Efficacy of Combined Influenza and 23-valent Pneumococcal Polysaccharide Vaccines in Patients with Chronic Illness

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Outlines

- Study 1: Follow-up study on the efficacy of combined influenza and PPV23 in patients with chronic illness (HK-09-01-16)
- Study 2: Efficacy of combined influenza and PPV23 in patients aged 50-64 years (HK-09-01-16)
- Study 3: Efficacy of combined influenza and PPV23 in smokers (HK-09-01-17) - Poster

Background: Study 1 & 2

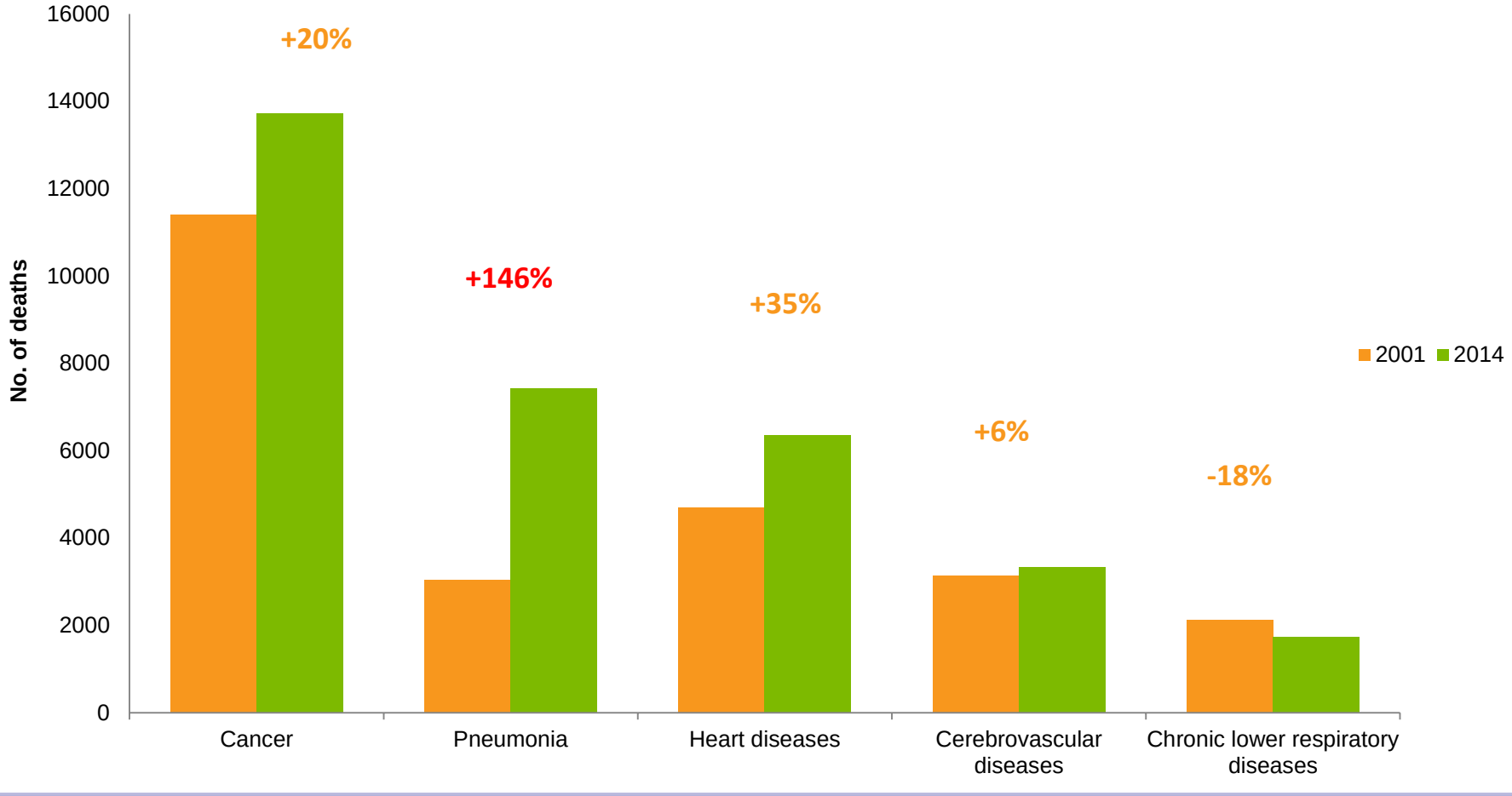
- Pneumococcal and influenza infections can cause serious morbidity and mortality, especially in the elderly population

- WHO estimates influenza and pneumococcal disease causes 500,000 and 1.6 millions deaths annually respectively

- In Hong Kong, the overcrowded living conditions facilitate the transmission of both influenza and pneumococcal infection.

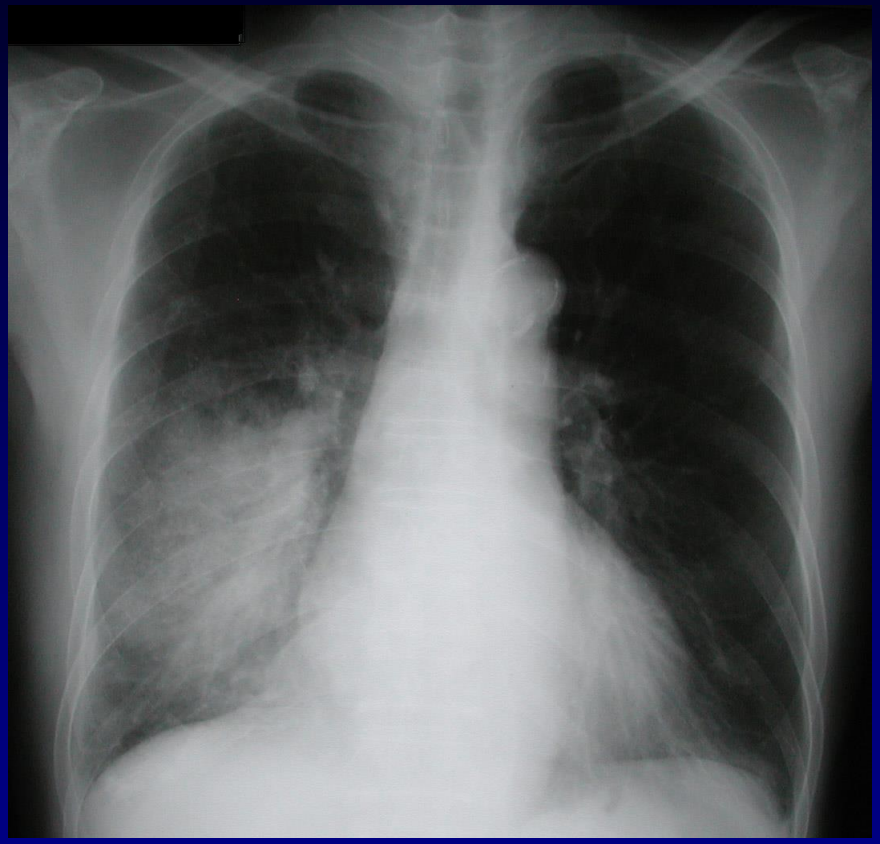
http://www.who.int/ith/diseases/pneumococcal/en/
http://www.who.int/topics/influenza/en/

