td>
</tr>
<tr>
<td>DTaP</td>
<td>Dos 1</td>
<td>Dos 2</td>
</tr>
<tr>
<td>Hib</td>
<td>Dos 1</td>
<td>Dos 2</td>
</tr>
<tr>
<td>Polio (IPV)</td>
<td>Dos 1</td>
<td>Dos 2</td>
</tr>
<tr>
<td>Measles</td>
<td>Sabah sahaja</td>
<td>Dos 1</td>
</tr>
<tr>
<td>MMR</td>
<td>Sabah sahaja</td>
<td>Sabah sahaja</td>
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<tr>
<td>MR</td>
<td>Booster</td>
<td></td>
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<tr>
<td>DT</td>
<td>Booster</td>
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<tr>
<td>OPV</td>
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<tr>
<td>HPV</td>
<td>Booster</td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>Booster</td>
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### Jadual Baru:

<table>
<thead>
<tr>
<th>IMUNISASI</th>
<th>Umur (Bulan)</th>
<th>(Tahun)</th>
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<tbody>
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<td>Dos 2</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Dos 1</td>
<td>Dos 2</td>
</tr>
<tr>
<td>DTaP</td>
<td>Dos 1</td>
<td>Dos 2</td>
</tr>
<tr>
<td>Hib</td>
<td>Dos 1</td>
<td>Dos 2</td>
</tr>
<tr>
<td>Polio (IPV)</td>
<td>Dos 1</td>
<td>Dos 2</td>
</tr>
<tr>
<td>Measles</td>
<td>Sabah sahaja</td>
<td>Dos 1</td>
</tr>
<tr>
<td>MMR</td>
<td>Sabah sahaja</td>
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<tr>
<td>MR</td>
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<tr>
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<tr>
<td>Tetanus</td>
<td>Booster</td>
<td></td>
</tr>
<tr>
<td>JE (Sarawak)</td>
<td>Dos 1</td>
<td>Dos 2</td>
</tr>
</tbody>
</table>

*Jadual baru Imunisasi MMR digunakan bermula tahun 2016*
Some concerns of parents
Common questions about vaccines

• Do I need to vaccinate my child against diseases that aren’t common anymore?\(^{15}\)
• Are vaccines safe?\(^{16}\)
• Do vaccines cause autism?\(^{16}\)
• Are preservatives found in vaccines?\(^{16}\)
• Can my child get a disease from a vaccine?\(^{16}\)
• My child is allergic to eggs
• Are vaccines halal?

Ref 15: CDC, p 8
Ref 16: IOM, p 1, 4
Some vaccine side effects

• Common side effects\textsuperscript{5}
  – Redness, swelling, and pain at injection site
  – Low-grade fever

• Uncommon, serious side effects\textsuperscript{5}
  – Allergic reaction

Ref 5: AAP, p 38, 46
Advice on vaccination of those with egg allergy

• Influenza vaccines (containing <1 μg of ovalbumin per dose) can be given to most people with egg allergy, including anaphylaxis
  – Those with severe allergy should be vaccinated in settings where anaphylaxis can be recognised/treated

• MMR vaccines can be given to any egg allergic person
“Natural Immunity”
(Getting Immunity By Getting Sick)

• What is it? Does it work? What are the costs?

• Some people believe that it’s better to get a disease naturally than to be vaccinated against it.

• One theory is that chickenpox, for example, helps mature the immune system.

• And a mature immune system should be better able to fight infection from diseases, right?

• What are the facts about natural immunity?
Choosing Natural Immunity Is Risky!

- Chickenpox kills children in the United States every year.
- Before a chickenpox vaccine was licensed, almost 7,000 children per year were hospitalized for serious complications of chickenpox like encephalitis, hepatitis, flesh eating-strep, and toxic shock syndrome.
Choosing Natural Immunity Can Be Risky To Others.

- A parent who is not immune to chickenpox can easily catch the disease from an infected child. 1 in 5 adults who get chickenpox develops pneumonia, which can be deadly.
- If a “routine” disease like chickenpox can have these results, natural immunity is a risky alternative to vaccination.
Childhood Diseases Carry Serious Risks.

