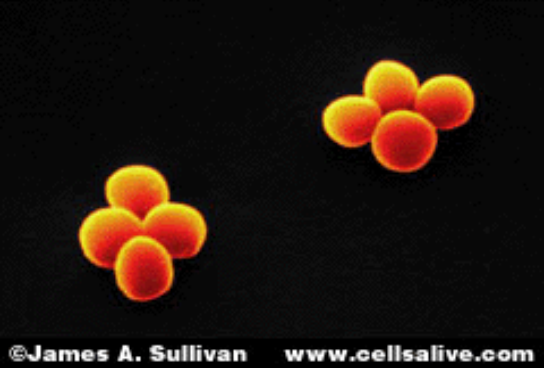
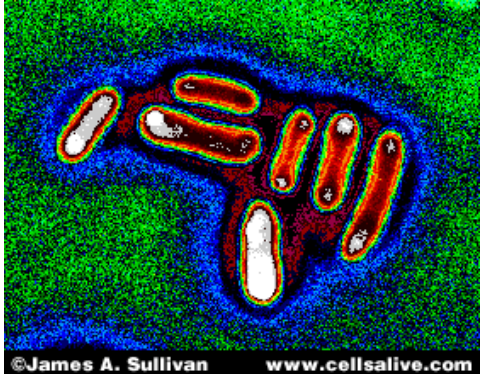
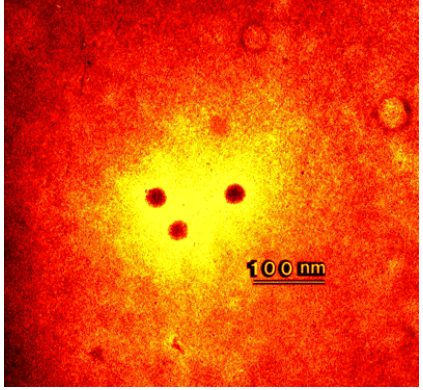
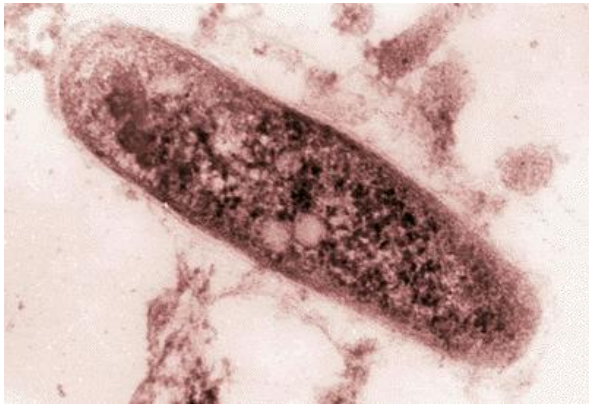
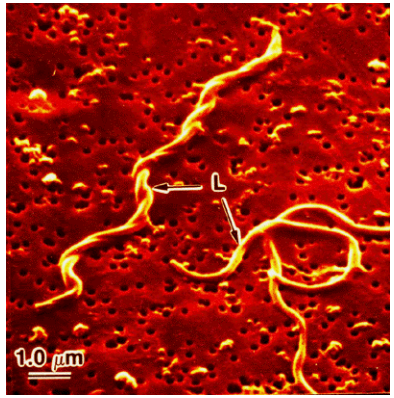






Infectious Disease Epidemiology:
Influenza and Strep. Pneumona epidemiology and prevention





Dr Munir Abu-Helalah

Associate Professor of Epidemiology and Preventive Medicine

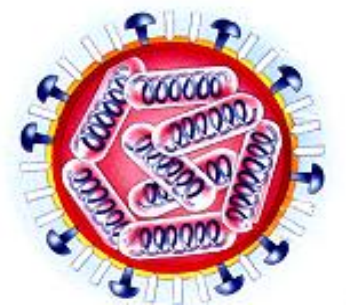
Influenza Virus

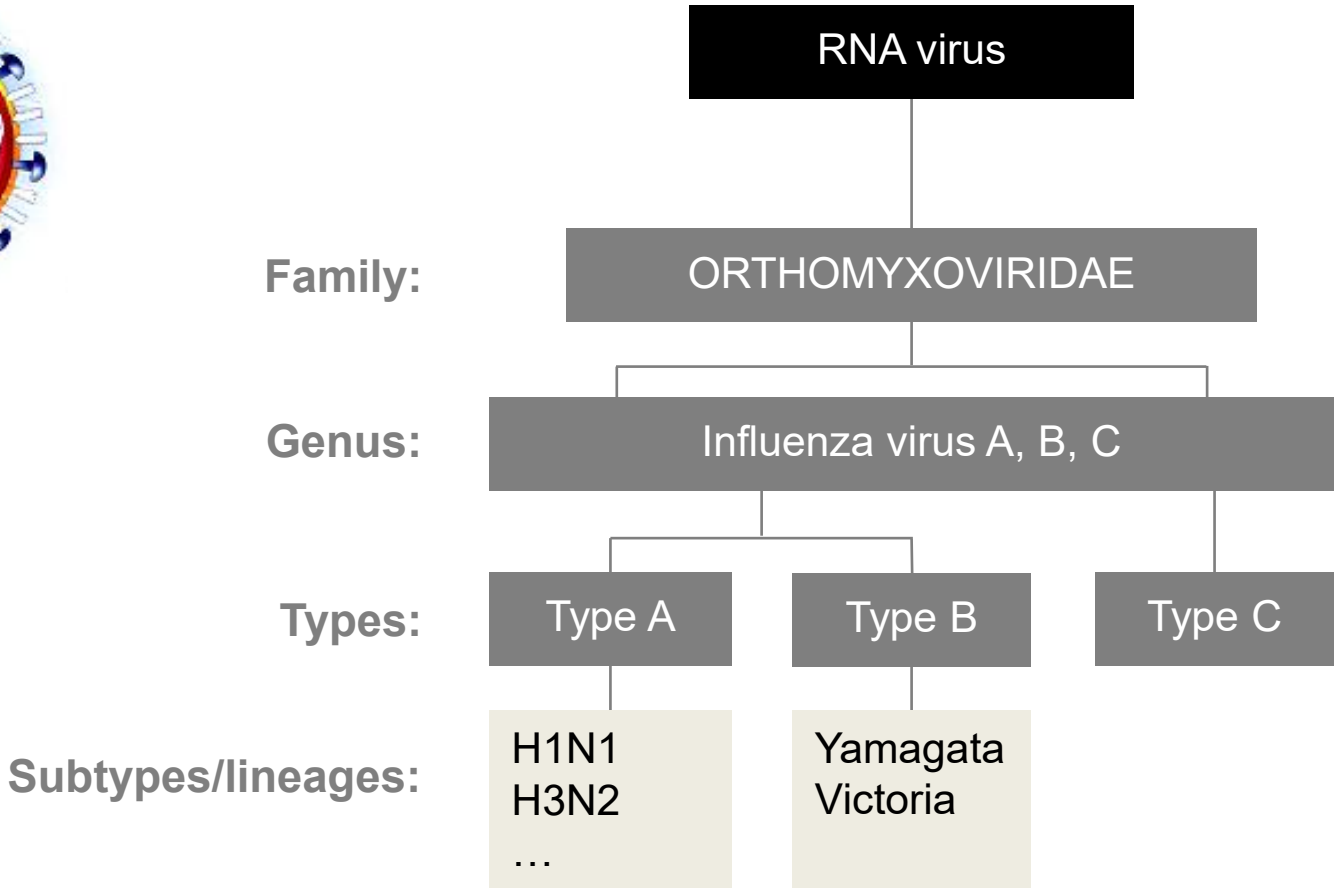
- Influenza uptake in Jordan based on all amount of seasonal vaccine delivery to Jordan: **1.5%-2.5%**

  In the USA: 40-50% of the total population receives vaccine annually. Public Health experts consider this figure:
  "Unmet Need!"

  What do we miss in Jordan in term of flu vaccines selection and utilization??