Pneumonia – 2nd Leading Cause of Death in Hong Kong



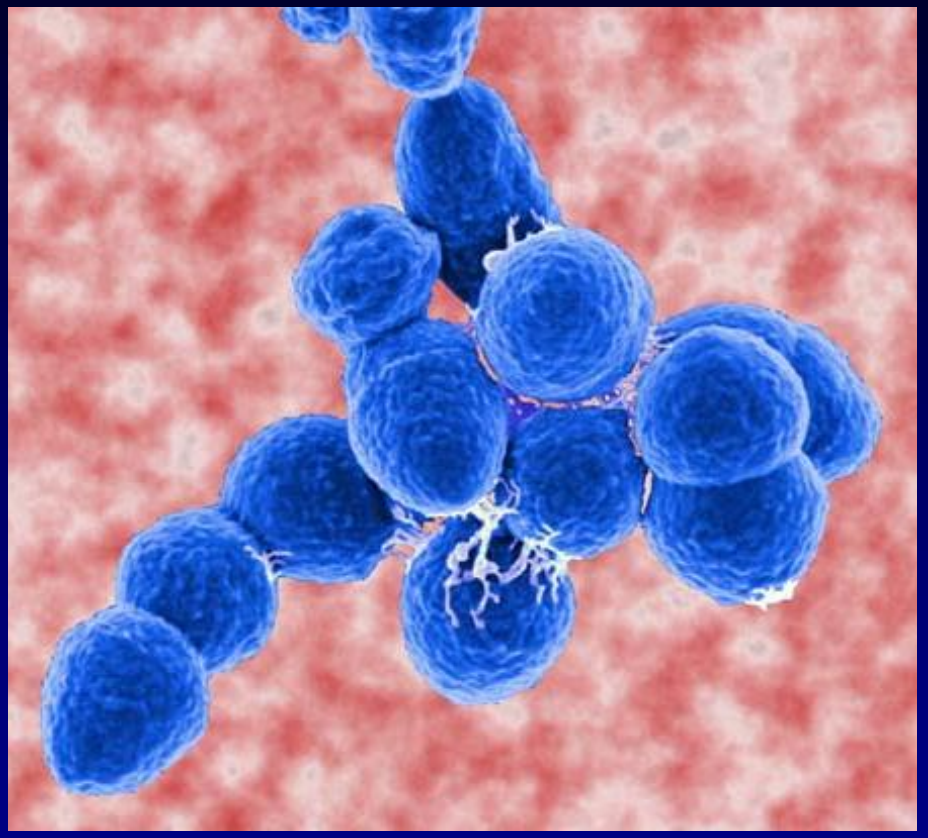
Centre for Health Protection, Department of Health, Hong Kong. Number of Deaths by Leading Causes of Death 2001 2014. Available at: http://www.chp.gov.hk/en/data/4/10/27/380.html

Streptococcus pneumoniae



S. pneumoniae: G+ve diplococci
Polysaccharide capsule: defines serotypes, virulence factors and vaccine targets
29.2% of all-cause CAP

Song et al. *Int J Antimicrob Agents* 2008;31:107 114



S. pneumoniae: Total 94 serotypes
Varied distribution, pathogenicity
<30 serotypes accounted for 90% isolates

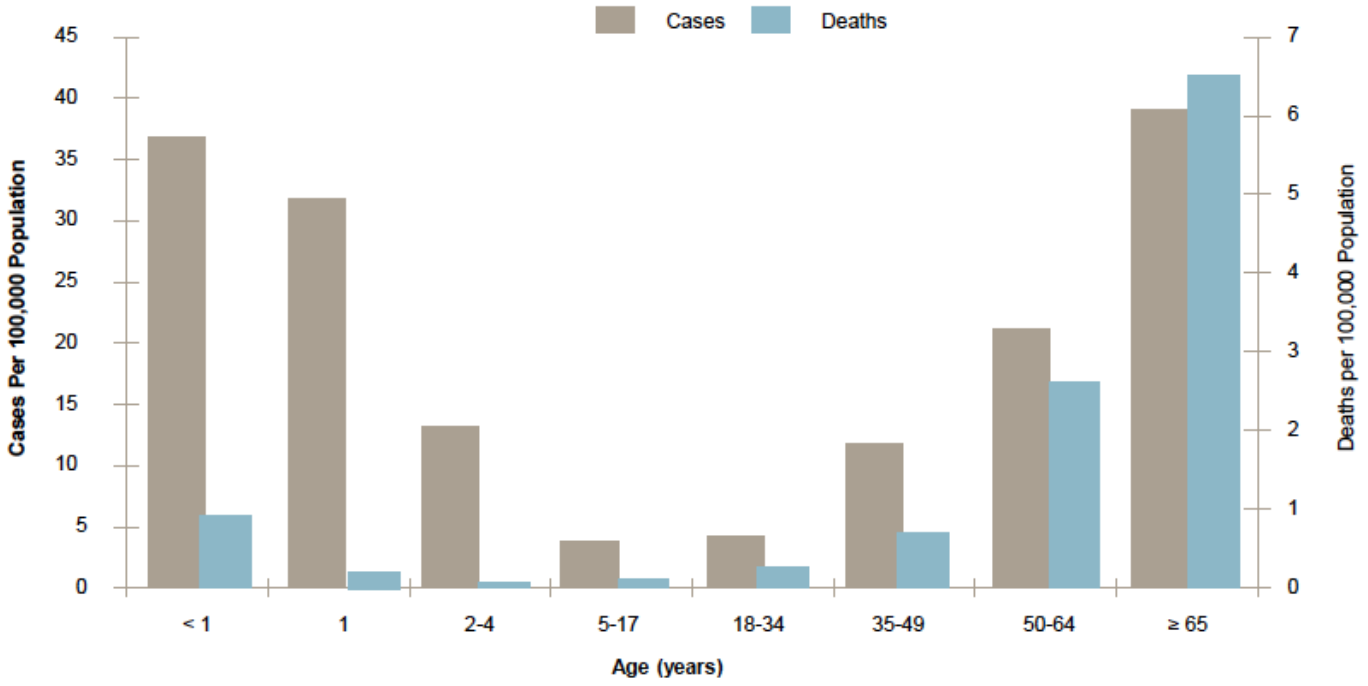
Park IH et al. J Clin Microbiol 2007;45:1225 3