- **Hib or pneumococcal disease** can cause bacterial meningitis, leading to brain damage or death.

- **Pertussis (whooping cough)** can cause coughing spells so bad that it is hard for infants to eat, drink, or breathe. These spells can last for weeks. Pertussis can lead to pneumonia, seizures, brain damage, and death.

- **Polio** may lead to paralysis and death. Polio used to be very common in the United States, killing and paralyzing thousands of people a year.

- **Tetanus (lockjaw)** infection can cause painful tightening of the muscles. It can lead to "locking" of the jaw so the victim cannot open his mouth or swallow. Tetanus results in death in about 10% of cases.
HERD IMMUNITY

- Children who are immunised are protected from the disease. They cannot get the disease and they cannot give the disease.
- If enough children are vaccinated against a disease then the disease cannot spread into the community.
- This is called “herd immunity”
Anti Immunization Movement

Johor baby dies of diphtheria, wasn't vaccinated

By Ibrahim Isa - October 17, 2018 @ 10:53pm

JOHOR BAHRU: A 14-month-old baby girl has died, believed to be due to diphtheria, on Monday.

Health director-general Datuk Dr Noorhisham Abdullah in a statement said the baby did not receive diphtheria immunisation because the family had refused it.

"The child started out having fever and sore throat on Oct 4 and was taken to a private clinic by her mother for initial treatment on Oct 11. The next day, the child was taken to the emergency unit of a hospital after having breathing difficulties and loss of appetite.

"The patient was then admitted into the paediatric ward and later the paediatric's intensive care unit on Oct 13 as she had become weaker and needed respiratory aid," Noorhisham said.

On Monday, the patient succumbed to severe diphtheria with multiorgan failure, he informed.

He added that test was done on a throat swab sample of the patient and it showed the presence of the corynebacterium diphtheriae bacteria and the ministry was now waiting for lab confirmation.
MMR and Autism

• The original paper (now RETRACTED) – Lancet, 1998

2. Time trends in autism and in MMR immunization coverage in California - JAMA, 2001
3. A population-based study of measles, mumps, and rubella vaccination and autism - NEJM, 2002
5. MMR vaccination and pervasive developmental disorders: a case-control study - Lancet, 2004
7. Vaccines for measles, mumps and rubella in children - Cochrane Collaboration, 2005
9. How the case against the MMR vaccine was fixed by Brian Deer, BMJ, 2011
10. Wakefield’s article linking MMR vaccine and autism was fraudulent - BMJ Editorial, 2011
The case for vaccines

The case against

Every government, every major health agency of every country around the world, the consensus of respectable, peer-reviewed medical journals, medical doctors, researchers and scientists

vs

a handful of pseudoscientific paperbacks and self-published bunk

Refutations to Anti-Vaccine Memes

The Vaccine Meme Machine
The Cold Chain
Store in Freezer
5°F (-15°C) or colder
- MMR
- Varicella
- Zoster
- MMR

Store in Refrigerator
35°F–46°F (2°C–8°C)
- MMR
- Inactivated Combination Vaccines
- Vaccines containing Diphtheria, Tetanus, and/or acellular Pertussis
- Hepatitis A
- Hepatitis B
- Hib
- HPV
- Influenza (LAIV & TIV)
- IPV
- Meningococcal (MCV & MPSV)
- Pneumococcal (PCV & PPV)
- Rotavirus

* Do not expose to light.
+ Unreconstituted lyophilized (freeze-dried) MMR may be frozen or refrigerated.
Dengvaxia (Sanofi)
Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

Maria Rosario Capeding, Ngoc Huu Tran, Sri Rezeki S Hadinegoro, Hussain Imam HJ Mohammad Ismail, Tawee Chotpitayasunondh, Mary Noreen Chua, Chan Quang Luong, Kusnadi Rusmil, Dewa Nyoman Wireawan, Revathy Nallusamy, Punnee Pitisuttithum, Usa Thisyakom, In-Kyu Yoon, Diane van der Vliet, Edith Langevin, Thelma Laot, Yanee Hutagalung, Carina Fregio, Mark Boaz, T Anh Wartel, Nadia G Tornieporth, Melanie Saville, Alain Bouckenoooghe, and the CYD14 Study Group*

Summary
Background An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children.
Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease


BACKGROUND
A candidate tetravalent dengue vaccine is being assessed in three clinical trials involving more than 35,000 children between the ages of 2 and 16 years in Asian-Pacific and Latin American countries. We report the results of long-term follow-up interim analyses and integrated efficacy analyses.