Influenza virus classification[1,2]



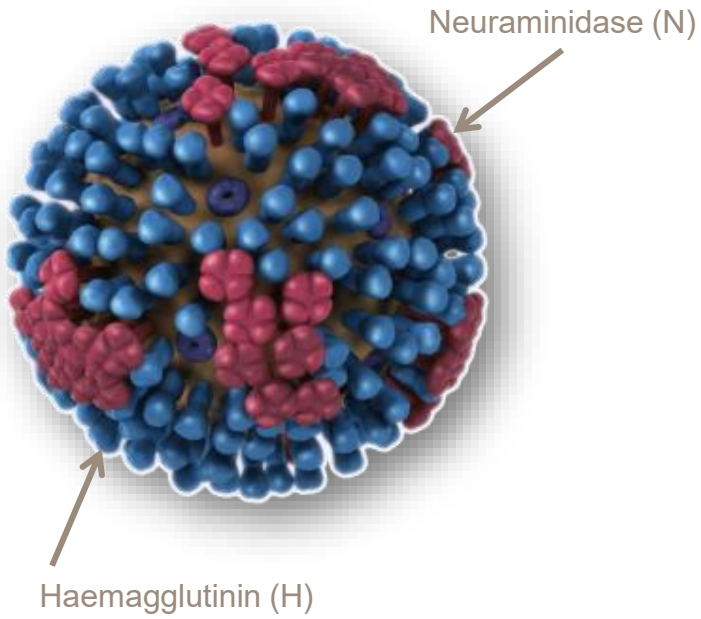


• **References: 1.** Kingsbury DW. Virology, 2nd edition, New York; 1990. p. 1076-87 **2.** Keiji Fukuda et al, Vaccines, 2004

Influenza as a cause of disease

- **Type A** influenza virus
  - Affects both humans and animals
  - Divided into subtypes, based on two surface proteins: haemagglutinin and neuraminidase
  - Main circulating strains are H1N1 and H3N2
- **Type B** influenza virus
  - Affects predominantly humans
  - Not divided into subtypes, but split into two lineages: Victoria and Yamagata
- **Type C** influenza virus
  - Rarely reported in humans, and most cases subclinical

Influenza A virion showing the two major surface glycoproteins



- CDC, Centers for Disease Control and Prevention
US CDC. The pink book: influenza. 2012 (accessed April 2014); Nelson MI, Holmes EC. *Nat Rev Genet* 2007;8:196–205.

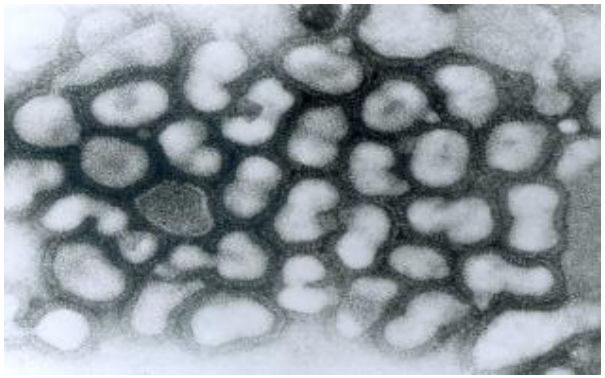
Overview: influenza

- Influenza is an acute viral infection of the respiratory tract
- There are three types of influenza virus: A, B and C
- Influenza A and influenza B are responsible for most clinical illness

Emergency hospital during the flu pandemic in 1918

Source: US National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington DC, USA (NCP1603)

Electron micrograph of cells infected with influenza A virions



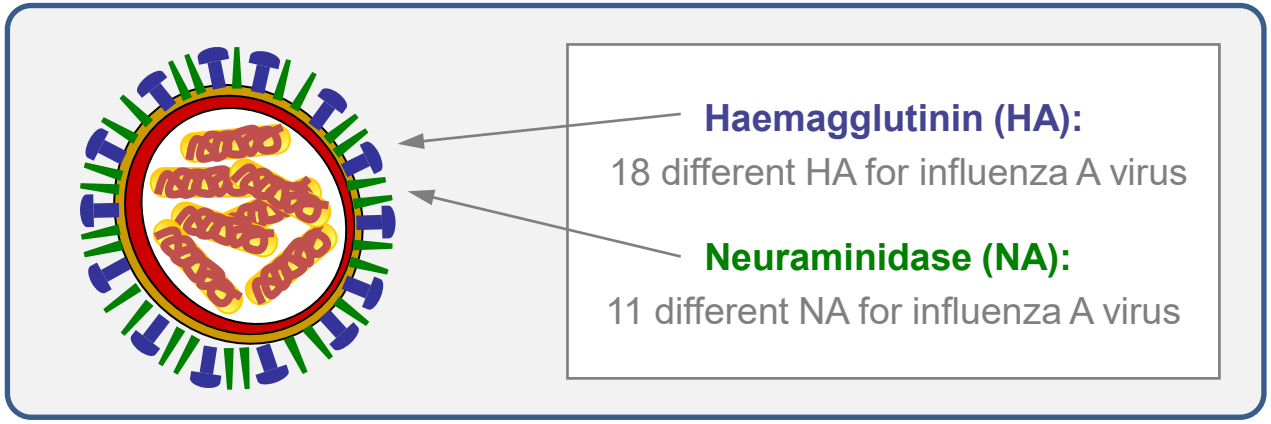
Source: US CDC

- WHO, World Health Organization
  WHO. Influenza (seasonal) 2009. Fact sheet No. 211 (accessed April 2014); US CDC. The pink book: influenza. 2012 (accessed April 2014).

Constant and rapid genetic evolution of influenza[1]

Surface antigens of influenza viruses change:

- Antigenic **drift**:
  - **Minor changes** associated with annual outbreaks or epidemics
  - **<u>Impact : updating vaccine yearly to match predicted strains that will be circulating</u>**
- Antigenic **shift**:
  - **Major changes** resulting in new subtype with a new HA protein (and sometimes NA)
  - Can lead to pandemics



Reference: 1. ECDC Fact Sheet for Health Professionals http://ecdc.europa.eu/en/healthtopics/seasonal_influenza/basic_facts/Pages/factsheet_professionals_seasonal_influenza.aspx

Antigenic shift

- is the process by which two or more different strains of a virus, or strains of two or more different viruses, combine to form a new subtype having a mixture of the surface antigens of the two or more original strains.
- The term is often applied specifically to influenza, as that is the best-known example, but the process is also known to occur with other viruses, such as visna virus in sheep.
- Antigenic shift is a specific case of reassortment or viral shift that confers a phenotypic change.

- Antigenic shift, however, occurs only in influenza A because it infects more than just humans.

- The most recent 2009 H1N1 outbreak was a result of antigenic shift and reassortment between human, avian, and swine viruses

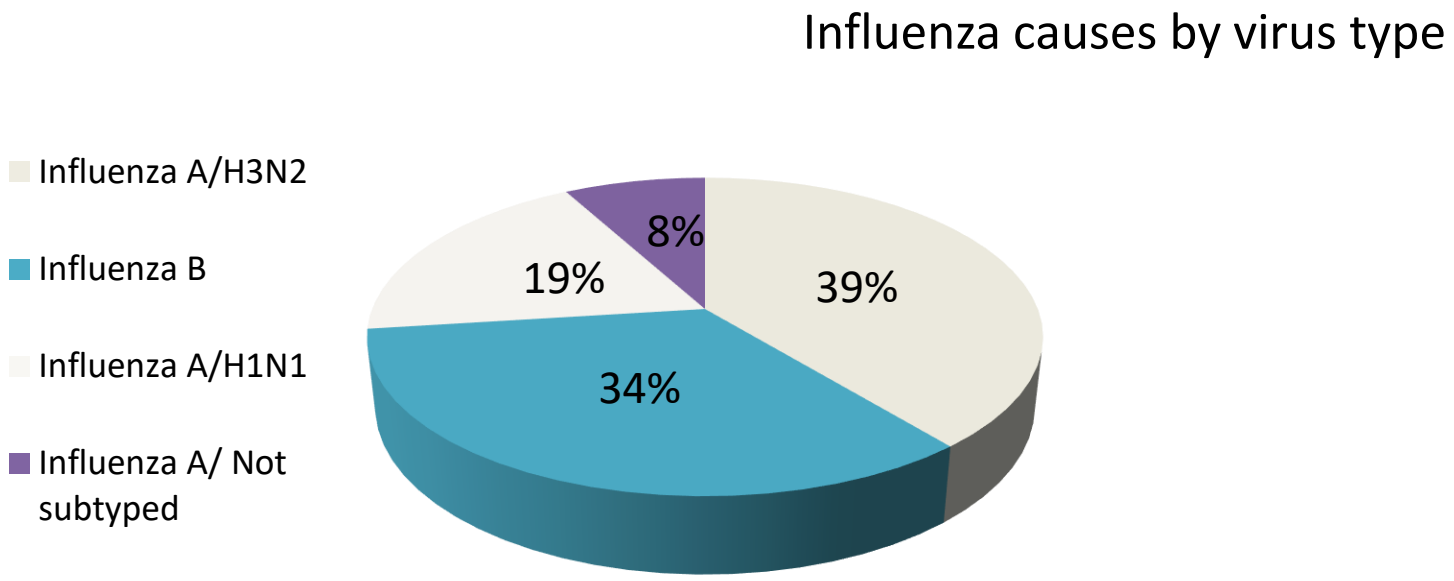
1. *Narayan, O; Griffin, DE; Chase, J (1977). "Antigenic shift of visna virus in persistently infected sheep". Science. **197** (4301): 376–378. doi:10.1126/science.195339. PMID 195339.*)
2.^ Jump up to:[a] [b] *Treanor, John (15 January 2004). "Influenza vaccine--outmaneuvering antigenic shift and drift". New England Journal of Medicine. **350** (3): 218–220. doi:10.1056/NEJMp038238. PMID 14724300.*