CDC Epidemiology & Prevention of vaccine preventable disease 2009

Streptococcus pneumoniae

ABC SURVEILLANCE REPORT – US DATA – 2009

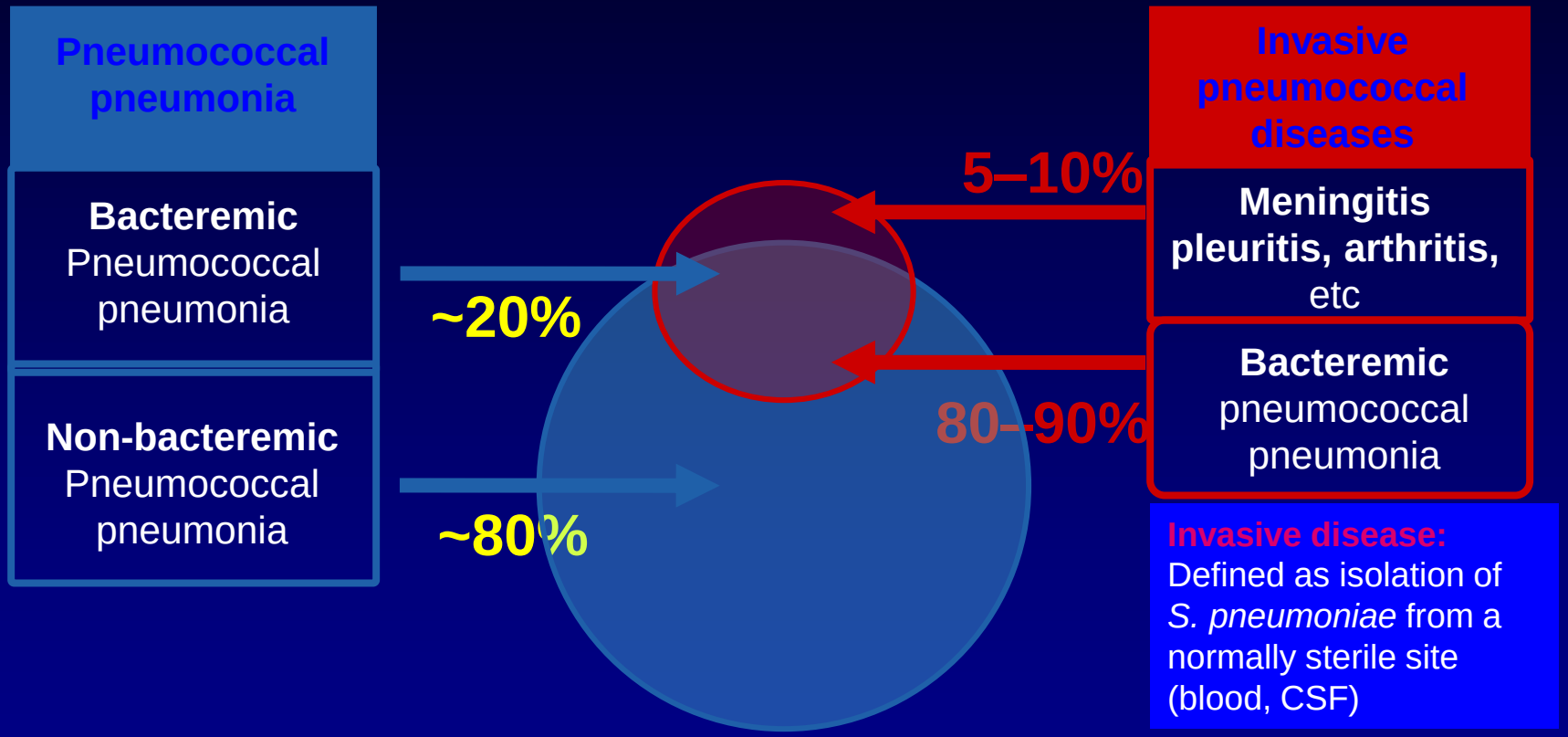
Streptococcus pneumoniae



CDC ABC Surveillance report. http://www.cdc.gov/abcs/reports-findings/survreports/spneu09.html. Accessed Nov 2011.

Courtesy of Professor Keith Klugman

The overlap between pneumococcal pneumonia and IPD



Large circle: Pneumococcal pneumonia
Small circle: Invasive pneumococcal disease

Lynch JP III, *Semin Respir Crit Care Med,* 2009
Fedson, Musher, *Vaccines,* 2004

Background

Table 1. Observational studies of pneumococcal polysaccharide vaccine effectiveness (VE) against invasive pneumococcal disease (IPD) in older adults.

Reference, study design	Study population	Subgroup	No. of cases of IPD	VE[a] (95% CI)
Shapiro and Clemens [2]				
Case control	Adults with an indication for pneumococcal vaccination admitted to Yale-New Haven hospital in Connecticut	All	90	67 (13–87)
		Immunocompromised	20	0 (−1228 to 93)
	Denver Veterans Administration hospital			
Sims et al. [4]				
Case control	Immunocompetent persons ≥55 years of age admitted to 1 of 5 hospitals in Pennsylvania	All	122	70 (36–86)
Shapiro et al. [5]				
Case control	Adults with an indication for pneumococcal vaccination admitted to 1 of 11 hospitals in Connecticut	All	983	56 (42–67)
		Immunocompetent	808	61 (47–72)
		Immunocompromised	175	21 (−55 to 60)
Indirect cohort[b]	Adults with an indication for pneumococcal vaccination admitted to 1 of 11 hospitals in Connecticut	All	932	48 (3–72)
	tion for pneumococcal vaccination admitted to the University of Virginia Health Sciences Center in Virginia			

Jackson LA. *Clin Infect Dis* 2008;47:1328 38

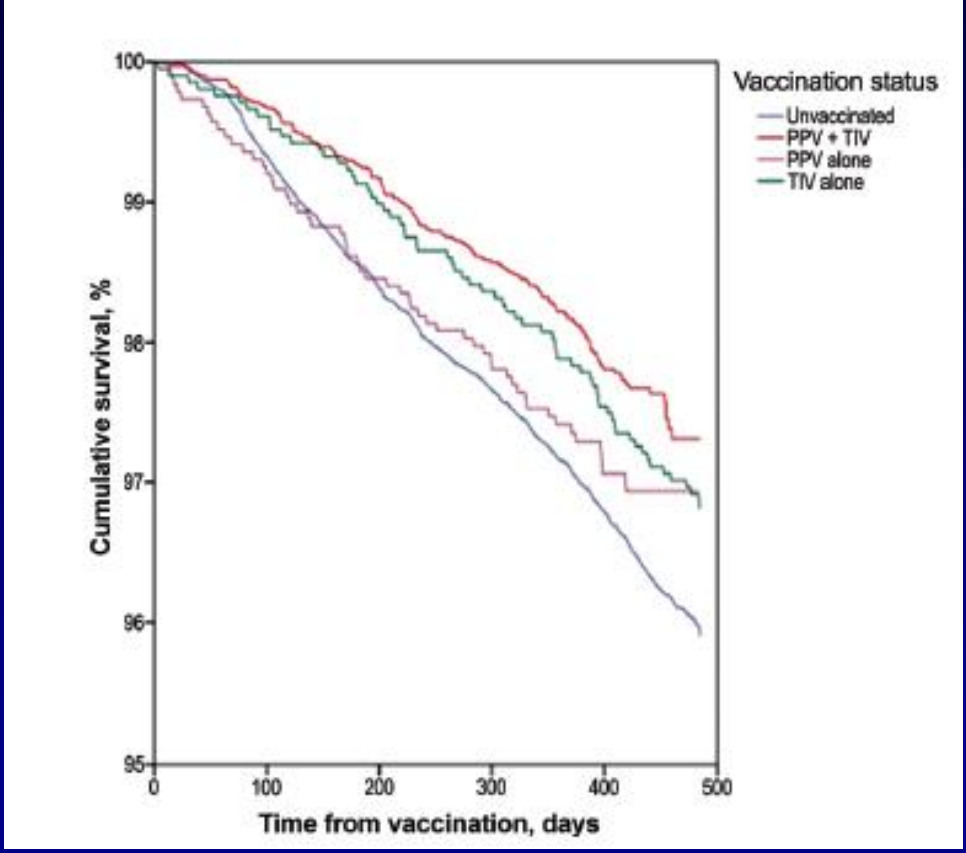
Background

Table 2. Vaccine effectiveness (VE) against all-cause pneumonia reported by clinical trials in older adults.