METHODS
We are assessing the incidence of hospitalization for virologically confirmed dengue as a surrogate safety end point during follow-up in years 3 to 6 of two phase 3 trials, CYD14 and CYD15, and a phase 2b trial, CYD23/57. We estimated vaccine efficacy using pooled data from the first 25 months of CYD14 and CYD15.

*The authors’ full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Saville at Sanofi Pasteur, 2 Ave. Pont Pasteur, 69367 Lyon CEDEX 07, France, or at melanie.saville@sanofipasteur.com.

A complete list of investigators in the CYD-TDV Dengue Vaccine Working Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 27, 2015, at NEJM.org.
Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

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Summary

Background An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children.

Methods We did an observer-masked, randomised controlled, multicentre, phase 3 trial in five countries in the Asia-Pacific region. Between June 3, and Dec 1, 2011, healthy children aged 2–14 years were randomly assigned (2:1), by computer-generated permuted blocks of six with an interactive voice or web response system, to receive three injections of a recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV), or placebo, at months 0, 6, and 12. Randomisation was stratified by age and site. Participants were followed up until month 25. Trial staff responsible for the preparation and administration of injections were unmasked to group allocation, but were not included in the follow-up of the participants; allocation was concealed from the study sponsor, investigators, and parents and guardians. Our primary objective was to assess protective efficacy against symptomatic, virologically confirmed dengue, irrespective of disease severity or serotype, that took place more than 28 days after the third injection. The primary endpoint was for the lower bound of the 95% CI of vaccine efficacy to be greater than 25%. Analysis was by intention to treat and per protocol. This trial is registered with ClinicalTrials.gov, number NCT01373281.
STUDY DESIGN

• Multi-centred, observer-masked RCT
• Participants are healthy children aged 2-14 years
• Involves 5 Asia Pacific countries (12 centres)
• Randomisation stratified by site & age

OUTCOME INVESTIGATED?

Incidence of virologically confirmed dengue\(^1\)
Secondary outcomes: hospitalisation, severity
10,275 volunteers

6851 received vaccine
6710 included in per-protocol analysis

3424 received placebo
3350 included in per-protocol analysis
### RESULTS

<table>
<thead>
<tr>
<th>Vaccine group (N=6848)</th>
<th>Control group (N=3424)</th>
<th>Vaccine efficacy (% [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong>&lt;sup&gt;+&lt;/sup&gt; (n)</td>
<td><strong>Person-years at risk†</strong></td>
<td><strong>Incidence density‡ (95% CI)</strong></td>
</tr>
<tr>
<td>Primary analysis (per-protocol)§</td>
<td>117</td>
<td>6526</td>
</tr>
<tr>
<td>Intention-to-treat analysis¶</td>
<td>286</td>
<td>13571</td>
</tr>
</tbody>
</table>

Defined as a first episode of virologically confirmed dengue by either dengue non-structural protein 1 antigen ELISA, dengue screen PCR, or a serotype-specific PCR. †The cumulative time (in years) until the participant was diagnosed with virologically confirmed dengue or until the end of the active follow-up period, whichever came first. The person-years at risk presented in the tables is the sum of individual units of time for which the participants contributed to the analyses. ‡Calculated as the number of cases divided by the cumulative person-years at risk. §Per-protocol efficacy population included participants who received three injections, according to protocol, and did not present with any of the criteria in a pre-specified list (appendix); virologically confirmed dengue occurring at least 28 days after the third injection. ¶Intention-to-treat efficacy population included all participants who received at least one injection, and participants were analysed in the group to which they were randomised, irrespective of per-protocol criteria; virologically confirmed dengue occurring from baseline.

