Influenza but not pneumococcal vaccination protects against all-cause mortality in patients with COPD

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ABSTRACT

Background: Influenza and pneumococcal vaccination are recommended in patients with chronic obstructive pulmonary disease (COPD). A recent study from Tayside found a reduced risk of all-cause mortality with vaccination in patients with COPD. The Health Improvement Network (THIN) database was used to test this hypothesis in a different data source.

Methods: The THIN database was searched for patients with COPD. Vaccination status against *Pneumococcus* and the annual influenza vaccination status were determined. Mortality rates were calculated in the periods December to March and April to November. Relative risks for the effect of vaccination on all-cause mortality were estimated by Poisson regression, adjusting for age, sex, year and serious co-morbidities.

Results: 177 120 patients with COPD (mean age 65 years) were identified, with a mean follow-up of 6.8 years between 1988 and 2006. Vaccination rates against influenza rose from <30% before 1995 to >70% in 2005 in patients aged 60 years or more. The cumulative vaccination rate against pneumonia rose from almost zero to 70% in patients aged 70 years or more over the same period. For all-cause mortality the adjusted relative risks associated with influenza vaccination were 0.59 (95% CI 0.57 to 0.61) during the influenza season and 0.97 (95% CI 0.94 to 1.00) outside the season in patients not vaccinated against pneumonia, and 0.30 (95% CI 0.28 to 0.32) and 0.98 (95% CI 0.96 to 1.11), respectively, in patients vaccinated against pneumonia. The relative risk associated with pneumococcal vaccination was >1 at all times of the year.

Conclusions: Influenza but not pneumococcal vaccination was associated with a reduced risk of all-cause mortality in COPD.

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide resulting in more than 2.7 million deaths in 2000.[1] COPD exacerbations are a common cause of mortality and morbidity and prevention is an important strategy as effective treatment of exacerbations is still inadequate. Vaccinations against influenza and pneumococcus are recommended in NICE guidelines for COPD.[2]

A recent study used data from the Tayside Respiratory Disease Information System (TARDIS) to develop a score predicting mortality in patients with COPD. This showed a reduced risk of all-cause mortality in patients vaccinated against influenza and *Pneumococcus*.[3] As testing for the effect of vaccination was not the primary objective of that study, we tested the hypothesis using a different source of data, The Health Improvement Network (THIN). THIN is a medical research database of over 4.25 million anonymised patient records from information entered by more than 300 general practices throughout the UK that have joined the scheme. An audit of this database confirmed a high level of completeness of recording of clinical information.[4]

Published randomised controlled trials have not demonstrated a mortality benefit for these interventions,[5–9] and observational studies have an important role in addressing this gap in knowledge. Many previous published studies of the effectiveness of influenza vaccine have possible biases as they include only one or a few influenza seasons, thus not controlling for the variability from season to season.[10] Such studies attempt to control for confounding factors by adjusting for co-morbidities, as shown by Jackson *et al*;[11] such adjustment is unlikely to remove all bias. This may be due to the presence of functional limitations in the group defined as free of co-morbidity by diagnosis code criteria. Such uncontrolled functional limitations appear to be important confounders of the association of vaccination and risk of death.[12]

In this study we ascertained the effectiveness of influenza and pneumococcal vaccination in a community population of patients with COPD over an 18-year period in order to obtain a long-term view of the effectiveness of vaccination.

METHODS

Study population and study cohort

The study population consisted of all patients over 40 years of age permanently registered with practices contributing to the THIN database with a diagnosis coded as COPD, chronic obstructive airway disease (COAD), chronic bronchitis or emphysema. Patients with any history of lung fibrosis, sarcoidosis, lung cancer or lung surgery were excluded. The study period was from 1988 to 2006.

Outcomes

We defined three outcomes: all deaths; the subset of deaths where a respiratory code was recorded on the day of death or was cited as the cause of death; and the subset of deaths where a respiratory code was cited as the cause of death (see online Appendix 1 for Read codes).