Reference	Vaccine valency	Study population	VE[a] (95% CI)	No. of cases of pneumonia/ no. of vaccinated persons	No. of cases of pneumonia/ no. of nonvaccinated persons
Austrian [24][b]					
Study 1	12	Inpatients at the Dorothea Dix psychiatric hospital in Raleigh, North Carolina	−22 (−49 to 0)	154/607	144/693
Study 2	12	Members of the Kaiser Permanente Health Plan in San Francisco ≥45 years of age	2 (−16 to 7)	268/6782	274/6818
Gaillat et al. [25][c]	14	Residents of 48 long-term care institutions in France	79 (53 to 91)	7/937	27/749
Simberkoff et al. [26]	14	US veterans, immunocompetent, and either aged ≥55 years or with renal, hepatic, cardiac, or pulmonary disease; alcoholism; or diabetes mellitus	−39 (−110 to 8)	56/1145	41/1150
Koivula et al. [27]	14	Residents of age of a small town in Finland ≥60 years	−17 (−66 to 17)	69/1364	64/1473
Örtqvist et al. [28]	23	Immunocompetent persons 50–85 years of age who had been previously discharged after a hospitalization for community-acquired pneumonia in Sweden	−20 (−72 to 11)	63/339	57/352
Honkanen et al. [29]	23	Persons ≥65 years of age in Northern Finland	−20 (−50 to 10)	145/13980	116/12945
Alfageme et al. [30]	23	Immunocompetent patients with COPD 61–73 years of age in Seville, Spain	3 (−52 to 38)	33/298	34/298

Jackson LA. *Clin Infect Dis* 2008;47:1328 38

Background



- 64 weeks
- Dual vaccinees:
- Fewer deaths
  - HR 0.65 (0.55-0.77)
- Fewer pneumonia
  - HR 0.57 (0.51-0.64)
- Fewer ischemic stroke
  - HR 0.67 (0.54-0.83)
- Fewer acute MI
  - HR 0.52 (0.38-0.71)

Hung IF et al. Clin Infect Dis 2010;51:1007 16

Background: Study 1 & 2

- Long-term effect of dual vaccinations on these subjects and its effect in the 50-64 years age group remained unknown

- To answer these questions, we performed a long-term follow-up study on the elderly subjects we recruited in the initial study and another prospective study on the 50-64 years old with chronic illness.

Study 1: Patients & Methods

- Recruited from the original prospective cohort study
- Between 2007 - 2014
- Single Centre: QMH
- Study protocol approved by the HKU/ HA IRB

- Inclusion
  - Age ≥ 65
  - At least one chronic illness: asthma, COPD, CAD, HT, DM, stroke, chronic renal or liver disease, malignancy

- **Exclusion**
  - Allergy to egg, vaccine components
  - Deviation from their initial vaccine group
  - All patients in the PPV+TIV or TIV group received TIV annually including the A/H1N1/2009pdm monovalent influenza vaccine

Study 1: Methodology

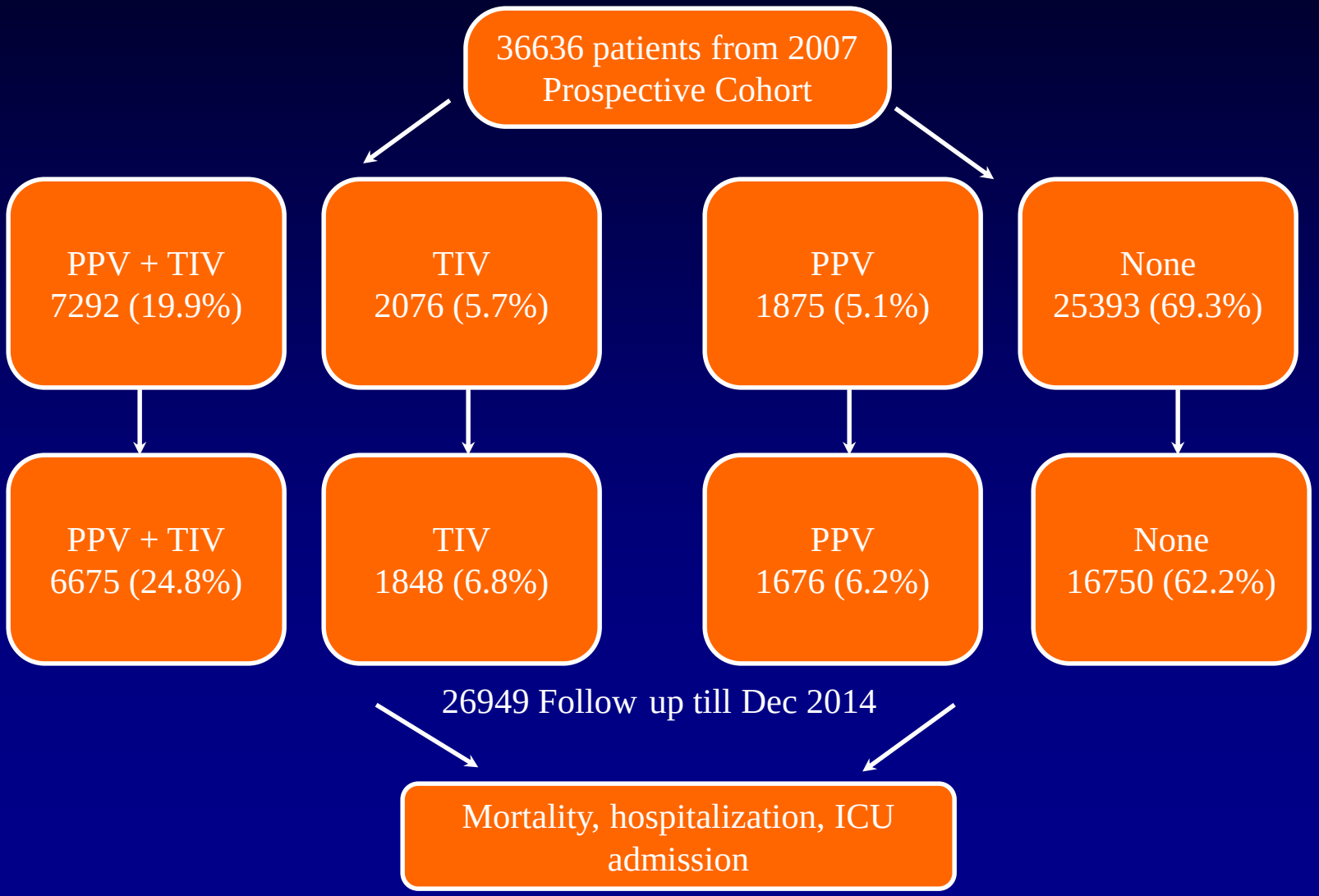
- Participants to choose their own vaccination
- 4 groups
  - PPV + TIV
  - PPV
  - TIV
  - No vaccination
- PPV23: Pneumovax (Pasteur Merieux) IM
- TIV: Vaxigrip (Sanofi Pasteur) IM

- Diagnosis: ICD-9-CM
- Primary: mortality
- Secondary: hospitalization, ICU admission

Study 1: Methodology

- Statistical analysis
  - SPSS 20.0 software
- X^2 categorical variables
- Mann-Whitney U test continuous variables
- Cox proportional hazard models
- Log-rank test: vaccine effectiveness
- P values <0.05