Antigenic drift

- Antigenic shift is contrasted with antigenic drift, which is the natural mutation over time of known strains of influenza (or other things, in a more general sense) which may lead to a loss of immunity, or in vaccine mismatch.
- Antigenic drift occurs in all types of influenza including influenza A, influenza B and influenza C.
- Affected species include other mammals and birds, giving influenza A the opportunity for a major reorganization of surface antigens.
- Antigenic drift has been responsible for heavier-than-normal flu seasons in the past, like the outbreak of influenza H3N2 variant A/Fujian/411/2002 in the 2003–2004 flu season.
- All influenza viruses experience some form of antigenic drift, but it is most pronounced in the influenza A virus.

1. *Narayan, O; Griffin, DE; Chase, J (1977). "Antigenic shift of visna virus in persistently infected sheep". Science. **197** (4301): 376–378. doi:10.1126/science.195339. PMID 195339.*)
2.^ Jump up to:[a] [b] *Treanor, John (15 January 2004). "Influenza vaccine--outmaneuvering antigenic shift and drift". New England Journal of Medicine. **350** (3): 218–220. doi:10.1056/NEJMp038238. PMID 14724300.*

Influenza is caused by A and B virus strains worldwide

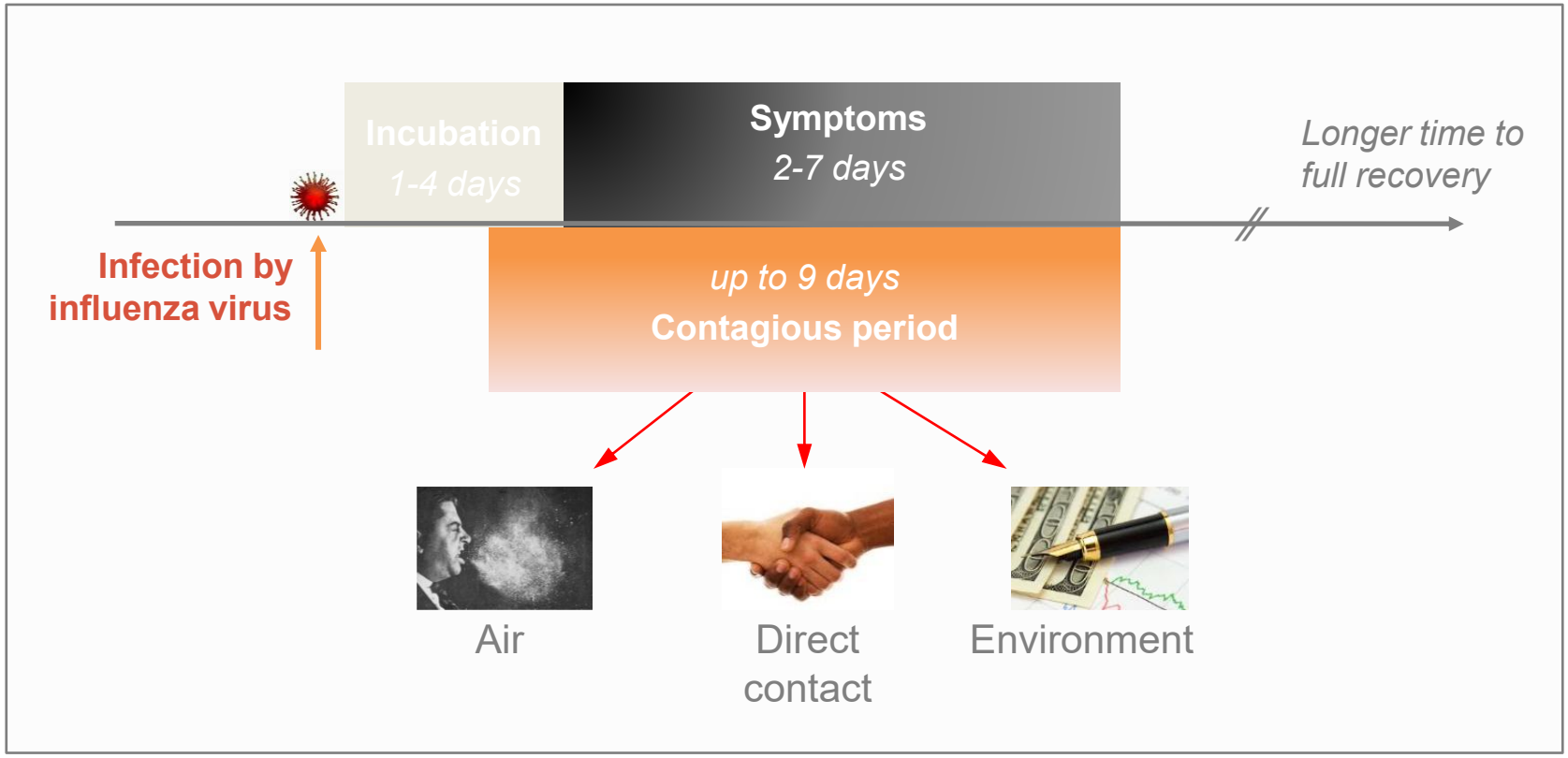


- Global Influenza Surveillance and Response System (GISRS):
  - Analysis of laboratory-confirmed influenza surveillance data by type and subtype (A/H3N2, A/H1N1 and B) from July 2016 to August 2016
  - These latest data were collected from NICs and other national influenza laboratories in 50 countries, areas or territories

NIC, National Influenza Centre

– Compiled laboratory confirmed data from the Global Influenza Surveillance and Response System (GISRS) by WHO FluNet summary 2016. Available from: http://www.who.int/influenza/gisrs_laboratory/updates/summaryreport/en/ [Accessed January 2017]

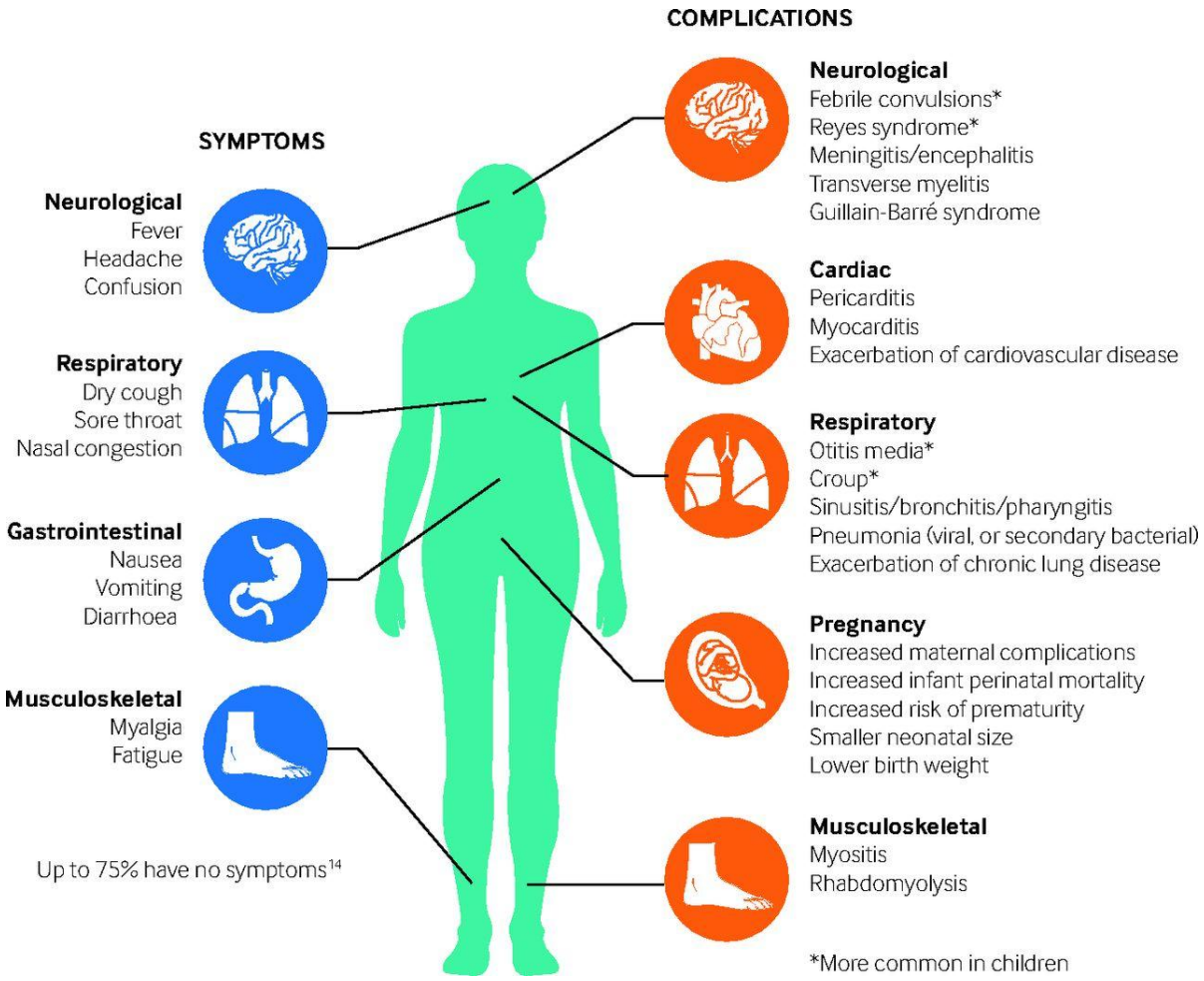
Influenza is a highly transmissible viral disease