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**Table 2: Efficacy of CYD-TDV vaccination against symptomatic, virologically-confirmed dengue due to any serotype**

- Incidence density significantly lower in vaccine group compared to control (1.8 vs 2.1)
- **Vaccine efficacy = 56.5% (CI 43.8-66.4)**
Interesting points:

- Efficacy is **higher in participants with pre-existing dengue neutralising antibodies** than in those who were seronegative\(^1\)

- **Vaccine is most effective for serotype 3** and least effective for serotype 1

- **54 (1\%) participants in the vaccine group and 33 (1\%) of those in the control group had serious adverse events** within 28 days of vaccination\(^1\)
Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease


ABSTRACT

BACKGROUND
A candidate tetravalent dengue vaccine is being assessed in three clinical trials involving more than 35,000 children between the ages of 2 and 16 years in Asian–Pacific and Latin American countries. We report the results of long-term follow-up interim analyses and integrated efficacy analyses.

METHODS
We are assessing the incidence of hospitalization for virologically confirmed dengue as a surrogate safety end point during follow-up in years 3 to 6 of two phase 3 trials, CYD14 and CYD15, and a phase 2b trial, CYD23/57. We estimated vaccine efficacy using pooled data from the first 25 months of CYD14 and CYD15.

RESULTS
Follow-up data were available for 10,165 of 10,275 participants (99%) in CYD14 and 19,898 of 20,869 participants (95%) in CYD15. Data were available for 3203 of the 4002 participants (80%) in the CYD23 trial included in CYD57. During year 3 in The authors’ full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Saville at Sanofi Pasteur, 2 Ave. Pont Pasteur, 69367 Lyon CEDEX 07, France, or at melanie.saville@sanofipasteur.com.

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A long-term safety analyses based on data collected during year 3 of phase 3 trials in:

- Five Asian–Pacific countries (CYD14)
- Latin American countries (CYD15)
- CYD23 extension study (CYD57) in Thailand
Figure 1. Overview of the Surveillance Phase and Long-Term Follow-up Phase of the CYD-TDV Candidate Vaccine Trials.

CYD-TDV is a candidate recombinant, live, attenuated, tetravalent dengue vaccine that has been assessed in two phase 3 randomized efficacy studies (called CYD14 and CYD15) involving a total of more than 31,000 participants between the ages of 2 and 16 years in Asian-Pacific and Latin American countries. In addition, 3203 of 4002 participants (80%) who were between the ages of 4 and 11 at initial enrollment in the phase 2b CYD23 trial in Thailand are being followed in the CYD57 trial. The trials had similar designs. According to the study designs, the long-term follow-up phase will continue for a total of 6 years after enrollment.
During year 3, severe dengue was reported in 18 of 22,177 participants in the vaccine group and in 6 of 11,089 in the control group\(^2\)

The pooled relative risk of hospitalization for virologically confirmed dengue in the vaccine group for the three trials was 0.84\(^2\)

Pooled vaccine efficacy against dengue of any severity and any serotype among children aged >9 years was 65.6\(\%\)\(^2\)
Philippines

Suspended dengue vaccine was given to 730,000 children, Philippines says

Sanofi’s Dengvaxia immunisation could worsen disease in some patients not previously exposed to virus
The Philippines has ordered an investigation into the immunisation of more than 730,000 children with a dengue vaccine that has been suspended following an announcement by French drug company Sanofi that it could worsen the disease in some cases.

The World Health Organisation said it hoped by the end of the year to conduct a full review of data on the vaccine, commercially known as Dengvaxia. In the meantime, the WHO recommended it be used only in people who had a prior infection with dengue.

Last week, the Philippines department of health halted the use of Dengvaxia. Brazil, where dengue is a significant health challenge, had already recommended restricted use of the vaccine.

Dengue is a mosquito-borne tropical disease, killing about 20,000 people a year and infecting hundreds of millions.

Sanofi explained its “new findings” at a news conference in Manila but did not say why action was not taken after a WHO report in mid-2016 that identified the risk.

While Sanofi’s Dengvaxia is the first approved vaccine for dengue, scientists already recognised it did not protect equally against the four different types of the virus.