Study 1: Results



Study 1: Results

Baseline characteristics of the 26,949 study subjects

	Unvaccinated (n=16,570) %	PPV + TIV (n=6,675) %	TIV alone (n=1,848) %	PPV alone (n=1,676) %	*P*-value
Median age (range) years	75 (70-80)	77 (71-83)	75 (70-80)	75(71-80)	0.81
Male	46.9	40.5	44.3	45.8	< 0.001
Asthma	2.1	2.2	2.2	2.8	0.32
COPD	2.1	4.4	4.6	4.1	<0.001
IHD	7.9	7.5	7.2	7.3	0.55
Myocardial infarction	1.4	1.4	1.3	1.1	0.89
Heart failure	6.3	6.9	6.8	7.5	0.07
Hypertension	61.7	60.6	60.6	59.8	0.22
Diabetes	24.3	25.7	24.6	24.5	0.15
Ischemic stroke	7.2	7.9	7.5	7.4	0.28
Chronic liver disease	0.3	0.2	0.1	0.3	0.20
Chronic renal disease	2.3	2.4	2.5	2.6	0.55
Cancer	5.4	5.2	5.5	5.9	0.66
Smoker	13.5	14.2	13.8	14.8	0.21

Note: PPV: pneumococcal polysaccharide vaccine; TIV: trivalent influenza vaccine; COPD: chronic obstructive pulmonary disease, IHD: ischemic heart disease

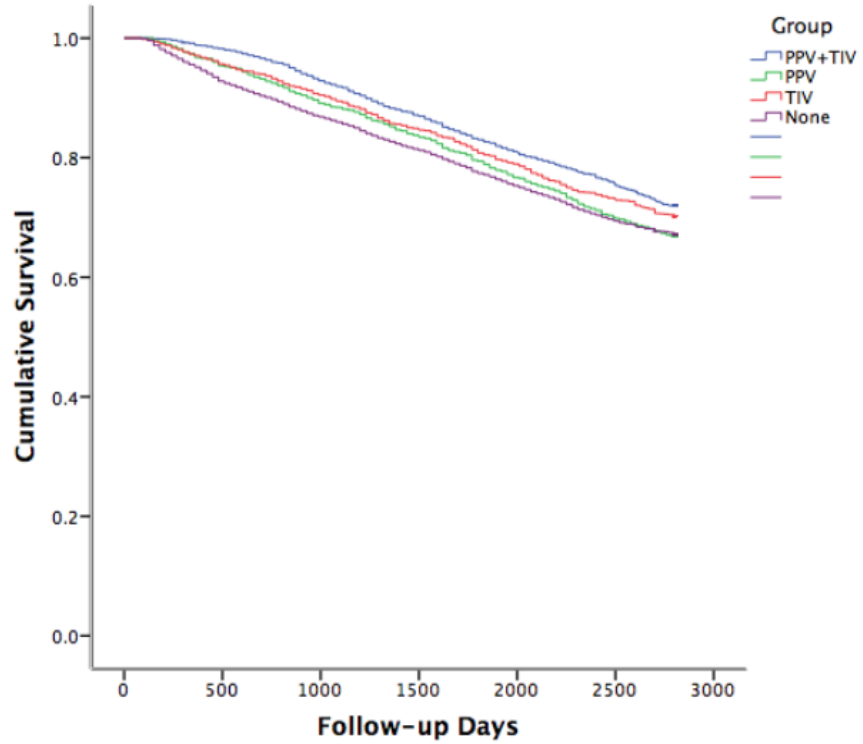
Study 1: Results

7 years follow-up:

- Median age: 75 years (IQR:70-80)
- Mortality rate:
  - PPV+TIV 28% vs. TIV 29.8% vs. PPV 33.1% vs. none 32.9% ($p<0.001$)

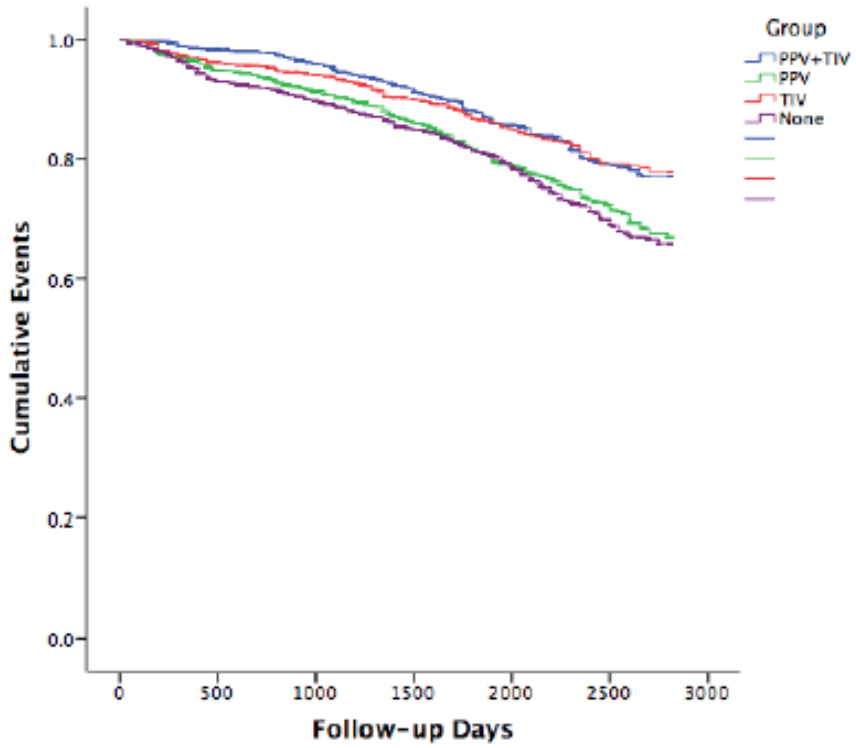
- PPV+TIV vs. none
  - Deaths: HR, 0.80; 95% CI 0.76-0.84; $p<0.001$
  - CVS events: HR, 0.59; 95% CI 0.55-0.63; $p<0.001$
  - Pneumonia: HR, 0.53; 95% CI 0.49-0.58; $p<0.001$
  - Influenza: HR, 0.32; 95% CI 0.22-0.46; $p<0.001$
  - CVA: HR, 0.68; 95% CI 0.61-0.75; $p<0.001$
  - ICU admission: HR, 0.58; 95% CI 0.47-0.71; $p<0.001$