Reference: 1. CDC: Seasonal flu; Clinical signs and symptoms of influenza (https://www.cdc.gov/flu/professionals/acip/clinical.htm)

Symptoms and complications of Influenza

- Influenza is characterized by sudden onset of fever, myalgia, headache, malaise, dry cough, sore throat, and nasal congestion Gastrointestinal symptoms including nausea, vomiting and diarrhea are also common.
- Influenza can cause severe illness or death, particularly in high risk populations



Reference: 1. S Ghebrehewet, *BMJ 2016;355:i6258* http://www.bmj.com/content/355/bmj.i625

Clinical symptoms and complications of influenza

- The symptoms[1] of influenza are **similar for influenza A and B**[2]

Sudden onset of fever, extreme fatigue

Nasal congestion

Non-productive cough, sore throat

Headache

Myalgia, especially of back muscles

Gastrointestinal: abdominal pain, diarrhoea and vomiting

- Compared with otherwise healthy adults, influenza can cause more serious illness and greater mortality in following **risk groups**[3]:

Children aged <2 years

Older adults aged ≥65 years

Pregnant women

Individuals with weakened immune systems

Individuals with chronic medical conditions
e.g. heart, lung, kidney, liver, blood or metabolic diseases

- CDC, Centers for Disease Control and Prevention; WHO, World Health Organization

1. US CDC. The Pink Book: influenza. 2012 (accessed April 2014); 2. Hite LK *et al. Int J Infect Dis* 2007;11:40–7; 3. WHO. Influenza (seasonal) 2009. Fact sheet No. 211. Available at: http://www.who.int/mediacentre/Factsheets/ (accessed March 2014).

Influenza B clinically similar to A except for age distribution[1]

Age

- All age groups can be infected but 5–14/19 yo olds more susceptible to type B virus[2-3-4-10]
- Influenza B outbreaks can be observed in nursing homes[5]
- During severe influenza B season, influenza B may represent more than 50% of fatal cases in adults > 60 yo[9]

Symptoms

- Clinical symptoms and outcomes similar for A and B infections[1–2]
- Minimal and inconsistent differences across age groups[2]
- Very few differences in clinical presentation of influenza B lineages[2]
- Knowledge gaps still exist[7]

Hospitalizations

- No difference in frequency of hospital admission between influenza A and B
- Influenza B ranks between A/H3N2 and A/H1N1 in frequency, hospitalization rates, morbidity and mortality[7]
- Similar rate of confirmed pneumonia in patients with influenza A and B[1]

Deaths

- Substantial impact on mortality:
  - 25% of all influenza related mortality in the US (1976–1999) attributed to influenza B[6]
  - 22% to 44% of pediatric deaths in the US (2004-2011) attributed to influenza B[6]
  - **Mortality associated with influenza B was greater than that of influenza A in children <16 yo** [8]

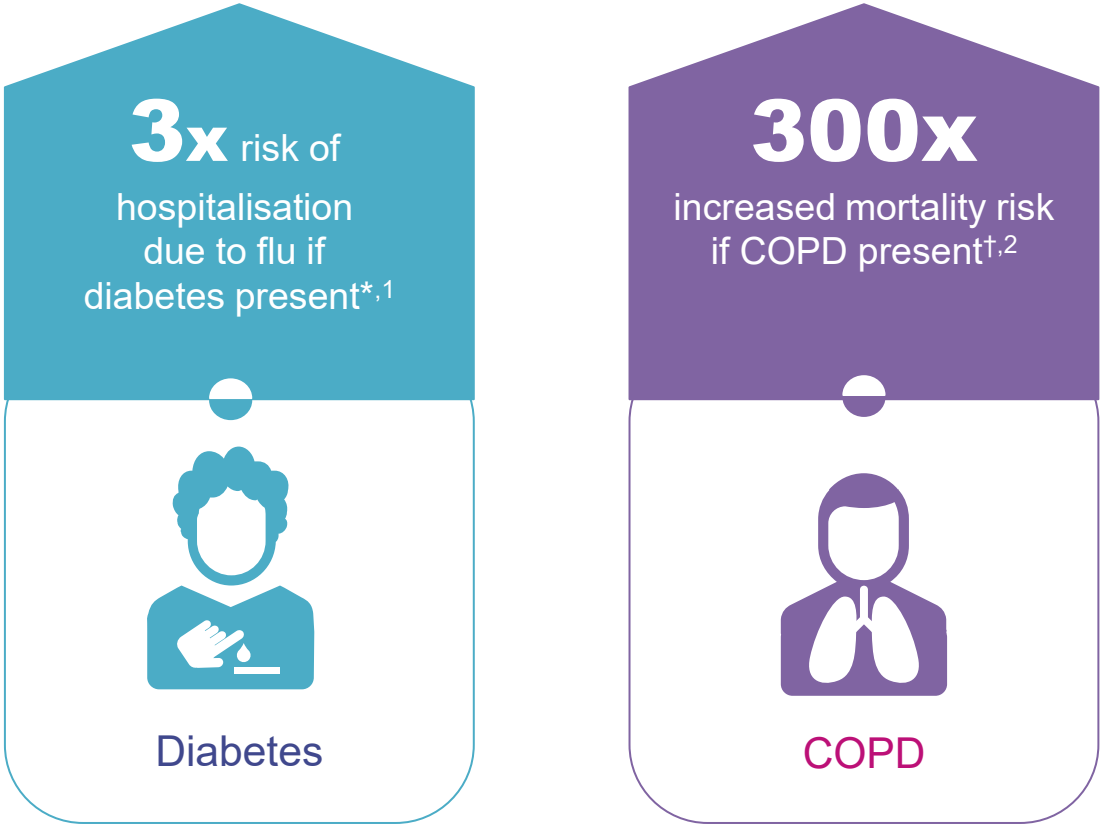
- **References: 1.** Irving SA, *et al. Influenza Other Respir Viruses* 2012; 6(1):37. **2.** Mosnier A, *et al BMC Infect Dis* 2015; 15:357. **3.** Caini S, *et al Influenza Other Respir Viruses* 2015; 9(Suppl 1):3. **4.** Heikkinen T, *et al Clin Infect Dis* 2014; 59(11):1519. **5.** Camilloni B, *et al Vaccine* 2010; 28(47):7536. **6.** Glezen PW, *et al. Am J Public Health* 2013; 103(3):e43. **7.** van de Sandt CE, *et al. Future Microbiol* 2015; 10(9):1447. **8.** Tran D, *et al. Pediatrics* 2016; 138(3):e20154643. 9. Adhoch, *et al*. Eurosurveillance 2018; 23(13) Accessed date June 12 2018 10.Caini, *et a*l. Influenz**a** Other Respir Viruses. 2018

Influenza vaccination and antimicrobial resistance (AMR)

- References: 1*http://www.who.int/mediacentre/news/releases/2016/commitment-antimicrobial-resistance/en/* .2, Wilby KJ, Vaccine 2012 **3.** Kwong JC, *et al. Clin Infect Dis* 2009; 49(5):750 4, Nichol KL,. JAMA 1999;281:137–44.