Bias and confounding factors

Age, gender and co-morbidity were used as covariates to attempt to adjust for any confounding bias that could have affected the likelihood of vaccination. To identify serious co-morbidities that were likely to be risk factors for death, we used the list of serious diseases included in the Charlson

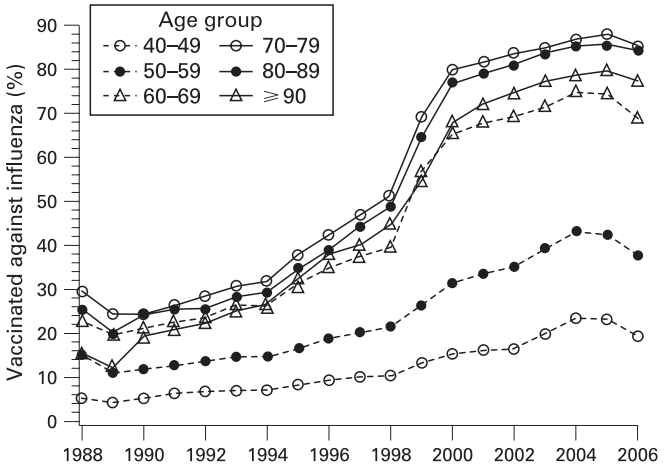

Figure 1 Trends in vaccination rates against influenza in patients aged >40 years with chronic obstructive pulmonary disease.

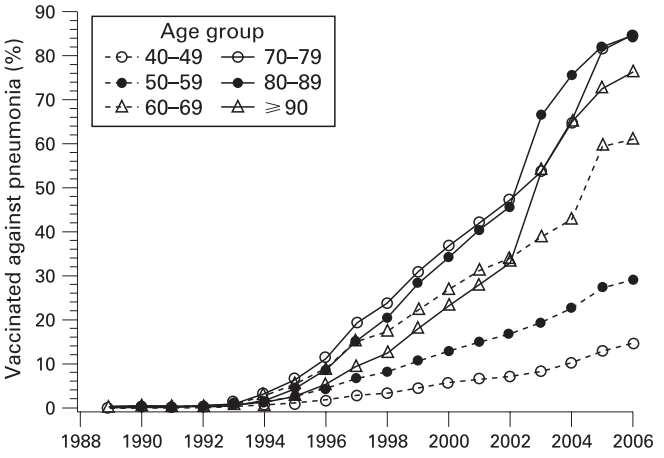

Figure 2 Trends in vaccination rates against pneumonia in patients aged >40 years with chronic obstructive pulmonary disease.

co-morbidity score.[13] We defined a flag variable for each of these disease groups for each patient in each year. We did not calculate the Charlson score, but used the individual indicator variables in our statistical models.

An apparent vaccination effect outside the influenza season would probably be due to bias associated with unidentified risk factors. A difference between the apparent vaccination effects in the influenza season and in the rest of the year in the same patient population may be a better measure of any benefit provided by vaccination. We therefore estimated the ratio of relative risks in the influenza season and in the rest of the year (ie, the interaction between influenza vaccination and season).

Statistical methods

A retrospective analysis was performed of the cohorts of patients who were vaccinated against influenza, pneumonia, both or neither between 1988 and 2006. The study period for each patient was divided into consecutive 1-year periods starting on 1 December each year.

Patients were regarded as immunised against pneumonia in a given year if they had been vaccinated at any time before 1 December of that year. Patients were regarded as immunised against influenza in a given year if they received a vaccination at any time after 1 August of that year and before 1 August of the next year. We assumed that immunity to influenza was acquired 30 days after vaccination. In patient-years where influenza vaccination occurred, the time before vaccination is "immortal" time (ie, death could not have occurred in this period). We discarded time before the date that immunity was acquired (ie, the immortal period plus the first 30 days after vaccination).

We identified deaths from any cause in December to March and April to November for unvaccinated patient-years, and in the periods of immunity between these dates for vaccinated patient-years. Relative risks for the effect of vaccination on all-cause mortality were estimated for each period by Poisson regression, using time at risk as an offset variable and adjusting for age, sex, year and 15 co-morbidities. We also included a factor to indicate whether or not the influenza vaccine used each year included all the strains of virus in circulation in that season.

Preliminary analyses suggested a strong interaction between pneumonia and influenza vaccination, so we estimated the interaction between influenza vaccination and season separately in patients who had and had not been vaccinated against pneumonia.

RESULTS

A total of 177 120 patients with COPD with an average of 6.8 years follow-up between 1988 and 2006 were identified. Their mean age at the start of each influenza season was about 65 years. Figure 1 shows that the rate of vaccination against influenza among patients aged ⩾60 years rose from 20–30% in the early 1990s to at least 70% (and 80% in patients aged ⩾80 years) after 2000. Figure 2 shows that the cumulative rates of vaccination against pneumonia rose from almost zero in 1993 to at least 75% in patients aged ⩾70 years in 2006.