Kaplan-Meier survival of 26,949 patients



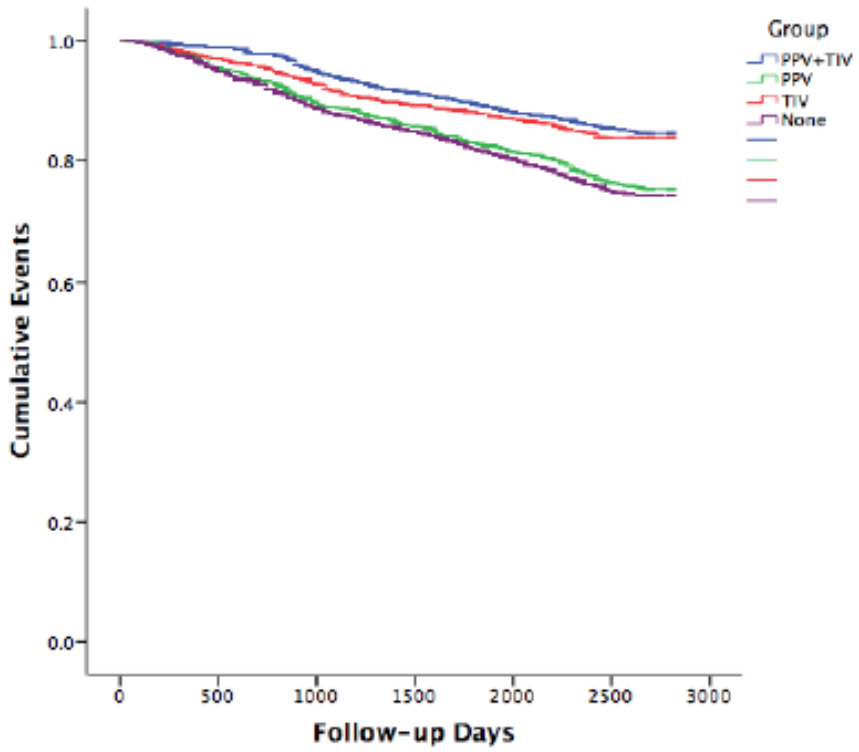
P<0.001

Hospitalization for CVS events



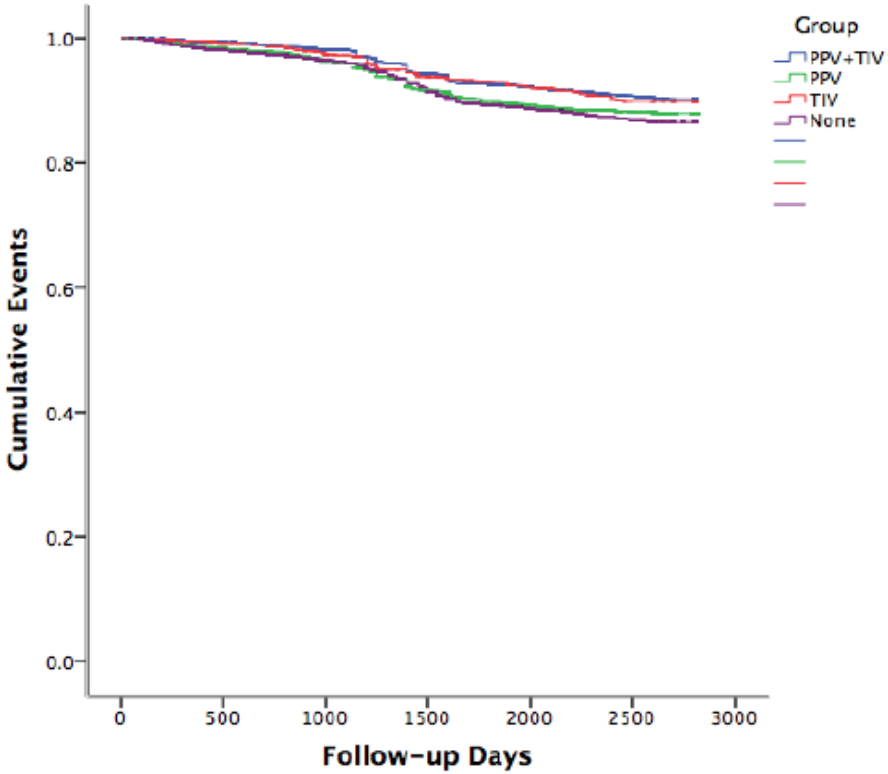
P<0.001

Hospitalization for Pneumonia



P<0.001

Hospitalization for CVA



P<0.001

Study 1: Discussion

- Sustained protection of PPV + TIV in elderly with chronic illness
- Confirmed long-term efficacy reduced mortality, hospitalization for CVS and respiratory complications, ICU admission
- Highlighted the importance of annual influenza vaccination
- Waning of PPV protection around 5 years
- Limitation: non-randomized, lack of immunological response data

Study 2: Patients & Methods

- Prospective open label RCT
- Between 2010 - 2014
- Single Centre: QMH
- Study protocol approved by the HKU/ HA IRB
- Inclusion
  - Age 50-64 years
  - At least one chronic illness: asthma, COPD, CAD, HT, DM, stroke, chronic renal or liver disease, malignancy
  - Written informed consent (patient or next of kin)
- **Exclusion**
  - Allergy to egg, vaccine components
  - Received chemo or radiation therapy within 12 months
  - HIV infection

Study 2: Methodology

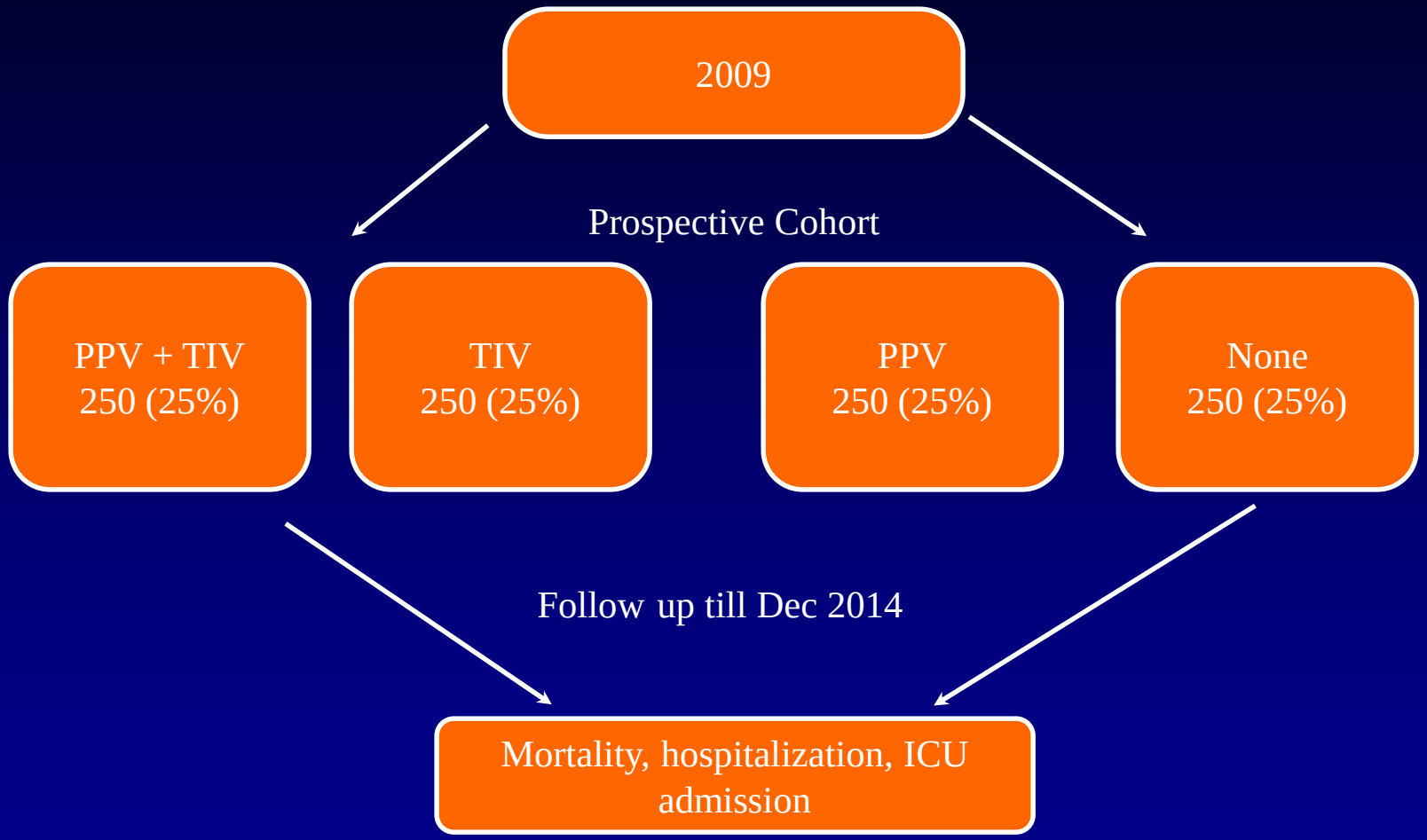
- Participants recruited from QMH SOPD
- Oct 2010 to April 2012
- Randomized into 4 groups
  - PPV + TIV
  - PPV
  - TIV
  - No vaccination
- PPV23: Pneumovax (Pasteur Merieux) IM
- TIV: Vaxigrip (Sanofi Pasteur) IM