Concomitant NCDs increase the risk of complications of influenza

For individuals with influenza:



- COPD, chronic obstructive pulmonary disease; NCD, noncommunicable disease
- *Prevalence ratio for diabetes 3.10 (95% CI: 2.04–4.71) in 239 patients hospitalised with influenza A
  †Case fatality rate of influenza in patients with COPD ≥30% compared with 0.05–0.01% in otherwise healthy individuals

- \Allard R *et al*. *Diabetes Care* 2010;33:1491–1493; 2. Plans-Rubio P. *Int J Chron Obstruct Pulmon Dis* 2007;2:41–53

WHO recommendations for influenza vaccination

WHO Recommends[1]

- People at high risk of complications:
  - Pregnant women (highest priority)
  - Children aged 6 months to 5 years:
    - Children aged 6–23 months of age
    - Children aged 2–5 years of age
  - Elderly people (≥65 years of age)
  - People with underlying health conditions (diabetes, asthma, chronic heart or lung diseases, HIV/AIDS)
  - International travelers with any of the above
- People at high risk of exposure and/or capable of transmitting influenza to those at high risk of influenza related complications:
  - Healthcare workers

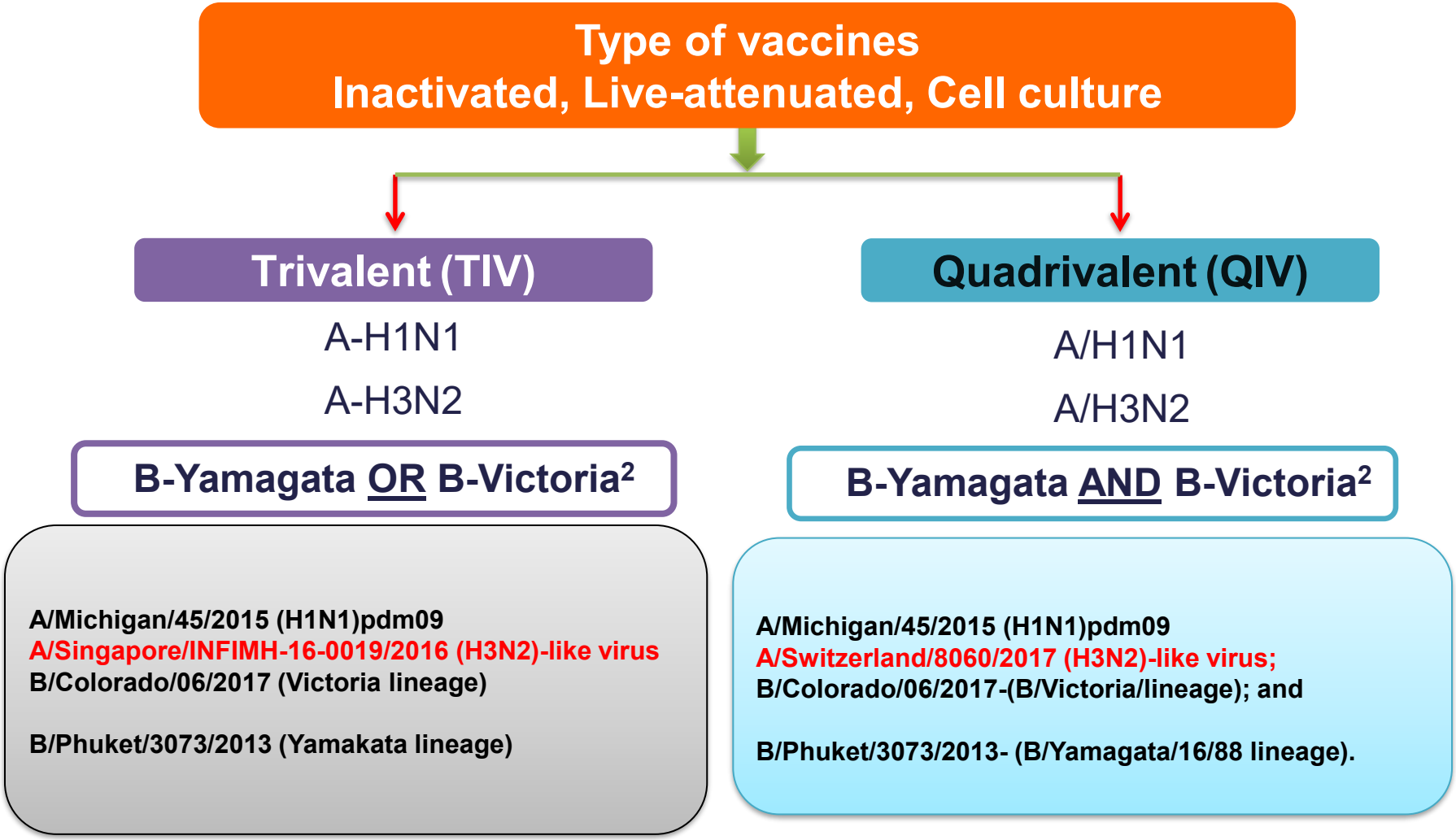
Reference: 1. WHO. Weekly epidemiological record No. 47, 2012, 87(47):461 (http://www.who.int/wer/2012/wer8747.pdf.)

Pregnant women are recommended by WHO for influenza vaccination

- Pregnant women have an increased risk of severe disease and death from influenza[1,2]
- The infection may also lead to complications for the fetus/newborn such as stillbirth, neonatal death, preterm delivery, and decreased birth weight[2,3]
- Furthermore, infants <6 months of age are also at high risk of influenza, but are too young to be vaccinated[3]

• **References: 1.** Omer SB, *et al. PLoS Med.* 2011;8(5):e1000441. **2.** Yudin MH. *Int J Womens Health*. 2014;6:681 **3.** WHO. Weekly epidemiological record No. 47, 2012, 87(47):461 (http://www.who.int/wer/2012/wer8747.pdf.)

Types of seasonal influenza vaccine



1. ACIP. *Morb Mortal Wkly Rep* 2014; **63**: 691–7; 2. Ambrose CS, Levin MJ. *Hum Vaccin Immunother* 2012; **8**: 81–8; 3. WHO recommendation. Access from http://www.who.int/influenza/vaccines/virus/recommendations/ Last accessed 30 October 2017

41 different influenza vaccine strains recommended for northern hemisphere composition since 1989

World Health Organization

2013–14

WHO recommended quadrivalent vaccine compositon[3]

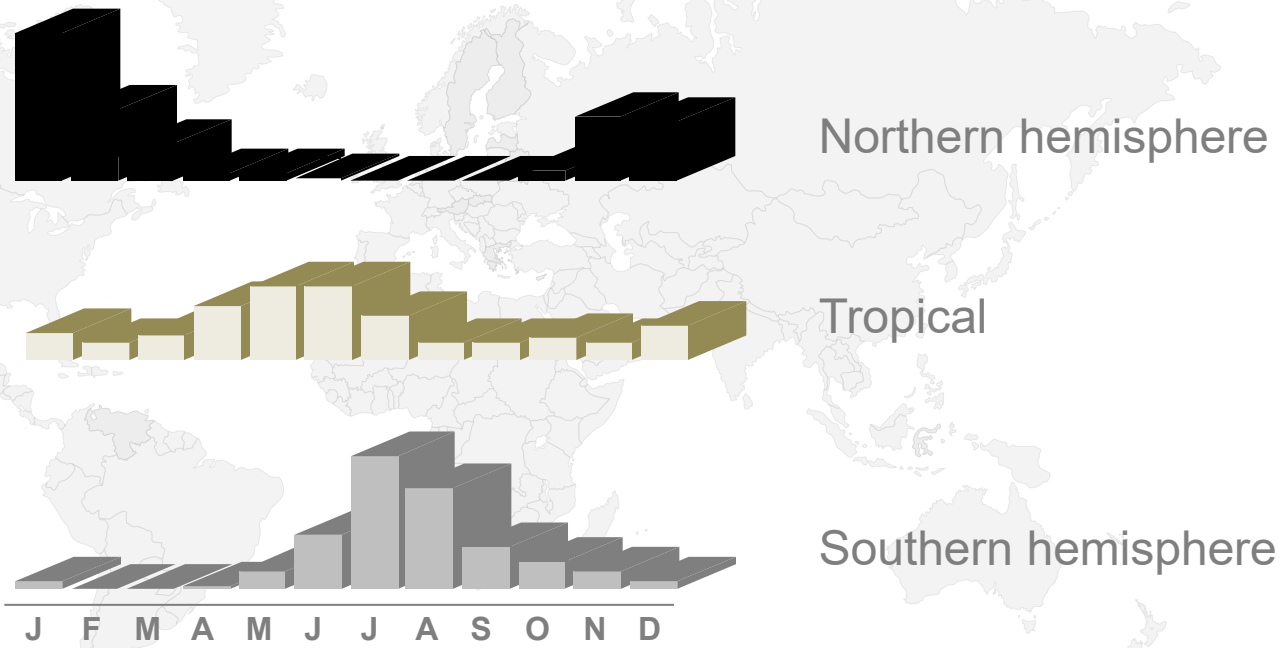
1989 ◀ ▶ **2019**

- 9 changes for H1N1
- 20 changes for H3N2
- 14 changes for B

1. Hay AJ, *et al. Philos Trans R Soc Lond B Biol Sci.* 2001; 356(1416):1861. **2.** www.who.int/influenza/vaccines/vaccinerecommendations1/en/index13.html (2001-2010). **3.** www.who.int/influenza/vaccines/virus/recommendations/en/ (2010-20169) 4. WHO. Recommended composition of influenza virus vaccines for use in the 2018-19 Northern hemisphere influenza season. http://www.who.int/influenza/vaccines/virus/recommendations/2019_20_north/en//