Table 1 shows sex and age distributions and the co-morbidities of vaccinated and unvaccinated patients in the 2006/7 influenza season. Vaccinated patients, particularly those who received both vaccinations, were older than unvaccinated patients. Most of the co-morbidities were substantially more prevalent in patients who received either vaccination or both.

Table 2 shows the unadjusted all-cause mortality rates and death rates associated with respiratory events for the periods December to March and April to November, pooled over the whole study period. The all-cause mortality rate was 52 deaths per thousand patient-years (ptpy) during the influenza seasons, and 46 deaths ptpy at other times. The unadjusted death rate was substantially higher among patients vaccinated against pneumonia than those who were not vaccinated (64 vs 48 deaths ptpy in the influenza season, 68 vs 40 deaths ptpy at other times). In April to November it was also higher in patients who had been vaccinated against influenza in the previous influenza season than in those who had not (63 vs 35 deaths ptpy), although the rates had been similar during the influenza season (53 vs 51 deaths ptpy).

The annual all-cause mortality rate varied little over the study period. However, death rates associated with a respiratory event increased substantially over the study period. This may be due to improvements made by GPs in their recording of cause of death, and a year effect was therefore included in all the statistical models to account for this trend.

Table 3 shows the relative risks of death from any cause for the other risk factors included in the models. Men were at higher risk than women and there was a strong trend with age. The relative risk (RR) of death in December to March vs April to

Table 1 Co-morbidity of patients with COPD aged at least 40 years vaccinated against influenza, pneumonia, neither or both in the 2006/7 influenza season

	None	Pneumonia only	Influenza only	Both
	No (%)	No (%)	No (%)	No (%)
Patients	31062 (100.0)	5635 (100.0)	9679 (100.0)	50699 (100.0)
Male	13286 (42.8)	2386 (42.3)	4102 (42.4)	23830 (47.0)
Age				
40–49	10577 (34.1)	557 (9.9)	1208 (12.5)	1471 (2.9)
50–59	10816 (34.8)	979 (17.3)	2596 (26.8)	4525 (8.9)
60–69	6083 (19.6)	1436 (25.5)	3248 (33.6)	13406 (26.4)
70–79	2088 (6.7)	1480 (26.3)	1468 (15.2)	18942 (37.4)
80–89	1206 (3.9)	964 (17.1)	929 (9.6)	10843 (21.4)
⩾90	292 (0.9)	219 (3.9)	230 (2.4)	1512 (3.0)
Myocardial infarction	479 (1.54)	377 (6.69)	536 (5.54)	4822 (9.51)
Congestive heart disease	476 (1.53)	411 (7.29)	440 (4.55)	4641 (9.15)
Peripheral vascular disease	994 (3.20)	482 (8.55)	617 (6.37)	4931 (9.73)
Cerebrovascular disease	936 (3.01)	589 (10.45)	793 (8.19)	5965 (11.77)
Dementia	72 (0.23)	64 (1.14)	76 (0.79)	364 (0.72)
Rheumatic disease	678 (2.18)	300 (5.32)	418 (4.32)	3165 (6.24)
Peptic ulcer disease	1155 (3.72)	432 (7.67)	560 (5.79)	4010 (7.91)
Mild liver disease	66 (0.21)	30 (0.53)	35 (0.36)	154 (0.30)
Diabetes	775 (2.50)	655 (11.62)	780 (8.06)	6964 (13.74)
Diabetes with chronic disorders	31 (0.10)	46 (0.82)	36 (0.37)	428 (0.84)
Hemiplegia or paraplegia	58 (0.19)	14 (0.25)	32 (0.33)	182 (0.36)
Renal disease	170 (0.55)	150 (2.66)	112 (1.16)	1455 (2.87)
Any malignancy	1546 (4.98)	672 (11.93)	892 (9.22)	7092 (13.99)
Moderate or severe liver disease	40 (0.13)	6 (0.11)	15 (0.15)	67 (0.13)
Metastatic solid tumour	41 (0.13)	32 (0.57)	23 (0.24)	172 (0.34)

Table 2 Number of deaths (N) and death rates (per thousand patient years) from all causes and associated with respiratory events, 1988–2006, in patients with chronic obstructive pulmonary disease aged at least 40 years