- Diagnosis: ICD-9-CM
- Primary: mortality
- Secondary: hospitalization, ICU admission

Study 2: Methodology

- Statistical analysis
  - SPSS 20.0 software
- X^2 categorical variables
- Mann-Whitney U test continuous variables
- Cox proportional hazard models
- Log-rank test: vaccine effectiveness
- P values <0.05

Study 2: Results



Study 2: Results

5 years follow-up:

- Median age: 57 years; 485 (48.5%) males
- Well matched baseline demographics

- Significantly fewer hospitalization for respiratory, CVS and cerebrovascular events ($p<0.001$)
  - PPV+TIV: 17.8% vs. TIV: 22% vs. PPV: 23.3% vs. none: 28%
- Less frequent hospitalization ($p<0.001$)
- No difference in mortality rate and length of stay
- Both vaccines well tolerated

Study 2: Discussion

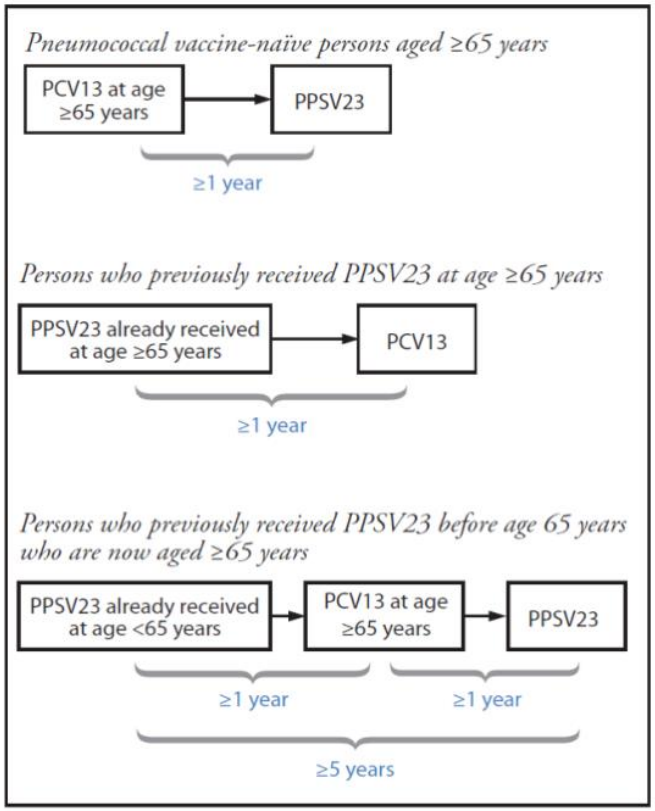
- Dual vaccination prevent hospitalization for CVS, pulmonary and cerebrovascular complications in age 50-64 years with chronic illness
- Pneumococcal vaccination justified in age 50-64 chronic illness
- No difference in mortality and LOS
- Limitation: small sample size, no immunological response data

Conclusions for Study 1 & 2

- Dual influenza and PPV vaccination strongly recommended for subjects with chronic illness >50 years
- Importance of annual influenza vaccination
- Protection against pneumococcal disease relied on strong herd immunity from children vaccination
- Clinical efficacy of PCV13 in adults to be determined
- Serotype replacement
- Head to head PCV vs PPV trial undergoing
- When to revaccinate

ACIP vs. JCVI Recommendation

BOX. Recommended intervals for sequential use of PCV13 and PPSV23 for immunocompetent adults aged ≥65 years — Advisory Committee on Immunization Practices, United States



Conclusions

34. The indirect impact of the childhood PCV13 vaccination programme on pneumococcal disease in older adults and those in clinical risk groups means that the additional benefit of the direct protection provided by wider use of PCV13 in older adults and clinical risk-groups in the UK is declining and is likely to diminish further over the next few years.

35. Analyses indicate that it would not be cost-effective to extend the PCV13 vaccination programme to those aged 65 years and over or to additional clinical risk groups, and it is likely to become less cost-effective over time. Use of PPV23 vaccine in those aged 65 years and over is likely to remain cost-effective at this time, although this programme may become less cost-effective over the next few years, and will be kept under review. Evidence suggests that vaccination of clinical risk groups with PPV23 should also continue at this time.

[26] Rozenbaum MH, *et al* (2012) Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis. BMJ; 345: e6879.

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

JCVI Joint Committee on Vaccination and Immunisation

36. JCVI has therefore concluded that there should be no changes to the advice on adult pneumococcal vaccination in the UK at this time. PPV23 should continue to be offered to those aged 65 years and over and the indicated risk-groups. PCV13 should continue to be offered to those risk-groups previously identified as being at particularly high risk of, and high mortality from, IPD, but should not be offered more widely to other risk-groups or older adults.

Joint Committee on Vaccination and Immunisation

November 2015

Acknowledgements

- Health and Medical Research Fund
- Department of Microbiology, LKS Faculty of Medicine, HKU
- Department of Medicine, LKS Faculty of Medicine, HKU
- School of Nursing, LKS Faculty of Medicine, HKU
- Hospital Authority


Thank you !

Background: Study 3

- Chronic smokers are at risk of acquiring severe pneumococcal and influenza infections
- Risk of pneumococcal pneumonia x 2 for 1 cigarette a day, x 4 for 15 to 24 cigarettes a day
- Higher chance of upper respiratory viral infection as well as nasopharyngeal pneumococcal carriage.
- Smoking affect the mucociliary function, as well as reducing the clearance of mucus, thereby compromising the local airway defences
- At risk populations not covered by the HA/ DH vaccination program
- To investigate the effect of dual influenza and PPV vaccination in chronic smokers

http://www.who.int/ith/diseases/pneumococcal/en/
http://www.who.int/topics/influenza/en/

Study 3: Patients & Methods

- Prospective open label RCT
- Between 2009 - 2014
- Single Centre: QMH
- Study protocol approved by the HKU/ HA IRB
- Inclusion
  - Age ≤ 50 years
  - Chronic smokers: at least 1 cigarette per day
  - Chronic illness allowed
  - Written informed consent (patient or next of kin)
- **Exclusion**
  - Allergy to egg, vaccine components
  - Received chemo or radiation therapy within 12 months
  - HIV infection