Influenza seasonality

Influenza activity and occurrence in different climates[1]



Temperate climates: yearly winter epidemics

Tropical climates: year-round transmission with several peaks

Reference: 1. WHO. Influenza (Seasonal). Fact Sheet No. 211 http://www.who.int/mediacentre/factsheets/fs211/en/

Global burden of pneumococcal diseases

- Major cause of mortality and morbidity worldwide

- The most common cause of community acquired pneumonia requiring hospitalization, accounting for up to 50% of these cases
- CDC data: most common pediatrics infection for which antibiotics are routinely prescribed.

Pneumococcal diseases burden

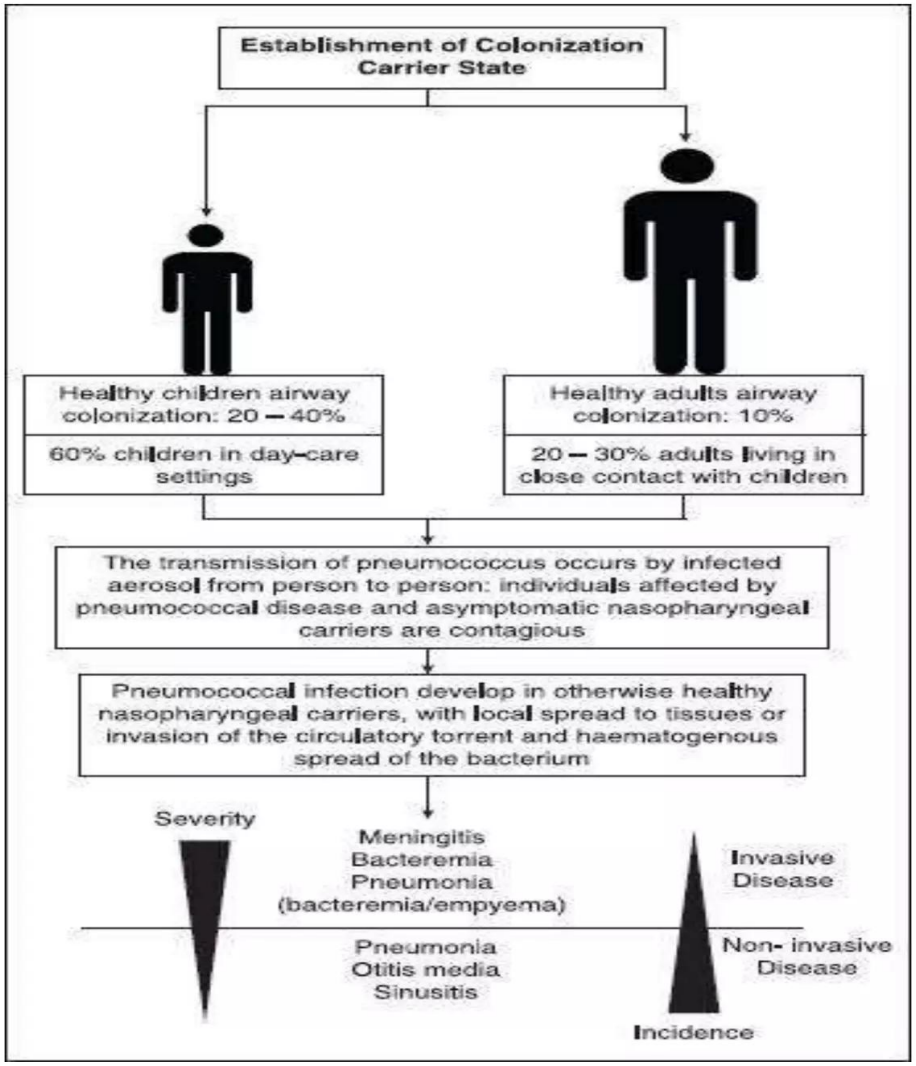
- Pneumococcal disease describes a group of infections such as meningitis, pneumonia, septicemia, sinus infections and ear infections caused by the Streptococcus pneumonia.

- Acute respiratory infections kill an estimated 2.6million children under five years of age annually.

- **Strep. Pneumonia causes over 1 million of these deaths**, most of which occur in developing countries

- Pneumococci are common inhabitants of the respiratory tract and may be isolated from the nasopharynx of asymptomatic human carriers , There is no animal or insect vector.

- Many people, especially children, have the pneumococci in their nostrils, pharynx, or throats without manifesting signs or symptoms of ill health or developing invasive disease , this is called asymptomatic carriage .