	Vaccinated against pneumonia	December to March			April to November		
		Vaccinated against influenza			Vaccinated against influenza		
		No	Yes	Total	No	Yes	Total
Time at risk 1988–2006 (1000 patient years)	No	198	91	289	373	120	494
	Yes	9	91	100	16	123	139
	Total	207	182	389	390	243	633
Deaths							
n	No	9328	4545	13873	12469	7133	19602
	Yes	1288	5128	6416	1218	8240	9458
	Total	10616	9673	20289	13687	15373	29060
Rate	No	47	50	48	33	59	40
	Yes	143	56	64	75	67	68
	Total	51	53	52	35	63	46
Deaths associated with a respiratory event							
n	No	2001	944	2945	2167	1202	3369
	Yes	237	996	1233	199	1344	1543
	Total	2238	1940	4178	2366	2546	4912
Rate	No	10.1	10.3	10.2	5.8	10.0	6.8
	Yes	26.3	11.0	12.3	12.3	10.9	11.1
	Total	10.8	10.6	10.7	6.1	10.5	7.8
Deaths with a respiratory event recorded as cause of death							
n	No	232	192	424	283	266	549
	Yes	96	567	663	89	754	843
	Total	328	759	1087	372	1020	1392
Rate	No	1.2	2.1	1.5	0.8	2.2	1.1
	Yes	10.7	6.2	6.6	5.5	6.1	6.1
	Total	1.6	4.2	2.8	1.0	4.2	2.2

Table 3 Adjusted relative risks (RRs) for all-cause mortality in patients with chronic obstructive pulmonary disease aged at least 40 years (from a multivariate Poisson model which also included year and vaccination status)

Risk factor	RR (95% CI)
Gender (men vs women)	1.41 (1.38 to 1.43)
Age	
40–49	0.1 (0.11 to 0.13)
50–59	0.3 (0.35 to 0.38)
60–69	1.00
70–79	2.1 (2.06 to 2.18)
80–89	3.7 (3.66 to 3.88)
⩾90	6.7 (6.49 to 7.00)
Season (December to March vs April to November)	1.3 (1.33 to 1.40)
Unexpected influenza strain	1.1 (1.13 to 1.25)
Myocardial infarction	1.2 (1.23 to 1.30)
Congestive heart disease	2.1 (2.12 to 2.22)
Peripheral vascular disease	1.3 (1.33 to 1.40)
Cerebrovascular disease	1.3 (1.34 to 1.40)
Dementia	2.3 (2.22 to 2.44)
Rheumatic disease	1.1 (1.09 to 1.18)
Peptic ulcer disease	1.1 (1.07 to 1.14)
Mild liver disease	2.1 (1.86 to 2.42)
Diabetes	1.2 (1.25 to 1.32)
Diabetes with chronic disorders	1.0 (0.90 to 1.19)
Hemiplegia or paraplegia	1.4 (1.35 to 1.61)
Renal disease	1.7 (1.71 to 1.87)
Any malignancy	1.4 (1.39 to 1.45)
Moderate or severe liver disease	2.9 (2.49 to 3.57)
Metastatic solid tumour	3.9 (3.70 to 4.21)

November was 1.37 (95% CI 1.33 to 1.40). Furthermore, in years when the influenza vaccine did not include all strains of the virus circulating during that season, mortality rates were also higher (RR 1.19 (95% CI 1.13 to 1.25)). All of the co-morbidities identified, except diabetes with chronic disorders, were also significant risk factors for death.

Table 4 shows the adjusted relative risks for the effect of vaccination against influenza and pneumonia. In December to March the RR associated with vaccination against influenza was 0.59 (95% CI 0.57 to 0.61) in patients not vaccinated against pneumonia, but vaccination against influenza provided no benefit to the same patients in the following April to November (RR 0.98 (95% CI 0.95 to 1.01)). Similar RRs were obtained from the two subsets of deaths associated with respiratory events. An RR close to 1 for influenza vaccination outside the influenza season suggests that confounding between vaccination and the major risk factors for death have been accounted for in the analysis, and that the RR estimated for the influenza season may be a good guide to the benefits of vaccination.

Patients vaccinated against pneumonia but not against influenza had a higher risk of death in both seasons (RR 1.68 (95% CI 1.58 to 1.78) in December to March, RR 1.28 (95% CI 1.20 to 1.36) in April to November). This pattern, too, was repeated from the two subsets of deaths associated with respiratory events. RRs greater than 1 for vaccination against pneumonia suggest that some confounding between vaccination and risk factors for death remains unidentified.

RRs for patients immunised against both pneumonia and influenza were similar to those for patients vaccinated against influenza only.