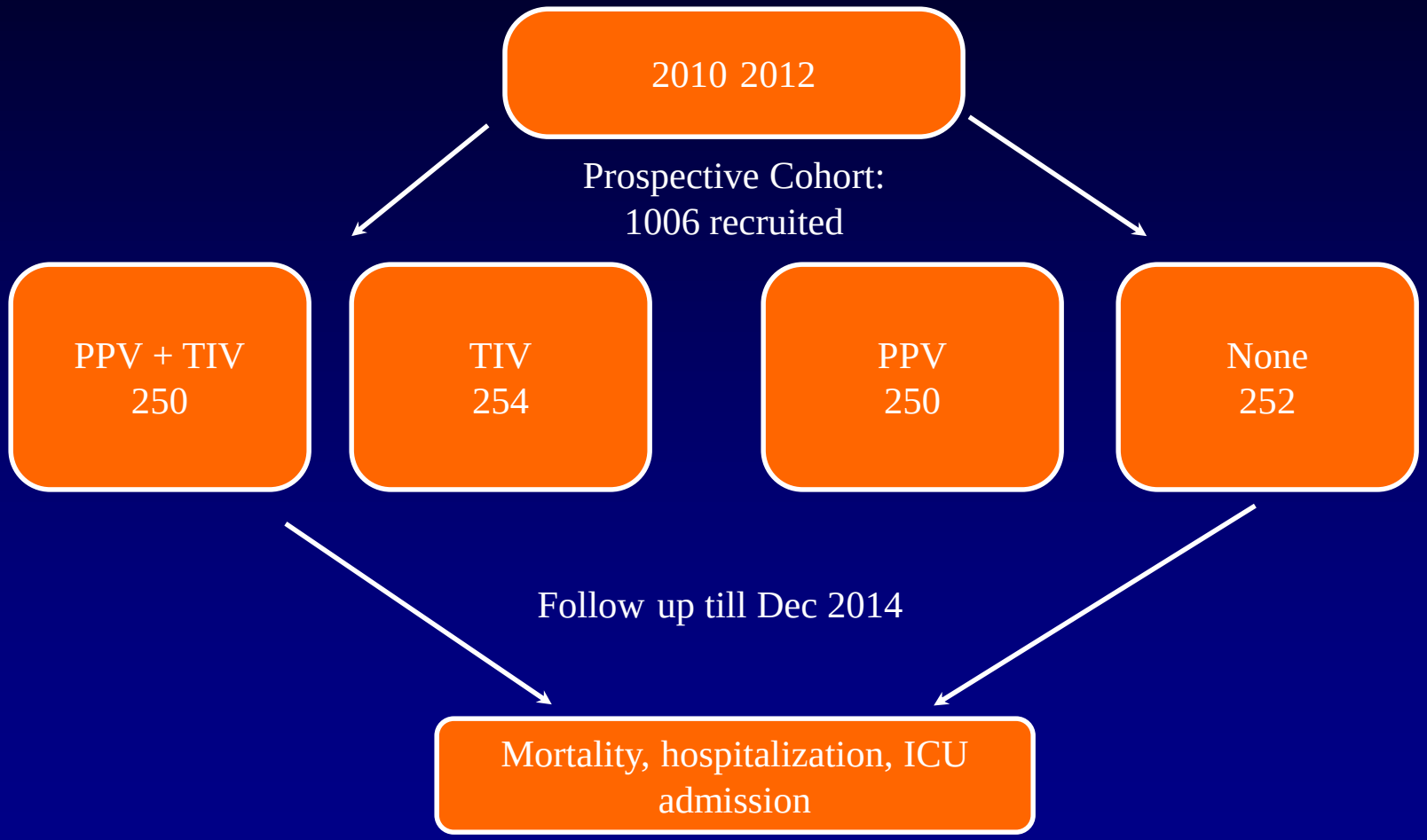
Study 3: Methodology

- Participants randomized
- 4 groups
  - PPV + TIV
  - PPV
  - TIV
  - No vaccination
- PPV23: Pneumovax (Pasteur Merieux) IM
- TIV: Vaxigrip (Sanofi Pasteur) IM
- TIV 2010-11 and 2011-12: A/California/7/2009 H1N1, A/Perth/16/2009 H3N2, B/Brisbane/60/2008
- Diagnosis: ICD-9-CM
- Primary: mortality
- Secondary: hospitalization, ICU admission

Study 3: Methodology

- Statistical analysis
  - SPSS 20.0 software
- X^2 categorical variables
- Mann-Whitney U test continuous variables
- Cox proportional hazard models
- Log-rank test: vaccine effectiveness
- P values <0.05

Study 3: Results



Demographics and Outcomes

	PPV+TIV (n=250)	TIV (n=254)	PPV (n=250)	None (n=252)	*P*
Age (Median; IQR)	48 (47-48)	48 (46-48)	48 (46-48)	48 (46-49)	0.221
Sex (male)	222	213	212	217	0.363
Mean Charlson's comorbidity index	0.360	0.40	0.63	0.37	0.980
Cardiovascular disease	120	143	139	132	0.326
Respiratory disease	29	26	33	37	0.307
Neurological disease	10	13	8	6	0.302
Metabolic disease	24	13	19	20	0.510
Gastrointestinal disease	35	30	20	28	0.329
Hematological disease	8	6	3	5	0.391
Dermatological disease	10	11	13	14	0.414
Rheumatological disease	7	7	6	5	0.550
Renal disease	7	5	9	5	0.550

	PPV+TIV (n=250)	TIV (n=254)	PPV (n=250)	None (n=252)	*P*
Overall hospitalization	23 (9.2%)	66 (26%)	74 (29.6%)	84 (33%)	<0.001
Mean length of stay in hospital (days)	2.69	6.65	7.05	4.17	<0.001
Frequency of hospitalization	0.19	0.49	0.60	0.38	<0.001
Cardiovascular disease	11 (4.4%)	29 (11%)	41 (16.4%)	36 (14%)	<0.001
Respiratory disease	12 (4.8%)	32 (13%)	31 (12.4%)	45 (18%)	0.002
Neurological disease	0 (0%)	5 (2%)	2 (0.8%)	3 (1%)	0.026
Mortality	10 (4%)	14 (6%)	10 (4%)	15 (6%)	0.320

Overall hospitalization: from vaccination to first episode of hospitalization

Frequency of hospitalization: total number of admissions

Study 3: Results

2 years follow-up:

- Median age: 48 years; 816 male (81.1%)
- Well matched baseline demographics

- Significantly fewer hospitalization for respiratory, CVS and cerebrovascular events ($p<0.001$)
  - PPV+TIV: 9.2% vs. TIV: 26% vs. PPV: 29.6% vs. none: 33.3%
- Less frequent hospitalization ($p<0.001$)
- No difference in mortality rate and length of stay
- Both vaccines well tolerated

Study 3: Discussion

- Dual PPV + TIV effectively prevent *S. pneumonia* and influenza infection in chronic smokers
- Reduces risk of exacerbating underlying CVS and respiratory disease
- Such reduction of hospitalization of smokers can greatly reduce the government expenses.
- Role of PCV13 to be determined
- Limitations in the study
  - Only recruited aged ≤50, therefore, the efficacy of dual vaccination on chronic smoker aged >50 remained unknown. Secondly, a
  - All participants recruited were from Queen Mary hospital and might not represent the population in Hong Kong as a whole
  - Dose effect of number of cigarettes smoked and smoking years not available for analysis
  - Effect on ‘healthy’ smokers unknown