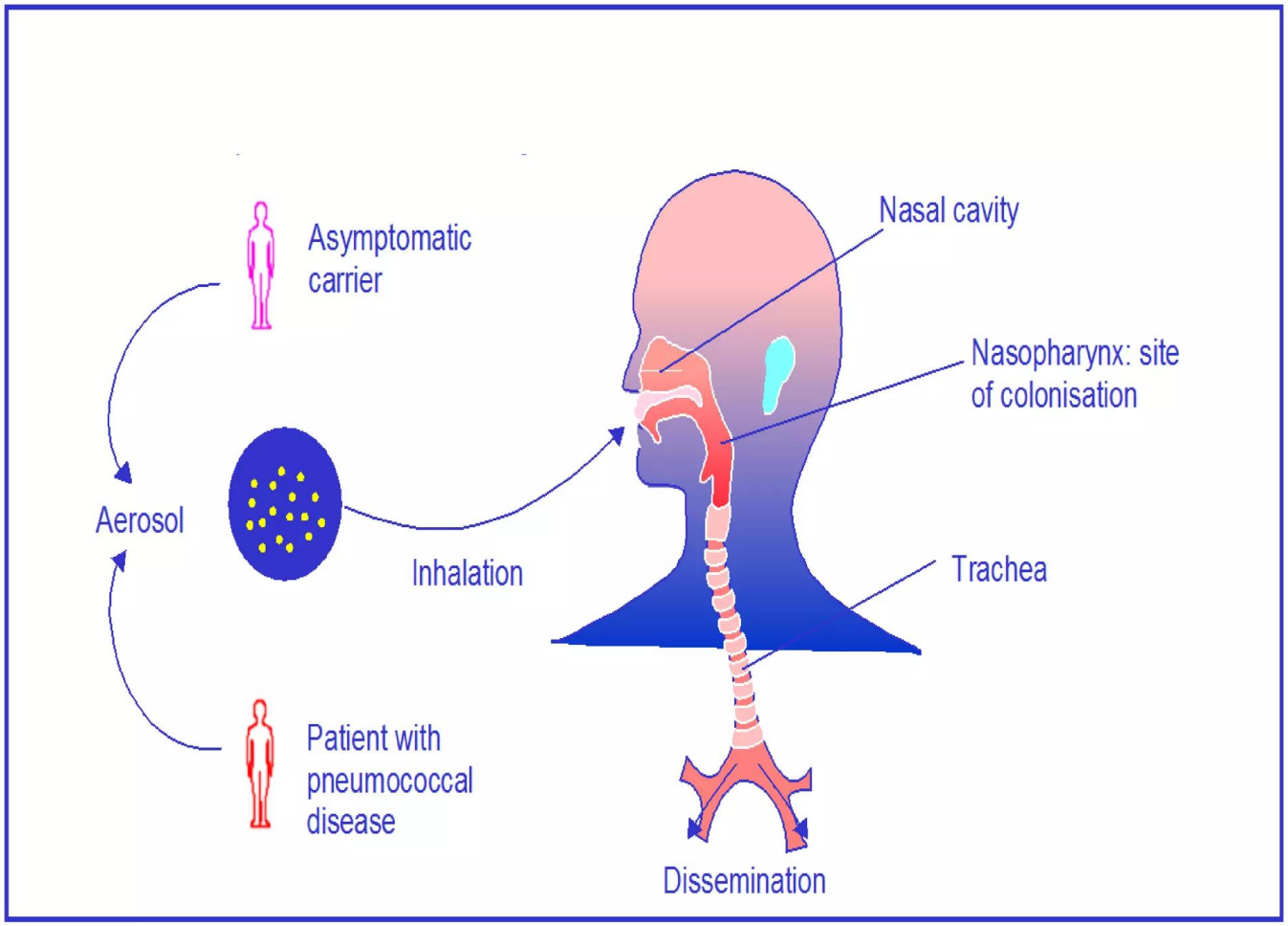

Establishment of Colonization
Carrier State
Healthy children airway colonization: 20 — 40%
60% children in day-care settings
Healthy adults airway colonization: 10%
20 — 30% adults living in close contact with children
The transmission of pneumococcus occurs by infected aerosol from person to person: individuals affected by pneumococcal disease and asymptomatic nasopharyngeal carriers are contagious
Pneumococcal infection develop in otherwise healthy nasopharyngeal carriers, with local spread to tissues or invasion of the circulatory torrent and haematogenous spread of the bacterium
Severity
Meningitis
Bacteremia
Pneumonia
(bacteremia/empyema)
Pneumonia
Otitis media
Sinusitis
Invasive Disease
Non- invasive Disease
Incidence

Pneumococcal colonisation

- Pneumococcal disease may take place when two situations coincide:

1. The host is colonized with a pneumococcal strain against which immunity has not yet been established .

2. An alteration of the natural barriers or host immune system has occurred.


Asymptomatic carrier
Aerosol
Inhalation
Patient with pneumococcal disease
Nasal cavity
Nasopharynx: site of colonisation
Trachea
Dissemination

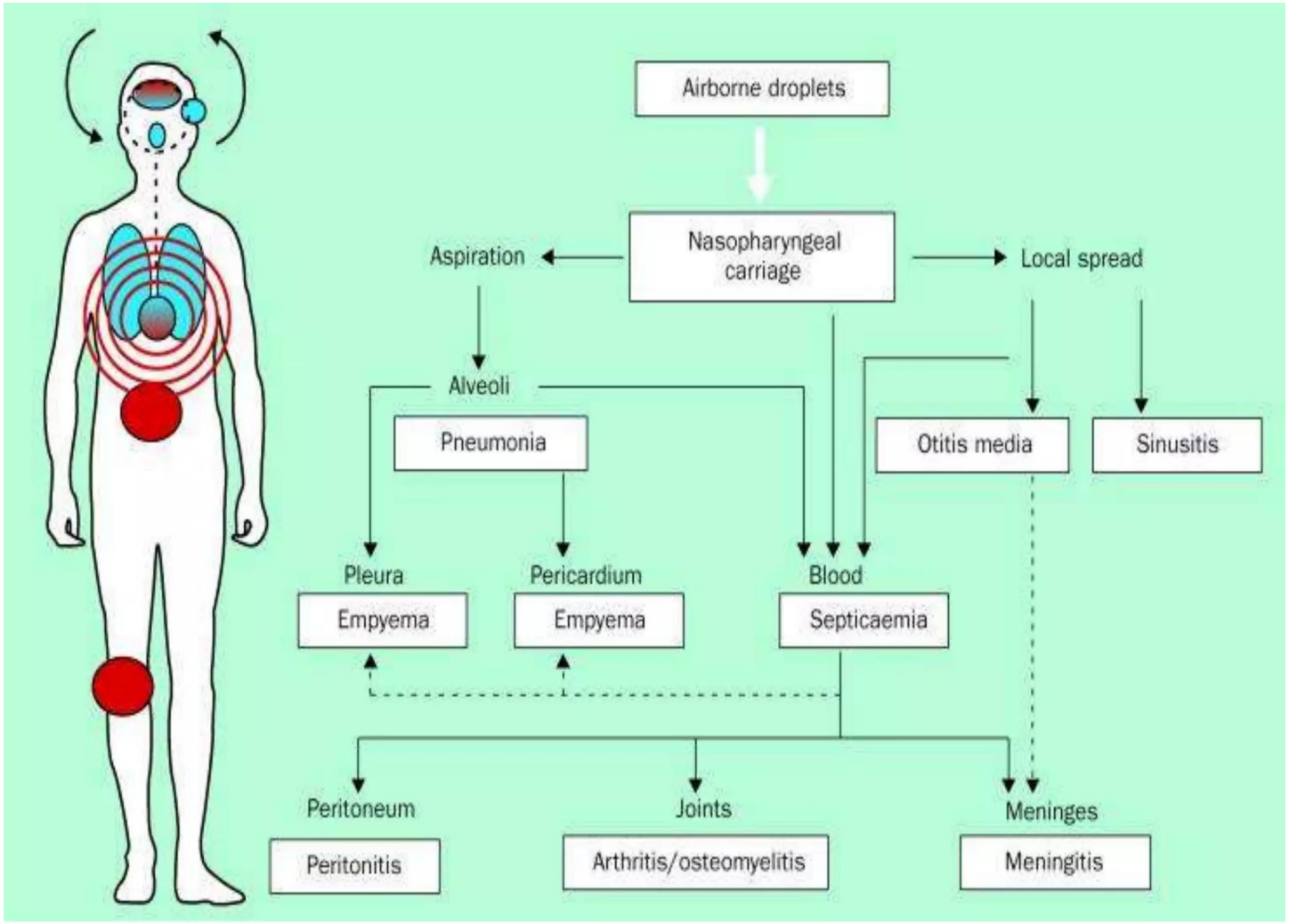

Airborne droplets
Nasopharyngeal carriage
Aspiration
Local spread
Alveoli
Pneumonia
Otitis media
Sinusitis
Pleura
Empyema
Pericardium
Empyema
Blood
Septicaemia
Peritoneum
Peritonitis
Joints
Arthritis/osteomyelitis
Meninges
Meningitis

Table 1 - Diseases caused by pneumococcus

Non-invasive diseases	Invasive diseases*
Acute otitis media	Bacteremia
Sinusitis	Bacteremic pneumonia / empyema
Conjunctivitis	Meningitis
Bronchitis	Sepsis
Pneumonia	Peritonitis
	Arthritis / osteomyelitis

* Invasive diseases: isolation of pneumococcus from usually sterile sites (blood, cephalorachidian, pleural or sinovial liquid).

Non-invasive disease

- Acute otitis media and pneumonia (without bacteraemia) are classified as non-invasive disease for surveillance purposes.
- Pneumococcal pneumonia is the most common clinical presentation of pneumococcal disease among adults.
- Pneumococcus is estimated to account for over a third of all community-acquired pneumonia in adults.

Conditions That Increase Risk for Invasive Pneumococcal Disease

Table 2. High-risk conditions for severe or recurrent pneumococcal disease in childhood and adolescence	
Risk group	**Disease or condition**
Immunocompetent children	Chronic pulmonary disease: severe asthma, bronchopulmonary dysplasia, cystic fibrosis, α1-antitrypsin deficiency, bronchiectasis
	Chronic heart disease, especially congenital cyanotic heart disease or conditions that can lead to heart failure or hemodynamic alterations
	Down syndrome[1]
	Diabetes mellitus
	Chronic liver disease
	Subarachnoid space fistulas
	Children with cochlear implants
Children with asplenia[2] (anatomic or functional)	Sickle-cell anaemia and other hemoglobinopathies
	Congenital or acquired asplenia, or splenic dysfunction
Immunocompromised children[2]	HIV infection
	Primary immunodeficiencies (excluding isolated IgA deficiency)
	Chronic kidney failure and nephritic syndrome
	Diseases that require treatment with immunosuppressive drugs or radiotherapy (including leukaemia, lymphoma, bone marrow or solid organ transplant)