Table 5 shows the results of subgroup analyses for patients who have and have not been vaccinated against pneumonia. They confirm that in both populations there is a strong interaction between season and the apparent effect of vaccination against influenza. In patients not vaccinated against pneumonia, the ratio of RRs for December to March vs April to November is 0.60 (95% CI 0.58 to 0.63) for all-cause mortality, very close to the apparent effect observed in December to March since the RR in April to November is close to 1.

In patients who had been vaccinated against pneumonia, those who were also vaccinated against influenza had a lower risk of death even outside the influenza season (RR 0.64 (95% CI 0.60 to 0.68)). However, the RR associated with influenza vaccination in these patients during the influenza season was lower still (0.30 (95% CI 0.28 to 0.32)) and the ratio of RRs (0.47 (95% CI 0.43 to 0.51)) suggests a substantial benefit from vaccination in these patients too.

DISCUSSION

Our study is the largest study of patients with COPD and provides data that supports vaccination in this patient group. Unlike a recent Cochrane review which showed no effect of influenza vaccination on mortality,[14] our study suggests that influenza vaccinations are effective in decreasing all-cause mortality. NICE guidelines advise vaccination of patients with chronic obstructive pulmonary disease against influenza and *Pneumococcus*. Rates of influenza vaccination in patients with chronic obstructive pulmonary disease aged >60 years have increased from <30% before 1995 to >70% since 2000. Immunisation against pneumococcal disease has risen from almost zero in 1995 to >70% in patients aged ⩾70 years.

Previous studies of influenza vaccination have shown significant protection against all-cause mortality in a cohort of elderly patients[15] and also in elderly patients with chronic lung

Table 4 Adjusted relative risks associated with influenza and pneumonia vaccination for all-cause mortality rates and death associated with a respiratory event in patients with chronic obstructive pulmonary disease aged at least 40 years

		December to March		April to November	
		Vaccinated against pneumonia		Vaccinated against pneumonia	
	Vaccinated against influenza	No	Yes	No	Yes
Deaths	No	1	1.68 (1.58 to 1.78)	1	1.28 (1.20 to 1.36)
	Yes	0.59 (0.57 to 0.61)	0.53 (0.51 to 0.56)	0.98 (0.95 to 1.01)	0.88 (0.85 to 0.91)
Deaths associated with a respiratory event	No	1	1.78 (1.55 to 2.04)	1	1.45 (1.25 to 1.79)
	Yes	0.63 (0.58 to 0.68)	0.61 (0.56 to 0.67)	1.03 (0.96 to 1.11)	1.03 (0.96 to 1.12)
Deaths with a respiratory event recorded as cause of death	No	1	2.29 (1.80 to 2.91)	1	1.93 (1.52 to 2.46)
	Yes	0.63 (0.55 to 0.77)	0.87 (0.74 to 1.03)	1.00 (0.85 to 1.19)	1.26 (1.09 to 1.46)

Table 5 Interaction between influenza vaccination and season for all-cause mortality rates and death associated with a respiratory event in patients with chronic obstructive pulmonary disease aged at least 40 years

	December to November	December to March	April to November	December to March vs April to November
Patients not vaccinated against pneumonia				
Deaths	0.79 (0.77 to 0.80)	0.59 (0.57 to 0.61)	0.97 (0.94 to 1.00)	0.60 (0.58 to 0.63)
Deaths associated with a respiratory event	0.82 (0.77 to 0.86)	0.60 (0.53 to 0.68)	1.03 (0.96 to 1.11)	0.61 (0.55 to 0.68)
Deaths with a respiratory event recorded as cause of death	0.80 (0.70 to 0.92)	0.61 (0.51 to 0.75)	0.98 (0.83 to 1.17)	0.63 (0.49 to 0.81)
Patients vaccinated against pneumonia				
Deaths	0.46 (0.44 to 0.48)	0.30 (0.28 to 0.32)	0.64 (0.60 to 0.68)	0.47 (0.43 to 0.51)
Deaths associated with a respiratory event	0.47 (0.42 to 0.52)	0.32 (0.28 to 0.37)	0.65 (0.56 to 0.76)	0.49 (0.40 to 0.60)
Deaths with a respiratory event recorded as cause of death	0.50 (0.48 to 0.52)	0.37 (0.30 to 0.46)	0.63 (0.510.79)	0.59 (0.43 to 0.80)

disease.[16] Our study is the first in a community-based population of patients with COPD of all ages.