ACIP risk groups for pneumococcal infection

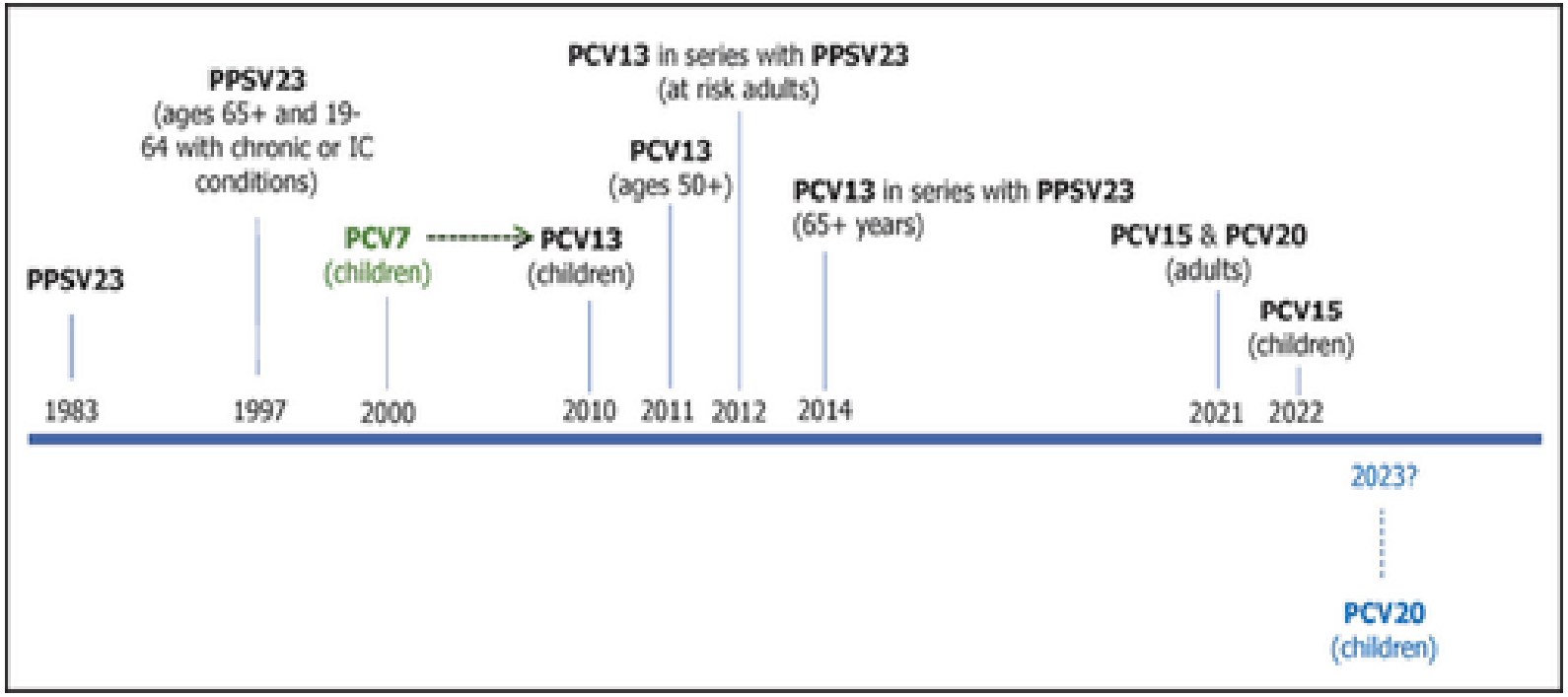
- (ACIP) recommends vaccination of:
  - All adults aged 65 years and over
  - Adults aged 19-64 years with the following underlying medical conditions:

1- Immunocompetent persons
- Chronic heart disease
- **Chronic lung disease**
- Diabetes mellitus
- Cerebrospinal fluid leaks
- Cochlear implant
- Chronic liver disease
- **Cigarette smoking**

2- Functional or anatomic asplenia
- Sickle cell disease
- Splenectomy
- congenital or acquired asplenia

3-Immunocompromised persons
- Congenital or acquired (HIV) immunodeficiet
- C R F & Nephrotic
- Leukaemias & Lymphomas
- Generalised malignancy
- *Diseases treated with immunosuppression(steroids >1 m or Biologics*
- Solid organ transplantation

1. Centers for Disease Control and Prevention. MMWR. Prevention of Pneumococcal Disease. ACIP Recommendations 2010;59:1102–1106.



[Pneumococcal Disease: Vaccines360 – Volume 1, Issue 1 - Classification of Vaccines for Pneumococcal Disease]

Box 1: Summary of current pneumococcal vaccines licensed for use	
PCV-7	4, 6B, 9V, 14, 18C, 19F, and 23F
PCV-10	PCV-7 plus 1, 5, and 7F
PCV-13	PCV-10 plus 3, 6A, and 19A
PCV-15	PCV-13 plus 22F and 33F
PCV-20	PCV-15 plus 8, 10A, 11A, 12F, and 15

vaccines

MDPI

Article

Epidemiology of *Streptococcus pneuMoniae* Serotypes in JordanAmongst Children Younger than the Age of 5: A National Cross-Sectional Study

Munir Abu-Helalah [1,*], Asma'a Al-Mnayyis [2], Hamed Alzoubi [3], Ruba Al-Abdallah [4], Hussein Jdaitawi [5], Omar Nafi [6], Kamel Abu-Sal [7], Alaa Altawalbeh [8], Alia Khlaifat [8], Enas Al-Zayadneh [9], Ihsan Almaaitah [10], Ibrahim Borghol [11], Fadi Batarseh [4], Omar Okkeh [4], Abdallah Dalal [4], Ahmad Alhendi [4], Mohammad Almaaitah [8], Adnan Al-Lahham [12], Mahmoud Gazo [13], Faisal Abu Ekteish [14] and Ziad Elnasser [3]

https://www.mdpi.com/journal/vaccines

Results1

- **Analysis of serotypes of 1015 strep. pneumonia cases.**
- Lobar pneumonia final diagnosis for 1006 cases

- The PCR positivity rate was 91.8% based on the serum samples of cases with radiological findings suggestive of lobar pneumonia.

Results1

- Only 23 culture-positive cases were identified in comparison to 992 PCR-positive but culture-negative cases.
- 6 Cases were diagnosed with meningitis, 3 cases with sepsis and the remaining 14 cases with pneumonia complicated with septicemia.

Serotype	Frequency for all participant	Frequency for cases <2 year of age, N=754	Mean age	age SD	Presence of Congenital disease	Presence of chronic illness	Percentage in pneumonia cases
PCV-10	**45.32%**	**45.23%**	**15.5**	**16.2**	**1.77%**	**7.09%**	**44.63%**
1	3.84%	3.32%	19.6	18.3	0.30%	0.89%	3.74%
4	0.79%	0.66%	16.5	17.9	0.00%	0.20%	0.79%
5	0.99%	0.93%	17.0	14.5	0.00%	0.10%	0.99%
6B	16.45%	15.65%	16.2	16.9	0.49%	2.86%	16.45%
7F	0.30%	0.40%	8.6	12.5	0.00%	0.10%	0.30%
9V	0.10%	0.13%	1.0	0.0	0.00%	0.00%	0.10%
14	12.12%	12.60%	14.5	16.3	0.59%	1.38%	11.72%
18C	1.08%	1.19%	12.7	16.1	0.00%	0.10%	1.08%
19F	8.18%	8.62%	15.3	14.5	0.30%	1.18%	8.08%
23F	1.48%	1.72%	9.7	12.6	0.10%	0.30%	1.38%
PCV-13	**61.87%**	**61.54%**	**15.5**	**16.6**	**2.76%**	**8.57%**	**60.79%**
3	1.18%	0.93%	20.0	17.5	0.10%	0.10%	1.08%
6A	13.60%	14.06%	14.5	17.6	0.79%	1.28%	13.50%
19A	1.77%	1.33%	18.7	17.9	0.10%	0.10%	1.58%
PCV-15	**64.14%**	**63.79%**	**15.5**	**16.6**	**2.76%**	**8.77%**	**63.05%**
22F	1.58%	1.59%	15.7	16.6	0.00%	0.20%	1.58%
33F	0.69%	0.66%	15.9	17.0	0.00%	0.00%	0.69%
PCV-20	**68.47%**	**68.44%**	**15.3**	**16.6**	**2.96%**	**9.36%**	**67.39%**
8							
10A	0.20%	0.13%	34.5	29.0	0.00%	0.00%	0.20%
11A	1.77%	1.86%	12.9	15.9	0.00%	0.30%	1.77%
12F	1.87%	1.99%	11.9	15.9	0.00%	0.10%	1.87%
15B	0.49%	0.66%	4.4	6.2	0.20%	0.20%	0.49%

DISCUSSION1

- This study presented serotypes of strep. pneumonia for 1015 IPD cases. Most of cases (992; 97.7%) would have been missed through the routine surveillance based on the culture outcomes that identified only 23 cases
- Majority of cases were identified through qPCR for blood samples of patients with lobar pneumonia.
- Data also revealed that counting on the routine culture techniques will largely underestimate the true burden of strep. pneumonia infections and other bacterial infections highlighting the importance of molecular techniques in the assessment of the burden of different pathogens in developing countries.