The strengths of this study are that data were collected in routine care from an unselected community population of patients with COPD throughout the UK. This increases the likelihood that the results will be applicable to other COPD populations. We adjusted for a number of possible confounders and measured the effect of vaccination during the influenza season relative to that among the same patients in the summer in an attempt to minimise the effects of unobserved confounding factors. Unlike most studies which often cover only one season, our study covered several influenza seasons which is especially important as the antibody levels may fall to non-protective levels within a year of vaccination resulting in lack of spillover protection from year to year.[17]

We used the THIN database, which is a relatively new primary care medical records database in the UK. It comprises prospectively collected data from September 2002. Some practices had electronic medical records as early as 1987 and these data were also included in THIN. The validity of the THIN database was confirmed in a recent study replicating well-established associations and by comparing results with other primary care databases.[18]

Limitations of the study include possible misclassification since COPD is often misdiagnosed or miscoded in electronic medical records. COPD is a diagnosis based on spirometry, but these results are not always available from routine records. The study population is therefore likely to include patients with a false positive diagnosis of COPD. However, such misclassification of disease is likely to bias the study towards the null unless vaccination has a similar effect size in subjects without COPD. It is also possible that vaccination status misclassification may have occurred; however, this seems less likely. There may also be a channelling bias in this study (ie, patients at most risk of hospitalisation or death may be more likely to be vaccinated). If this had occurred, then vaccination would be expected to be associated with a worse outcome and an observed benefit would be more impressive of efficacy.

We attempted to adjust for this using confounding factors where recorded, but some bias due to unrecorded factors may remain. It may also be true that patients with good health behaviour may seek vaccination more frequently than those with poor heath behaviour. This healthy user effect may partly explain the present results. Also, the completeness of cause of death records appeared to vary substantially over the study period.

It would have been ideal to adjust for years with an influenza epidemic as the protective effect would be expected to be greater but we did not have this information. However, we were able to identify years in which the influenza vaccine included all the strains of virus that were in circulation during the subsequent season, and mortality rates were lower in these years. Pneumococcal vaccination is thought to offer protection against bacterial septicaemia,[19] but these data were not available.

CONCLUSION

Influenza vaccination was associated with a reduced risk of all-cause mortality in patients with COPD but pneumococcal vaccination was not, possibly due to the effect of unidentified confounding factors.

Competing interests: SS has received funding from GlaxoSmithKline, AstraZeneca and Boehringer Ingelheim to attend meetings. He has been a consultant to GlaxoSmithKline. SM has been a paid consultant to Pfizer Inc. JHW has no conflicts of interest. TMM has been paid speaker's fees or travel costs by Pfizer, Novartis, Servier and Takeda. His department has had research grants from GlaxoSmithKline, Aventis, Novartis, AstraZeneca, BMS, Boehringer Ingelheim, Pfizer and Novartis. TMM has been paid consulting fees by Pfizer, Novartis, Kaiser Permanante, Quintiles, Takeda, AstraZeneca, Sankyo Recordati and Speedel.

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Lung alert

A new vaccine to reduce the incidence of pneumococcal pneumonia?

It is well known that viral infection predisposes the host to subsequent bacterial infection. It is thought that viruses reduce host immunity and thus help to facilitate and exacerbate secondary bacterial infection.

In this study, mice were exposed to influenza A or human metapneumovirus (hMPV) and then subsequently exposed to *Streptococcus pneumoniae* 5 days later. Singly infected mice acted as controls. Large increases in host immunological responses were noted. These rises were similar in both dual-infection groups and were significantly greater than those in mice with a single infection. The dual-infected groups showed greater airway obstruction, significant weight loss, increased pulmonary destruction (especially interstitial and alveolar inflammation) and higher pneumococcal titres in the lungs. In both co-infection models, the mortality at day 5 was 100%. Interestingly, contrasting with data on influenza, delayed superinfection 14 days after hMPV infection did not increase clinical symptoms, implying that there is no long-lasting effect on host response with hMPV.

The authors suggest that hMPV, like influenza, predisposes to secondary bacterial infection and that local inflammation and tissue damage which occurs may contribute to the increased morbidity and mortality in this group. Targeting viruses by preventing infection or minimising the inflammatory response may therefore be an important means of treatment in the future to help to minimise bacterial infection.

► Kukavica-Ibrulj I, Hamelin ME, Prince GA, *et al*. Infection with human metapneumovirus predisposes mice to severe pneumococcal pneumonia. *J Virol* 2009;**83**:1341–9.

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